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LECTURES ON PATHOLOGY

LECTURES ON PATHOLOGY

[DELIVERED IN THE UNITED STATES, 1924]

BY

LUDWIG ASCHOFF, M.D.

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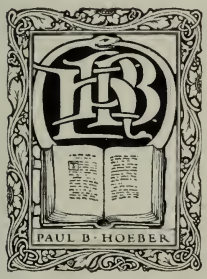
WITH THIRTY-FIVE ILLUSTRATIONS



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PREFACE

The following lectures were delivered in the spring of 1924, in part as the Edward G. Janeway Lectures of the Mount Sinai Hospital in New York, the Lane Lectures of the Leland Stanford Medical School in San Francisco, the Osler Memorial Lecture of the County Medical Association in Los Angeles, and a Harvey Lecture in New York. With the kind consent of the various hospital administrations and medical societies they are here collectively published. At the request of my friends I decided to add other lectures delivered for medical bodies at various places: Chicago German Medical Society; Colorado Springs Medical Society; New Haven, Yale Medical School; New York, Lenox Hill Hospital; New York, Mount Sinai Hospital; Philadelphia County Medical Society; Pittsburgh, Mercy Hospital; Rochester, Minn., Mayo Clinic; and Salt Lake County Medical Society.

I realize that these lectures do not give a final solution of the questions considered. I hope, however, that they will furnish a proper groundwork for further discussion of problems which are being zealously investigated by both Americans and Germans. I have added a few references to European literature from which a more complete bibliography may be obtained. I take it for granted that the American literature is well enough known to my readers to require no further references.

I am deeply indebted to the various gentlemen who translated the lectures and assisted in their preparation for publication.

LUDWIG ASCHOFF.

September 3, 1924.

CONTENTS

LIST OF ILLUSTRATIONS

I

RETICULO-ENDOTHELIAL SYSTEM[1]

You have conferred upon me the honor of inviting me to deliver the Janeway lectures this year. In spite of the many misgivings and difficulties which confronted me I accepted the invitation gladly because I felt I was returning to a circle of friends. Although I did not know personally the great clinician in whose memory these lectures are given, I had the pleasure of meeting his son during my last visit to New York. Well do I remember the interesting discussion which we had concerning the problem of the arteriosclerotic contracted kidney and its diverse modes of development.

I have been requested to address you concerning the reticulo-endothelial system. I consented reluctantly, because the question of the independence of this system and its function is still so disputed and its domain is so closely related to almost all the problems of anatomy, hematology, pathology of metabolism, pharmacotherapy and even tumor formation, that there is danger either of overstepping the boundaries or of drawing the line too close. What I can present is only a provisional classification, an effort to show the relationship of this system to the various fields of medicine. If I leave open large gaps, touch upon some of the questions but lightly, and record too much that is undetermined, I must beg you to bear in mind the insufficiency of our present state of knowledge concerning this system and its functions. But I hope to be able to show you that we have already collected sufficient data to permit us to speak of a special system. At any rate, as the author of the name, I feel the responsibility of justifying the conception which it is intended to convey, and shall endeavor to present briefly my reasons for holding this view.

[1] Edward G. Janeway Lecture.

RETICULO-ENDOTHELIAL SYSTEM

When Landau and I proposed, in 1913, to group together a special type of cells of wide distribution in the mammalian organism as a system of reticulo-endothelial cells, we had reached this conclusion only from a large number of individual observations of previous investigators, the value and importance of which were forcibly impressed upon us by our own studies.

Confining ourselves to human beings and the usual experimental animals, we note that the attention of investigators was directed long ago to the loose connective-tissue cells, especially of the omentum, which Ranvier had described as clasmatocytes. He depicts them as cells which frequently show multiple ramifications and which are possessed of an oval nucleus and finely granular protoplasm. Fragments of their processes can become detached from the cell body and are found interspersed among the meshes of the connective tissue. He denies their histoid character, and derives their origin from leucocytes (lymphocytes) which, having emigrated from the vessels, have the faculty of resuming their original form in the presence of inflammatory irritation. The lymphocytic wandering cells, according to Ranvier, not only have phagocytic functions, but also serve as carriers of nutritive material which they deposit in certain areas by the process of self-destruction, especially under the influence of inflammation.

Whereas Ranvier pictured his clasmatocytes as metamorphosed leucocytes, Marchand made the important and monumental discovery that the cells in question are not emigrated blood cells but cells arising from connective-tissue elements particularly of the adventitia. In the presence of inflammation, these cells are converted into the macrophages which Metchnikoff had already described. He further states that they can also be transformed into lymphocyte-like and perhaps even into leucocyte-like elements; in short, into any variety of blood-cell formation. For this reason he designates them as leucocytoid cells, and ascribes their source to Saxer's primary wandering cells.

The origin of these cells continued to be the subject of great controversy. The problem was further advanced by the

studies of Dominici, Renaut and Maximow. The cell in question is a special type of connective-tissue cell derived from mesenchymal wandering elements which have been converted into more or less sessile connective tissue, and especially adventitial cells (Renaut's rhagiocrine cells; Dominici's *cellules lymphoconjunctives;* Maximow's polyblasts). It remained undetermined whether these cells arise solely by reproducing themselves or only from emigrated primordial lymphocytes. The problem has been solved in accordance with Marchand's view. This type of cell is mesenchymal, and later assumes the properties of a wandering cell of histiogenic, but not of hematogenous, origin. Could such cells be transformed into fixed connective-tissue cells, ordinary white blood corpuscles (leucocytes and lymphocytes), into plasma cells or mast cells? The answer is intimately related to the problem of the specificity of these cells and their conception as a system.

Before discussing this question, the *distribution of this cell-type* must be briefly considered. Ranvier and Marchand and all other investigators call attention to the extensive distribution of these cells in the connective tissue. It is true that they emphasize their concentration in certain areas, such as Ranvier's taches laiteuses of the omentum and the adventitial sheaths of the vessels. Their relationship to the macrophages of Metchnikoff is emphasized by all; in fact, they are regarded as identical. In the fifth chapter of his celebrated treatise on "Immunity," in which he briefly summarizes his conceptions of the comparative pathology of inflammation, Metchnikoff enters into an exhaustive discussion of the macrophages. For me, this chapter has always been one of the most significant in the whole conception of *defensio*—by which term is indicated the reactive processes of inflammation. Here Metchnikoff sharply differentiates between the circulating ameboid cells of the blood and the fixed ameboid cells of the rest of the body. He ascribes to the latter, despite their fixed position in the connective tissue, the capacity for ameboid activity and the phagocytosis of foreign and native substances. He includes among them the nerve cells, the large cells of the splenic pulp and lymph nodes, certain endothelial cells, the neuroglial cells, and

finally, certain cells of the ordinary connective tissue. All these cells—and this is their distinctive feature—have the property of phagocytosis. With the exception of the nerve cells, all are mesoblastic. That the ganglion cells have phagocytic power he demonstrates by their behavior toward the lepra bacillus. He also discusses the relationship of the so-called dust-cells of the lung and the Kupffer cells of the liver to the macrophages. He particularly emphasizes that not all young motile cells have a phagocytic function under ordinary circumstances. He draws a sharp line between the circulating lymphocytes and this type of cells. I have frequently seen emphasized this distinction in referring to these studies. Of the corpuscular elements of the blood and lymph, only the large mononuclear cells are related to the macrophages, according to Metchnikoff. It is clear, therefore, that Metchnikoff was the first to speak—not explicitly, it is true, but he does speak—of a system of cells widely distributed throughout the body, which he designates the system of macrophages. Whether the cells of Metchnikoff are actually functionally related, is the second great question, and this involves a consideration of the extent and magnitude of the system. This question is intimately related to the one of specificity. To group together certain cells in system form is justified only by their possession in common morphological and physiological properties of a very special character.

Is the phagocytosis of relatively coarse foreign bodies (parasites, cells, cell products) the determining factor? We shall exclude from consideration the circulating microphages, the polymorphnuclear leucocytes. It is well known that every conceivable type of cell can occasionally engulf coarse foreign bodies; in other words, assume the character of macrophages. Thus red blood corpuscles can be phagocytosed by the liver cells, dying epithelial cells of the kidney by the living ones, the decomposition products of muscle fibers by the myoblasts, the constituents of degenerated nerves by Schwann's cells and, in the case of brain softening, by the glia cells. There is scarcely a fixed cell in the animal organism that is not capable, under exceptional circumstances, of engulfing other cells, foreign bodies and parasites. Are these cells to be regarded on this account as functionally

equivalent? Not at all. One must therefore seek other criteria. Phagocytosis is but one highly developed property of these cells. The *intensity* and *frequency of phagocytosis* is the determining factor in this connection. Metchnikoff brings the Kupffer stellate cells into close relationship with the pulp cells of the spleen, the cells of the lymph nodes and large omentum, because they all so frequently phagocytose white and red blood corpuscles. Metchnikoff regards the Kupffer stellate cells for the most part as macrophages of the peritoneal cavity which have wandered into the liver. He shows that they can gain entrance into the large blood vessels and ultimately be discovered in the heart's blood. On the basis of his investigations, Metchnikoff also describes the occurrence of macrophages in the subcutaneous connective tissue. Thus, then, exists, if we add the reticulum cells of the bone marrow, a circle of cells whose particular function it is physiologically as well as pathologically to devour degenerated white and red blood corpuscles and to metabolize them. One might speak as Metchnikoff does, of a digestive system for the blood cells, a *blood destruction system* in contrast to a blood production system. That the blood platelets are destroyed in like manner, has been shown by subsequent investigations. The macrophage system acquired special importance when Metchnikoff demonstrated its relationship to antibody formation in the development of immune bodies. He discusses in great detail the various protective agencies which are produced by the macrophage system and includes among others the formation of macrocytase, the amboceptors of Ehrlich, the agglutinins and the coagulins. I have summarized the older literature on this subject in my review of Ehrlich's side-chain theory. Of greater importance, in my opinion, is Levaditi's observation that animals treated with hemolysins exhibit an enormous accumulation and digestion of the erythrocytes in the spleen. He regards this finding as support for Sawtschenko's conjecture that the amboceptors not only anchor themselves to the red blood corpuscles, but are also absorbed by the splenic cells which they stimulate to increased activity. Thus we find very diverse accounts of experimental efforts to prove the antigen-binding and antibody-producing functions

of the macrophage system. The studies of this early period are concerned with the observation, demonstrated by every conceivable form of experiment, that microorganisms and cells when introduced into the animal body, are taken up on the one hand by the microphages and on the other by the macrophages; and that in the latter case the process of phagocytosis and digestion is accompanied locally by the development of immune bodies.

The characterization of these cells as agents of blood destruction and antibody formation was not sufficiently exhaustive. Apart from the circumstance that certain groups such as the macrophages of the skin, the omentum and various lymph nodes assumed the function of blood destruction only under pathological conditions, the participation of this system in immune body or antibody formation in individual instances was difficult to demonstrate. It was therefore imperative to continue the search for a common, permanently valid and easily demonstrable distinguishing characteristic. At this juncture, the *method of vital staining* appeared to render the necessary assistance.

Ranvier had already attempted to identify his clasmatocytes by the use of dyes. His method, however, was not a very happy one, the possibility of confusion with the connective-tissue mast cells being too great, and he was unquestionably led into error. The first to demonstrate these cells by the use of dyes and to emphasize their broader distribution in the connective tissue, was Ribbert. He employed the lithium carmine method for their identification. He was able to show that glands of external secretion, with the exception of kidney and liver, were unable to take the dye. The muscle fibers, ganglion and glia cells also remained unstained. The ordinary vascular endothelium, as a rule, did not take the dye. Positive results were observed only in the liver (Kupffer stellate cells), spleen, bone marrow and adrenals. Moreover, the dye was stored by the cells of the splenic pulp, the endothelium of the sinuses of the lymph nodes, and the reticulum cells of the thymus. Besides the endothelial and reticulum cells mentioned, certain connective-tissue cells also took the dye in similar manner. Ribbert concludes his observations concerning *intra vitam* carmine

staining of healthy animals with the words: "This concludes what I have to say concerning the localization of the carmine deposits, the most interesting characteristic of which is that the dye does not appear in all cells of the body, but only in very special ones for which an intimate relationship to carmine may be postulated."

Through Ribbert the first fundamental step toward the exact characterization of the system was made. The cells of this system are characterized by a fine granular stain of their cytoplasm by lithium carmine, and by their more or less definitely branching form. Of particular importance to us is Ribbert's demonstration of the specific capacity of these elements for absorbing all sorts of substances introduced into the circulation, not only carmine, but iron, lipoids and many others. These observations on the experimental absorption capacity of these cells shed a new light on the phenomena of natural storage (*Speicherung*). To be sure the phagocytosis of both corpuscular and dissolved substances on the part of certain of these cells, especially the Kupffer cells, had been demonstrated long before Ribbert's work appeared. I need refer but to the old experiments of von Recklinghausen and Ponfick on the absorption of cinnabar. Moreover Ponfick, on the strength of these observations, had grouped together the elements which Metchnikoff later described as macrophages. What was wanting, however, was a strict line of division between true phagocytosis of corpuscular elements and the granular cytoplasmic deposition of dissolved dyestuffs. Carmine granules are also phagocytosed by leucocytes, whereas carmine in solution is never taken up by the latter. *The striking phenomenon was thus the uniform granular deposition of a dyestuff in solution which had the capacity of penetrating the living cells without in any way injuring them.*

Was this *intra vitam*, finely granular staining by a dyestuff in solution (such as carmine), sufficient for the characterization of these cells? Perhaps so, if one places the emphasis on the words "dyestuff in solution." This means simply that these cells also manifest a strong power of attraction for fluids having a fine phase of dispersion, but not that this function is exercised in contrast to the phagocytosis of corpuscular elements. In short, there is nothing that these cells

are unable to absorb. Thus one had to correlate "storage" (*Speicherung*) with phagocytosis. Ribbert did not explicitly draw the comparison between his cells and the macrophages of Metchnikoff, and did not discuss the subject further.

With the introduction into therapy of the new dyestuffs by Ehrlich, the study of these cells gained new impetus. Bouffard was the first to show that the dyes of the benzidine series also stain these cells *intra vitam*. But the investigator who again emphasized the special staining qualities of these cells, and in a definite manner identified them with Ranvier's clasmatocytes, was Goldmann. By so doing he performed a great service in promoting the further development of the subject.

In like manner Goldmann pronounced the identity of the cells with the leucocytoid cells of Marchand, the *cellules rhagiocrines* of Renaut, and the polyblasts of Maximow. He clearly showed the similarity of his pictures with those which Ribbert had obtained by the use of the lithium carmine method.

Thus the method of vital staining, which had been systematically employed by Ribbert and extended by the newly discovered dyestuffs by Goldmann, furnished a better means of studying the system of macrophages previously described by Metchnikoff. These investigations shed no new light on the finer histology or distribution of these cells. The careful descriptions of Marchand, Renaut, Weidenreich and Maximow could only be confirmed. Moreover, nothing new was added to the information contributed by Metchnikoff, Ranvier and Renaut concerning their function. Metchnikoff had regarded them as important members of the digestive apparatus, bearers and excretors of digestive ferments, Ranvier had pictured them as carriers for the distribution of nutritive materials, and Renaut had attributed to them in addition to their capacity of storage and absorption (*Speicherung*), a sort of secretory function. The latter believed that they can be transformed into fixed connective-tissue cells, thereby losing their secretory power only to resume in the presence of inflammation their original form of wandering cells of a definitely glandular character. Goldmann agreeing with Renaut feels justified in speaking of an "internal secretion" of the connective tissue.

In order to decide such questions concerning the *function of these cells*, it was necessary to institute a very exact experimental study of all the organs, employing the most varied methods. The resumption of the study of renal function by Suzuki, with the aid of the lithium carmine method so successfully applied by Ribbert, furnished the occasion for a renewed investigation of the problem of differentiation between the histiogenic and the hematogenous wandering cells with special reference to the rôle played by each in normal and pathological tissue formation. This was done by Kiyono. New contributions were furnished elsewhere by Tschaschin with the aid of Goldmann's dyes. Moreover, Kiyono had this entire system of cells investigated by his pupils from the point of view of comparative histology. Comprehensive studies of vital staining were also reported by Capelle and Chiminata. On the basis of the foregoing material, the following conclusions have been established:

Intra vitam staining by lithium carmine, pyrrhol-blue, trypan-blue etc., results in the appearance of dye granules in certain cells of the connective-tissue series, in consequence of which these cells can be distinguished at once from most of the parenchymatous cells, from the ordinary blood cells, myeloid as well as lymphoid, from the lymphocytes of the lymph nodes, and from the plasma cells and mast cells. These granules are of variable size, and stain with varying degrees of intensity. Arranged according to the fineness and compactness of these granules, an ascending series of vitally staining mesenchymal elements can be tabulated as follows:

1. The *endothelial cells* of the blood and lymph vessels. They take the dye only when the staining has been carried to an advanced degree and only in the form of the very finest granules.

2. The *fibrocytes* or ordinary connective-tissue cells. They store the dye in variable degree after sufficiently prolonged staining, also in the form of rather fine granules. They are more easily stained than the endothelial cells.

3. The *reticulum cells* of the splenic pulp, the cortical nodules and pulp cords of the lymph nodes, and ultimately of the remainder of the lymphoid apparatus. These cells readily take the dye and stain more deeply than the connec-

tive-tissue cells, but in the rapidity and intensity of the stain fall behind the members of the following groups.

4. The *reticulo-endothelial cells* of the sinuses of the lymph nodes, the blood sinuses of the spleen, the capillaries of the liver lobules (Kupffer's stellate cells), the capillaries of the bone marrow, the adrenal cortex, and the hypophysis.

5. The *histiocytes*, as we have designated the wandering cells of the connective tissue, the clasmatocytes of Ranvier, etc., to distinguish them from the cells that give rise to connective tissue (the fibroblasts or fibrocytes). These cells stain almost as readily as those of Group 4, especially when in a state of heightened activity.

6. The *splenocytes* and vitally staining *monocytes* (endothelial leucocytes, blood histiocytes) which have their origin from the histiocytes (Group 5) and the reticulo-endothelial cells (Group 4).

How should we group together these cells which are so closely interrelated? We proposed at the time to eliminate Groups 1 and 2, which stain either faintly or not at all, and which, as we shall see, functoin differently from the other groups. These cells are also the least mobile and the most fixed.

On the other hand, it seemed desirable to combine under a single heading Groups 3 and 4, because of their common function of producing reticulum and of lining sinusoid blood and lymph spaces, and to call it the *reticulo-endothelial system*. This was all the more necessary because of the faculty which these cells have of functioning simultaneously as lining endothelial cells and producers of reticulum. This is illustrated by the endothelium of the lymph sinuses and by the Kupffer stellate cells of the liver which are regarded as the source of the reticulum fibers (*Gitterfasern*). The newer views concerning the syncytial nature of the mesenchyme and the differentiation of the various fiber systems (reticulum fibers, connective-tissue fibers, elastic fibers) within the syncytium, the less differentiated parts of which (nucleus and perinuclear protoplasm) can be detached to form independent cells (I refer to the studies of Weidenreich, Downey, O. Ranke, Hueck), justify us in our conception of a system of reticulo-endothelial cells endowed with the faculty of exercising a multiplicity of functions.

Kiyono also designated the reticulo-endothelial cells as *histioblasts*, because of their capacity of giving rise to freely movable cells which in every way resemble the histiocytes of the connective tissue.

Groups 5 and 6 were combined by Kiyono under the name of *histiocytic elements*. To them belong the histiocytes of the connective tissue (tissue histiocytes; clasmatocytes of Ranvier), the splenocytes and the blood histiocytes. The latter consist of reticulo-endothelial cells, splenocytes, and tissue histiocytes which have been mobilized and have either been shed into the circulation or have wandered into it.

Kiyono describes the histiocytes as follows: "The nucleus of these cells is roundish-oval or kidney-shaped, and smaller than that of the fibroblasts. The entire nuclear frame-work, however, is denser and contains here and there large nucleolus-like granules, in consequence of which it is darker in appearance. The protoplasm lies in the tissue clefts and emits processes in all directions. It has a finely reticulated structure, is stained more deeply, and the outlines of the cell body are much more sharply delimited than those of the fibroblasts. The primary form of these cells is generally rounded and they are smaller than the fibroblasts in spite of the great variability in the size of the clasmatocytes. They lie singly between the meshes of the collagenous fibers and are particularly abundant in the adventitia of the vessels, where the majority have preserved their rounded form."

At the same time he calls attention to the occasional occurrence of cells, particularly in the omentum, which, because of the fineness of their dye granules, their delicate chromatin network, their nucleus, and their large branching cell bodies, occupy an intermediate position between the clasmatocytes and the fibroblasts. Thus one might conclude that a transformation of histiocytes into fibroblasts was possible, as Marchand, Maximow and others assume. The tissue-culture experiments of Carrel, it is true, speak against this view. Graeff has designated the reticulo-endothelial cells (Groups 3 and 4) as the stationary histiocytes in contrast to the wandering histiocytes, by which term he designates the members of Groups 5 and 6.

In undertaking such a classification, it is not to be assumed that the Kupffer stellate cells, for instance, and the endothelial cells of the splenic sinuses, are entirely equivalent. The morphological character, the arrangement, the dissimilar rate of vital staining speak against such an assumption. What deserves emphasis is a certain fundamental similarity in relation to phagocytosis and storage of dyes and various other substances. But this is a matter of similarity and not identity. If one were to carry the differentiation too far it would be utterly impossible to speak of a system or even of a part-system. That is certain. It will also be the task of the future to establish still more exactly the differentiation within groups.

It would require a special treatise to discuss the numerous points of controversy concerning the nature and morphology of the individual cell types associated with the reticulo-endothelial system. The relation of the endothelial cells to the reticulum cells, of the reticulum cells to the parenchymatous cells of the lymph nodes and spleen, the question of the open or closed liver capillaries and splenic sinuses—all these are still mooted problems. I refer you to the studies of Schilling on the Kupffer stellate cells, of Downey and Heudorfer on the structure of the lymph nodes, and of Weidenreich, Mollier and Neuberg on the finer structural details of the spleen. What is of special interest to us is the relationship between the endothelial cells and the reticulum cells of the lymph nodes, for instance. I am wholly in accord with Downey, who has recently made a careful study of this problem, that reticulum cells and endothelial cells are one and the same type of cells.

We may well assume the same for the capillary endothelium of the bone marrow. The endothelial cells of the splenic sinuses, too, bear a close relationship to the reticulum cells proper of the pulp, at least according to Mollier's studies. As far as the parenchymatous cells are concerned, all investigators indicate that the pulp cells are closely related to the reticulum cells. The conditions are reversed in the lymph nodes in which the reticulum cells and lymphocytic elements react quite differently toward the vital dyes. It is therefore not to be conceded, until more conclusive proof is furnished, that a

relationship between the reticulum cells and lymphocytes exists, and that a transition from one to the other is possible. The germinal centers thus appear in a new light. Whereas they were previously regarded as the sites of lymphocytic production, it has recently been contended, especially by Hellmann, that cellular proliferations in these areas are the manifestation of defence reactions against various toxic-infectious injuries. From my experience with the lymph-node alterations accompanying appendicitis, there is no doubt that every injury to the lymphocytic elements, however slight, initiates a large cell proliferation of the reticulum which leads to extensive phagocytosis of the degenerated lymphocytes. Whether these changes can be identified with the cellular proliferations in true germinal center formation is still uncertain. But it is also undetermined whether the large cells comprising the true germinal centers are derived from reticulum cells or from altered lymphocytes. At any rate, we must still insist upon a definite distinction between reticulum cells on the one hand and lymphocytes on the other.

The question has been raised whether other cells which occasionally take the vital dye should not also be included in the reticulo-endothelial system. I refer especially to the so-called interstitial cells of the testis which have also been designated the puberty gland. These cells are functionally equivalent to the theca-lutein cells of the ovary, and, as is well known, play a much greater rôle in animals than in human beings. Originally, the tendency was to include the cells in the reticulo-endothelial system; but, in accordance with Goldmann's studies, more exact investigations, especially on the part of Japanese authors, have revealed that the true interstitial cells of the testis participate only to a minor degree in the storage of vital dyes. At any event they can be regarded at the most as accessory organs of the reticulo-endothelial system, if indeed they belong at all to the latter. That true histiocytes are also present in the connective tissue of the testis and ovary is self-understood.

The nature of the Rouget cells, which have lately aroused such great interest because of Krogh's studies of capillary contractility, is still disputed. The investigations of Dr. Kiyono at the Freiburg Pathological Institute have shown

that these cells are not contractile elements in the sense which Vimtrop, a pupil of Krogh's, regards them. They have much more the character of adventitial cells. It is true they are not mature histiocytes, but rather histioblasts; still they are to be included in the reticulo-endothelial system.

Of the connective-tissue cells, the fat cells still require mention. They, too, belong to the group of vitally stained cells, but have a very special function; and for this reason, like the interstitial cells of the testis, are but loosely related to the reticulo-endothelial system. They likewise represent an accessory branch of the reticulo-endothelial system, and hence are omitted from the general discussion.

This applies particularly to the epithelial supporting elements—the reticulum cells of the thymus and the glia cells of the brain. In my opinion they should not be included in the reticulo-endothelial system—the glia cells above all, because they do not participate at all in vital staining under ordinary conditions. It is true that recent investigations, especially on the part of Lubarsch and Spatz, have demonstrated iron-bearing glial cells, and even iron-bearing ganglion cells, in certain brain centers. But here, too, very special functions are involved, which have nothing to do with the functions of the reticulo-endothelial system. Likewise, for the chromatophores of the skin, the epithelial origin of which is still the subject of great controversy, a positive relationship cannot be demonstrated.

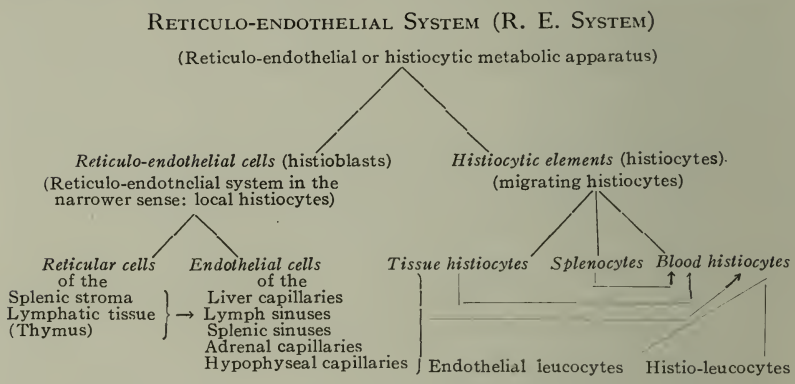
This brief review must suffice to show you that a successful study of the functions can be approached only by keeping before us the sharp delimitation and demarcation of the reticulo-endothelial system in the manner which I have indicated.

This delimitation appears all the more justified, inasmuch as the reticulo-endothelial or histiocytic system with its characteristic vital staining and characteristic functions can be demonstrated throughout the entire animal series from the mammals to the cyclostomes, as the comparative histological studies of Kiyono have shown. In all these animals, this system exhibits definite relationship to the blood-forming organs. Nevertheless, the distribution and arrangement of the system is quite varied.

In the works of Metchnikoff we already find references in this direction. It is important for us to know that the gross distribution in the usual experimental animals (birds and mammals) shows certain well-marked differences. In birds the main depot of the reticulo-endothelial system is in the liver, whereas only small collections are found in the spleen and bone marrow. On the contrary, the spleen in mammals is the principal seat of the macrophage system. To be sure there are other differences. Each animal (dog, mouse, rat, cat, rabbit, guinea pig) has its own peculiarities. Not even approximate figures for the quantitative distribution are available as yet for the individual animals. These are, in fact, difficult to obtain because of the intermingling of these cells with other structures. Not only does the quantitative distribution vary according to the type of animal, but according to the reactive capacity of the entire system or any of its individual provinces as well. In many animals, e.g., the birds (goose, dove), there is normally an active participation of the reticulo-endothelial cells, particularly of the liver, in the intracellular destruction of red blood corpuscles for their hemoglobin. In other animals, scarcely any such change is found under ordinary conditions, so that it appears doubtful whether a relationship exists at all. In certain animals (rat, mouse), the reticulo-endothelial system of the liver reacts very actively to extirpation of the spleen (Bittner, M. B. Schmidt, Lepehne, Kuczynski), in others very little (rabbit, guinea pig); on the other hand the Kupffer stellate cells of the liver in the horse are said to react very readily (R. H. Jaffé). Following splenectomy in the dog and mouse, there appears an intense erythrophagocytosis in the reticulo-endothelial cells of the mesenteric and retroperitoneal lymph nodes.

On the basis of the comparative histological investigations we are justified in dividing the entire reticulo-endothelial system into individual groups as indicated in the appended diagram. The intimate generic relationships between the various groups are shown in this diagram. We see that the relatively fixed reticulo-endothelial cells and the reticulum cells furnish the source for the more mobile pulp cells and histiocytic connective-tissue elements. All these cells, how-

ever, can ultimately gain entrance into the circulation either by being liberated from their local point of attachment, as in the case of the reticulo-endothelial cells, or by direct migration, as in the case of the splenocytes and histiocytes.



That such intravascular invasion occurs, was conjectured or rendered probable by all the earlier authors from Ranvier on. Because of their close relationship to the blood stream and their kinship to the remaining blood cells, Mallory designates them as "endothelial leucocytes." He regarded the entire vascular and lymphatic endothelial system as well as the endothelium of the connective-tissue clefts as the source of his "endothelial leucocytes." These cells were said to emigrate like ordinary leucocytes under the influence of inflammatory irritation. The significance of the tissue histiocytes was subordinated. Nevertheless it is possible to identify the "endothelial leucocytes" of Mallory with the macrophages of Metchnikoff, and to speak of an endothelial leucocytic apparatus.

Kiyono was the first to bring definite proof of the entrance of these cells into the circulation. He could show that the venous channels of the omentum, spleen, liver (as well as of the bone marrow), are relatively rich in vitally stained cells, which, judging from their whole appearance, must have arisen from the reticulo-endothelial cells, histiocytes and splenocytes. They can be traced to the lungs, where the great majority are filtered out in the capillaries. A certain number are still present in the pulmonary veins, only to

undergo rapid disintegration in the left side of the heart. The peripheral arterial blood, it is to be noted, contains but few such elements. In this manner the reticulo-endothelial system attains the closest relationship to the blood.

But a certain number of the reticulo-endothelial cells or blood histiocytes do pass the filter of the lungs and heart and enter the general circulation. However small their contribution to the morphological elements of blood, these cells are present and cannot be disregarded.

What significance has the entrance of the histiocytes into the blood? First of all, it shows that the reticulo-endothelial system is not a rigid system, but one which undergoes continual wear and tear and regeneration. This must always be kept in mind in experiments designated to eliminate these cells by blocking their activity. Such a blockage is conceivable only for a very short period. We shall return to this subject later. Inasmuch as these cells gain access to the blood principally in the abdominal organs and are filtered out for the most part by the lungs, it is evident that there exists, even physiologically, a remarkable relationship between the abdominal and the thoracic organs, more especially between liver and lungs. Goldmann indicated such a relationship, though in an altogether different sense. He found deeply stained lungs in intravitally stained animals whose liver was lightly stained, and lightly stained lungs in animals whose liver was deeply stained. Moreover a strikingly large number of "pyrrhol cells" were found in the peribronchial tissue. Goldmann makes no mention of the intravascular events. Furthermore, he was unable to furnish any explanation for the relationship observed between the liver and lungs. This cell transportation between the liver and lungs can be explained on the assumption that substances which are stored up in the reticulo-endothelial system in the liver can thus be liberated in the lungs. Whether the lung, in addition, plays a rôle as digestive organ for these liberated materials, and whether it is possible for the lung capillaries to be overtaxed or injured by disease of the liver, are questions which for the time being must remain unanswered.

The statement that histiocytes are normally present in the blood has been contested on the grounds that they are not

found in the peripheral circulation. Even if this were true, their regular occurrence in the blood of the heart and lungs would have to be recognized. But, as a matter of fact, they do appear in the peripheral blood, even under physiological conditions, as various observations have demonstrated. Mori and Sakai experimentally produced thrombi in peripheral vessels, and shortly thereafter injected China ink, which settled on the thrombus; somewhat later they injected lithium carmine, which penetrated the interior of the thrombus. Vitally stained histiocytes were found, although no histiocytes from without could have made their way into the thrombus; first, because of the short space of time, but most important of all, because of impenetrability for these cells of the layer of ink.

A further question to be considered is whether all the blood monocytes are histiocytic in character. Kiyono sought to solve this problem with the aid of supra-vital staining with toluidine-blue. He was able to show that there were at least three types of mononuclear cells in the blood:

1. The blood histiocytes—intra-vitally stained (histiogenic monocytes).

2. The transitional cells of Ehrlich which apparently belong to the myeloid series, with clear vesicular oval or kidney-shaped nucleus—supra-vitally stained. Monocytes of Naegeli (monocytes showing myeloid kinship).

3. Mononuclear cells with rounded or indented nucleus which are also found in lymph vessels, apparently of lymphoid origin. Neither intra-vitally nor supra-vitally stained (lymphogenic mononuclear cells).

Kiyono gives a critical review of the various theories concerning the origin of the monocytes. It is superfluous to go into the question here, dealing as we are with the participation of the reticulo-endothelial system in monocytic blood pictures. Kiyono specifically states that there are other types of monocytes besides those of histiocytic origin. He also states that the endothelial origin of the monocytes had already been advocated by Patella. The latter, however, believed that these monocytes were nothing but degenerated endothelial cells; and moreover, that all endothelium is implicated in their production.

The problem of histiocytic blood cells is closely bound up with that of blood production in general. It is impossible to discuss this subject in detail in a brief survey. It is well known that these reticulo-endothelial cells are regarded by many authors—in Germany by Schridde, and in Italy by Ferrata—as the source of all myeloid and lymphoid elements, depending upon their distribution in the blood and lymph vascular system. To show you how the blood cells develop from mesenchymal cells in accordance with the careful studies of Kiyono, Nakanoin and Katsunuma, permit me to draw your attention to their diagram of blood formation.

The irritative phenomena in the reticulo-endothelial apparatus resulting from vital staining led us to consider the actual *pathological processes*. We may first discuss the pathological occurrence of histiogenic monocytes in the blood, the co-called *histiocytosis*. These cells have been observed in a great variety of infectious diseases, e.g., subacute bacterial endocarditis (literature: Schilling, Simpson, Seyderhelm). The monocytosis (or better, histiocytosis) in typhoid fever is the oldest of these observations. A review of the subject is found in the paper by C. Holler. The critical judgment of histiocytosis is rendered difficult because we do not definitely know whether all the monocytes resembling either are really of the same origin. One should demand certain criteria for the diagnosis: specific granulation such as Naegeli assumes for the majority of the monocytes, or the staining of the segregation apparatus, as Simpson demands. I cannot agree with Holler's conclusion based on the paucity of vitally-stained monocytes in the peripheral blood, that the unstained monocytes which are found there have a like origin, but present themselves in a resting stage. Further investigations must be awaited. Histiocythemia or histiocytic leucemia is to be distinguished from histiocytosis. Whether such a form of leucemia exists is still disputed. If it is true, as Ferrata assumes, that the mother cells of the granulocytes develop from the histiocytes after passing through the stage of the so-called hemohistioblasts, then the possibility of a greater participation on the part of these elements in leucemic states must be admitted. One would speak of a monocytic or hemohistioblastic leucemia (Naegeli, Ferrata, and Reitano).

It is true that this picture could not be regarded as a true histiocytic leucemia.

To what extent the reticulo-endothelial system participates in ordinary leucemia processes is difficult to ascertain, in view of what I previously said concerning the normal processes of blood formation. In order to avoid unnecessary repetition I must refer to the original articles and reviews in the leading hematological journals.

The reticulo-endothelial system is as *significant for blood destruction* as it is for blood production. As a matter of fact, the function of blood destruction under physiological conditions occupies a much more prominent position. Since the studies of Ecker, Kölliker and Neumann, the destruction of blood corpuscles by certain elements of the bone marrow, spleen, liver and lymph nodes has been repeatedly confirmed. Although the phagocytosis of blood cells by the reticulo-endothelial system is universally recognized, the degree to which their events are physiological and pathological is still the subject of great controversy. Although the phagocytic disintegration of red blood corpuscles has been difficult to demonstrate in human beings, its physiological occurrence in certain animals, especially dogs, is incontestable. Irisawa was able to show this very well in young dogs. By the use of a variety of blood poisons, the destruction of erythrocytes by reticulo-endothelial cells can readily be observed. We are indebted to Mallory for a very thorough study of the participation of the endothelial leucocytes in the phagocytosis of red blood cells in typhoid fever. The number of diseases in which such an outspoken erythrophagocytosis has been observed has since greatly multiplied. It is equally well known that the red blood cells are not always engulfed as such, but may undergo preliminary erythrorrhexis with subsequent phagocytosis of the resulting fragments. These changes are beautifully illustrated in Weil's disease (Lepehne). The phagocytic activity of the reticulo-endothelial system is still more pronounced under the direct influence of blood poisons. Again, I cannot enter into detail, but shall confine myself by way of illustration to the arseniureted hydrogen poisoning of birds and the phenylhydrazine poisoning of dogs. The enormous phagocytosis of erythrocytes is well shown in

birds which have been poisoned by arseniureted hydrogen. Here, too, one can follow the intracellular disintegration of the ingested blood elements into the iron-containing and iron-free fractions of the liberated hemoglobin. It is well known that this storage of iron by the reticulo-endothelial cells of the spleen and particularly the liver of birds can be observed even under normal conditions. Thus in arseniureted hydrogen poisoning we have only an exaggeration of the physiological events. The accuracy with which we can follow the gradual accumulation of the iron-containing fraction of the hemoglobin in the reticulo-endothelial cells stands in contrast to the difficulty of determining the fate of the iron-free residue. A great question now attracting wide attention concerns the site of bile pigment after splitting off the iron: Is the liver cell only the excretory organ for this pigment? Or does the liver cell synthetize the bile pigment from a preliminary compound arising either in the reticulo-endothelial cells or in the blood itself? Is there an anhepatocellular icterus, or is all icterus hepatocellular? We are all familiar with the celebrated experiments of Minkowski and Naunyn in which, following liver extirpation in geese, no jaundice was observed, even in the presence of arseniureted hydrogen poisoning. These authors concluded from their experiments that the liver is solely responsible for bile-pigment production and the development of jaundice. These studies laid the foundation for the prevailing teaching of hepatic jaundice. In repeating these experiments, McNee established the fact that no toxic jaundice could arise without the intervention of the liver. He furthermore showed that in the presence of the poisoning such a vigorous reaction on the part of the reticulo-endothelial system set in, and such a copious desquamation of these cells into the blood stream resulted, that he justly inquired whether the reticulo-endothelial system was not after all the actual seat of bile-pigment formation. Inasmuch as the reticulo-endothelial cells are removed along with the parenchymatous cells, when the liver is excised, the question which of these two types of cells were responsible for bile-pigment production and jaundice, still remains unanswered. The new question thus reads: Is all bile-pigment formation and jaundice

hepatocellular, or is there also anhepatocellular bile-pigment production and the corresponding type of jaundice? Inasmuch as the spleen and bone-marrow in birds plays such an insignificant rôle in comparison with the reticulo-endothelial cells of the liver, the hepatectomy experiments could not solve the problem, for by removing the liver, the major part of the reticulo-endothelial system is coincidentally removed.

On this account Lepehne attempted to eliminate the activity of the reticulo-endothelial system by collargol injection. He came to the conclusion in his pigeon experiments that a marked diminution of bile-pigment production ensues in arseniureted hydrogen poisoning. Eppinger had similar results in experiments on dogs poisoned by toluylenediamine. By blocking the reticulo-endothelial system with intravenous injections of sugar of iron and subsequently poisoning the animals he was able to demonstrate either diminution or absence of jaundice. A paper by Elek, of Wenckeback's clinic, recently appeared, the author of which observed a substantial reduction of bile-pigment formation in bile fistula in dogs after blocking the reticulo-endothelial system by injections of colloidal iron. These positive results are opposed by a number of negative ones. Thus Bieling and Isaac, Rosenthal and Melchior observed lessening of bile-pigment formation in normal and poisoned animals, in spite of prolonged blocking (*Speicherung*) of the reticulo-endothelial system. Were these results to be confirmed, the participation of the reticulo-endothelial system in bile-pigment production would become very dubious. I have already indicated in another place that all these experiments, both positive and negative, are much too gross to permit the establishment of binding conclusions. If the determination of the paralytic and stimulating dose of the well-known pharmacodynamic substance for each type of animals is not always easy to establish, it is clear that the estimation of the dosage required for the paralysis and stimulation of the reticulo-endothelial system by the crude method of storage (*Speicherung*) offers still more serious difficulties. Even if we successfully determine the paralytic dose, we must realize that the reticulo-endothelial system undergoes a very rapid

cleaning and regeneration by continually shedding its cells into the circulation. It is therefore conceivable as an actual paralysis that is possible only for the briefest space of time. I shall return to this subject again.

Added to the difficulty of accurately estimating the dosage, is the circumstance that bile-pigment production proceeds very differently in the various types of animals. We emphasized in our earliest communications that in mammals, especially in certain herbivora, e.g., rabbits, in contrast to the birds, a direct participation of the reticulo-endothelial system in the digestion of the damaged red blood corpuscles cannot be demonstrated. In certain animals the lysis of the erythrocytes takes place in the blood itself, and the reticulo-endothelial system metabolizes only the liberated hemoglobin. In other cases, these cells seem to be only indirectly implicated, the further transformation of the liberated hemoglobin occurring in the blood and not intracellularly. In such cases it is conceivable that the bilirubin-forming ferments are produced by the reticulo-endothelial cells, although it must be admitted that no definite evidence has been furnished to support such a hypothesis. If we realize in what diversified manner hemoglobin is transformed into bilirubin outside of the liver cells, the dissimilar results obtained by storage (*Speicherung*) experiments in different types of animals will not surprise us.

For the time being, the decision must rest on the histological findings. These, too, have been questioned, the objection being raised that the transformation of red blood corpuscles within the reticulo-endothelial cells into iron and bile pigments as described by Minkowski, Naunyn and later by McNee and Kyes was incorrectly interpreted. It was contended that the changes noted were nothing but phagocytosis of the dissolved iron and bile pigment masses which circulated in the blood in all cases of icterus, including those due to mechanical causes. There is no doubt that the reticulo-endothelial cells, in the presence of severe stasis icterus, ingest not only bile casts that have been expressed from the columns of liver cells, but also bile pigments in solution. But bile-pigment absorption in stasis icterus presents quite a different picture from bile-pigment production in the reticulo-endothe-

lial cells in hemolytic jaundice. This can easily be demonstrated in pigeons by ligation of the common bile duct on the one hand, and by arseniureted hydrogen poisoning on the other. It is possible to follow step by step the gradual transformation of the red blood corpuscles into an iron-free pigment and an iron-free residue, which is never observed in stasis icterus. Moreover, it can readily be demonstrated that the liver in toxic hemolytic jaundice remains unaltered in the initial stages, whereas the reticulo-endothelial cells promptly manifest the most vigorous activity. The finding of numerous iron granules in the liver cells, which Minkowski and Naunyn regarded as evidence of the participation of the liver cells in bile-pigment production, is true in itself, but was falsely interpreted by these authors. The deposition of iron in the liver cells appears only in experiments of long duration in which the iron, because of its excessive production in the reticulo-endothelial system, is released into the circulation, the excretion proceeding by way of the liver cells.

All these facts point to the great significance of the reticulo-endothelial system for bile-pigment production, at least in birds. For mammals, too, anhepatocellular bilirubin formation has been proved by recent investigations. The experiments of Whipple and Hooper in 1913 have shown that the bile pigments are formed in spite of the exclusion of the liver and abdominal organs. At my suggestion, Dr. Makino repeated the liver extirpation experiment, employing the excellent method of Mann and Magath. He was able to demonstrate, in his hepatectomized dogs, definite bile pigment formation in the blood stream with or without the intravenous administration of hemoglobin. The pigment was formed in such quantities, within the four or five hours between the operation and the death of the animal, that the entire daily quotient of bile pigment could thus be accounted for. These experiments, in harmony with those of Whipple and Hooper, clearly demonstrate the possibility of extrahepatic bile-pigment production in the dog. It will be recalled, on the contrary, that bile-pigment formation outside of the liver, in birds, occurs either in traces or not at all. The dog possesses extensive areas of reticulo-endothelial tissue beyond the liver; but this is not the case in birds. It appears

therefore that bile pigment is produced in these domains when the liver has been removed. If, however, these extrahepatic reticulo-endothelial provinces are removed, as Rich has done, bile pigment is produced in the dog, either in minimal quantities or not at all.

The relationship of the reticulo-endothelial system to blood destruction points strongly to its *participation in the general metabolic functions.* I cannot enter here into the purely chemical and physiological aspects of the subject, and shall touch upon only a few of the morphological problems. It is well known, particularly since the investigations of Asher and his coworkers, that the spleen, which, in omnivora at least, must be regarded as the principal organ of the reticulo-endothelial system, plays a dominant rôle in the metabolism of iron. It has been frequently demonstrated that a marked disturbance of iron metabolism follows in the wake of splenectomy. Whereas iron is normally excreted chiefly by the large intestine, and only to a minor degree by the kidneys, a marked increase in renal excretion occurs following removal of the spleen. This is true at least for the rat, in which outspoken hemosiderosis of the kidneys develops. In rabbits it is possible to increase the renal excretion of iron by injecting collargol to block the activity of the reticulo-endothelial system. This augmented elimination of iron cannot be wholly accounted for by increased blood destruction. It is more probable that iron compounds, which are normally retained in the reticulo-endothelial cells of the spleen, are excreted in increased quantity after extirpation or paralysis of the latter. The observations of Kisch in human beings support this view. This investigator observed marked renal excretion of iron following the extirpation of enlarged spleens, particularly if iron was subsequently administered. Of special interest are the observations of M. B. Schmidt, Lepehne, Nishikawa and Takagi, Pearce, Austin and Musser, Karsner and Bock, concerning the proliferation and increased iron infiltration of the reticulo-endothelial cells of the liver following splenectomy. This activity on the part of the hepatic province of the reticulo-endothelial system doubtless compensates for the elimination of the splenic area. It has been definitely established that in

states of increased blood destruction not only does the hepatic reticulo-endothelium participate in the digestion of iron compounds, but the liver cells also excrete the iron in increased amounts. It is true that the experiments of Duggan and Pearce do not support the hypothesis of the biliary excretion of iron, but it is to be noted that their negative findings are opposed by the positive ones of Brugsch and Irger. I, too, have been able to demonstrate morphologically the increased iron excretion by the liver cells. Equally well known is the increased activity of the mesenteric lymph nodes following splenectomy. I refer to the studies of Chevalier, Pearce and Pepper, Pearce, Austin and Musser, as well as the comprehensive reports of Helly and Eppinger.

The increased participation of the reticulo-endothelial cells of the liver, bone marrow and lymph nodes in the *storage and metabolism of iron* is observed not only after splenectomy, but also in certain disease states. Pernicious anemia, as well as the sideroses in states of hunger and in the inanition of infants is of special interest in this connection. That these hemosideroses of the reticulo-endothelial system develop in consequence of a prolonged intravascular hemolytic process is evident from the well-known experiments of McMaster, Rous, Larimore and Olivier, who showed that the intravenous injection of hemoglobin was constantly accompanied by a progressive hemosiderosis, beginning in the spleen, lymph nodes and bone marrow, and spreading later to the liver, kidneys and salivary glands, and finally involving even the heart muscle. It is a remarkable fact that the spleen in pernicious anemia contains relatively small quantities of iron. It always gives the impression that the splenic domain of the reticulo-endothelial system has refused to function, in consequence of which the remaining provinces have been stimulated to greater activity. It is evident that the factors in the hemosiderosis of pernicious anemia are not the same as those in toxic hemolytic jaundice, in which the iron deposit in the spleen is very pronounced. The complexity of the various factors at play is well illustrated by the findings in familial hemolytic jaundice, in which neither the spleen nor the remainder of the reticulo-endothelial system exhibit a significant increase in iron deposition. At any

rate the rôle of the reticulo-endothelial system in iron metabolism merits renewed and thorough investigation. Morphology alone, unaccompanied by chemical studies, will not advance our knowledge; for the purely microchemical demonstration of iron does not furnish a satisfactory criterion of the total amount present. That the reticulo-endothelial system plays an active part in iron metabolism, however, is clear, from what I have just said.

A brief word concerning the *metabolism of fat:* It is well known that the most varied lipoids can normally be stored up in the spleen, especially in the reticulum cells. I have as yet been unable to demonstrate constant relationships between the lipoids and certain diseases. It has been established, however, that in diabetes a very characteristic cholesterol-ester infiltration of the Kupffer cells makes its appearance. Moreover, we know from the investigations of Chalatow and Anitschkow that an infiltration of the reticulo-endothelial system, especially of the spleen with cholesterol esters, can be artificially produced by feeding experiments. Such cholesterol-ester infiltration (*Speicherung*) appears spontaneously in states of hunger. It appears to be dependent upon an increased cholesterol content of the blood. In states of hypercholesterolemia, e.g., in diabetes, and in certain cases of icterus and contracted kidney, cholesterol-ester infiltrations are frequently observed, not only in the Kupffer stellate cells of the liver, but also in the histiocytic elements of the spleen and the skin. The cutaneous infiltration by lipoid-laden histiocytes can become sufficiently pronounced to result in tumor-like proliferations, which we generally term xanthelasmas.

That the reticulo-endothelial system also plays a great part in the *metabolism of proteins*, or at least of phosphorus-containing substances which do not belong to the category of true lipoids, has been amply demonstrated by the interesting observations made in Gaucher's disease, especially by Mandlebaum and Downey. Of the ultimate cause of the metabolic disturbance nothing is known. But we do know that this disorder is a system disease of the reticulo-endothelial elements or the histiocytic cell apparatus. The Gaucher cells are altered reticulo-endothelial cells.

Closely bound to the problem of the metabolic relationship of the reticulo-endothelial system is that of *ferment production*. Metchnikoff had already brought his macrophage system into relationship with the formation of his substance sensibilisatrice or Ehrlich's amboceptors. The old experiments of Sawtschenkow and Levaditi concerning the participation of the spleen in the digestion of hemolysin-laden erythrocytes, as well as the production of hemolytic antibodies, have been made the subject of renewed inquiry. Whereas the normal occurrence of hemolysis in the spleen is still disputed, the participation of the spleen and reticulo-endothelial system in general in the elaboration of experimentally produced hemolytic antibodies, has been established without question. I refer especially to the studies of Isaac and Bieling as well as to those of Murata, who observed a significant reduction in antibody formation in animals whose reticulo-endothelial system has been blocked. That bacterial toxins, e.g., tetanus and diphtheria toxin, are fixed and absorbed in the spleen and apparently in the reticulo-endothelial system, has been repeatedly demonstrated. Hahn, von Skramlik and Huenermann showed that in perfusion experiments of surviving organs of sensitized animals, the corresponding antigens are very actively absorbed by the reticulo-endothelial system, e.g., by the Kupffer cells of the liver. It appears that the reticulo-endothelial cells have some relation to the production of bacterial immune bodies.

Here we come to the question of how far the reticulo-endothelial system participates naturally in the *defence reactions* against bacterial infections. Wyssokowitsch showed that the great majority of intravenously injected bacteria are taken up with extraordinary rapidity by the endothelial cells of the spleen, liver and bone marrow. This observation has been repeatedly confirmed. It has developed that cells of the reticulo-endothelial system are responsible for the engulfing of parasites. This holds true, not only for the ordinary bacterial infections, but also for the protozoal infections, e.g., kala azar, rickettsia in typhus fever, etc. On the other hand, when the contention is made that the ordinary endothelial cells, e.g., of the lungs, also participate in the phagocytosis of parasites, I must question the validity

of such an assumption. I must also warn against the carrying over to human beings the experimental results of the intravenous administration into animals of the usual infectious agents. In the case of humans, the exciting agent is slowly introduced into the circulation, and accordingly a more sluggish reaction on the part of the reticulo-endothelial system results. Oeller and Siegmund concluded from their observations that the reaction of the reticulo-endothelial system was more pronounced when the animal was sensitized by repeated blood infections. Conversely it is possible, by radiating the animals, to suppress completely the reticulo-endothelial reaction against experimentally produced hematogenous bacterial infections. I cannot discuss the question of how far the phagocytosis of microorganisms is always a defensive reaction, and not oftener a manifestation of symbiosis. At any rate, it is clear that in subacute or chronic infectious diseases, especially in the so-called specific infections, an outspoken reaction of the reticulo-endothelial system is observed. After the studies of Mallory had indicated that the characteristic swelling of the lymphatic tissue in typhoid fever is due to a proliferation and multiplication of the endothelial leucocytes, later investigations, especially by Goldmann, Evans, Kiyono and others, with the aid of the vital staining method, have demonstrated that the histiocytic elements play a very special rôle in the formation of the tubercle. In fact it could be shown, as Mallory had done, that specific reaction products in other specific diseases, the leproma in leprosy, rhinoscleroma, actinomycosis, sporotrichosis, etc., derive their origin chiefly from the proliferated cells of the histiocytic system. Herxheimer, Choma and Gayo, among others, employing vital staining methods, have definitely established the histiocytic character of the lepra cells. A similar origin is true of the remaining granulomata. The striking thing is that the type of cellular accumulation, and the special cell alterations are rather characteristic of each of these infectious diseases. The epithelioid cell tubercle is characterized by its fibrillar intercellular substance and the giant cells, the lepra node by the bacilli-laden cells, the typhoid nodule by the more rounded blood cell-containing Mallory cells, the sporotrichoma by

the peculiar lipoid cells, the so-called pseudo-xanthoma cells. In all of these reactive processes the phagocytosis of bacilli by the histiocytes, and frequently their annihilation within the cell bodies of the latter, can be observed with great distinctness. The sequence of events can be beautifully demonstrated in sporotrichoma, in which, as the studies of d'Agata and Lawless have shown, the phagocytosed fungi are gradually digested within the cell bodies and slowly converted into the characteristic lipoid substances.

It must be borne in mind that the typical reaction products of the tubercle, gumma, leproma and sporotrichoma develop only when a certain state of immunity has been attained. This state of immunity, with its accompanying chronic productive reaction, is frequently preceded by a period of increased sensitization attended by phenomena of an exudative character. This is particularly characteristic of phthisis. In the sensitization period we find that the invasion of the lung by the Koch bacillus presents a picture more like caseous pneumonia than tubercle formation. What does the exudate of caseous pneumonia consist of? It is composed of fibrin, leucocytes in scant numbers, and above all, large cells, so that we speak of a large-cell exudate. What are these large cells? Most authors maintain that they are emigrated histiocytic elements. One would thus assume that depending on the reactive state of the organism, the histiocytes appear at one time as actively mobile exudative cells, and at another in the form of slowly evolving nodular growths. This is undoubtedly true in part. But whether all the large cells of the phthisical exudate are histiocytes, or whether some of them are not desquamated epithelial cells, is a problem difficult to solve.

We now touch upon a subject which concerns a very special function of the reticulo-endothelial system, namely, the clearing of the system of non-living foreign bodies, as, for instance, carbon. The so-called anthracotic processes in the lungs and lymph-nodes are accomplished mainly by the agency of the histiocytes. The removal and storage of these substances are taken care of by the histiocytes. All authors are agreed on this point. The question still undetermined, however, is the origin of the so-called "dust-cells," found

within the alveoli. According to the studies of Haythorn and Foot, these cells would have to be regarded as emigrated endothelial cells. On the other hand the studies of Westhues have been confirmed and extended by the recent investigations of Sacks, who clearly demonstrated that the cells in question are alveolar epithelial cells and not endothelial cells. If China ink is injected to identify the histiocytic apparatus, and a colored fluid or a lipoid suspension is introduced into the trachea, as Sacks has done, a marked lipoid infiltration of the alveolar epithelium is readily observed after very short intervals, whereas the ink-laden phagocytes of the blood and pulmonary tissue have manifested no evidence of migration into the alveolar spaces.

A final chapter which must be briefly considered is that of the *tumor-like overgrowths* of the reticulo-endothelial system. I can only mention a few of the salient facts without discussing them in detail. I have already spoken of the system diseases of the histiocytic apparatus in connection with Gaucher's disease. In the latter the reticulo-endothelial system appears to be secondarily involved, the primary cause of the metabolic disturbance being situated elsewhere. The same holds true for certain cases of hemochromatosis. Such secondary affections of the system contrast with the primary ones in which the pronounced splenic enlargement is the most prominent manifestation. It has been suggested that such cases might represent instances of primary hyperactivity of the reticulo-endothelial system, hypersplenism. Thus the splenomegaly of Banti's disease, or of the so-called anemia splenica infantum, have been regarded in the light of excessive functioning of the reticulo-endothelial cells of the spleen. The good results which attend splenectomy in cases of Banti's disease favor the view that the spleen is the primary seat of the disease. That a hypersplenism has thus been demonstrated, however, is questionable. A chronic infection having its principal localization in the spleen might be responsible for the entire disease. At any rate, the histological findings speak less for a toxic-infectious irritative process resulting not only in the proliferation of the histiocytic elements but also in the typical transformation of the entire splenic structure. The conditions in splenomegalic

cirrhosis of the liver are very similar, according to my own experience and the investigations of my pupil Duerr. I know of no certain instance of a purely idiopathic hyperfunction of the reticulo-endothelial system.

It must be admitted, however, that system-like diseases occur which belong to the group of leucemic proliferations. These are the peculiar cases of so-called monocytic or "stammzell" leucemia which have been reported by various authors. The genetic relationship between these monocytes and the reticulo-endothelial system is still undetermined. Finally circumscribed leucemic-like proliferations in isolated provinces of the reticulo-endothelial system have been described.

It is well known that the histiocytic apparatus and the apparently closely related hematopoietic system can be so greatly stimulated, particularly by metals in colloidal solution, that leucemic-like proliferations can be experimentally produced in this manner. Pentimalli has proved this for bismuth, whereas the older and more recent studies of Heinz, Nissen and others have demonstrated the ability of colloidal silver, etc., to produce such proliferative changes of the granulo-poietic system. Pentimalli was the first to show that in the use of colloidal metals, not only does the metal itself play a rôle, but the protein employed to prepare the colloidal solution also has to be taken into account. This observation offers a hint concerning the action of the widely-used non-specific therapy. These substances too, as the histological findings indicate, also act, at least in part, on the reticulo-endothelial system.

In conclusion, I must mention that true neoplasms of the reticulo-endothelial system, in all probability, also occur. Their differentiation from the tumors of the ordinary lymphatic and vascular endothelium is impossible, however, in the present state of our knowledge. The existence of primary endotheliomas of the spleen, bone marrow, lymph nodes, etc., and their variable and unique structure, has been clearly shown by the very careful studies of Ewing. I must content myself here with referring to his works.

In closing, I desire to express my profound regard and esteem for my colleagues in this country. We German pathol-

ogists realize what we owe to the pathological-anatomical investigations in the United States, particularly in the last decades. In Germany we are now compelled to carry on our scientific studies under very unfavorable conditions. But we do not despair, for results can also be obtained with simple methods, if the guiding thought is there. I hope that my remarks, designed less to exhaust the subject than to provide a general survey, have shown you that in the reticulo-endothelial system a guiding thought is offered, the critical application of which will bring fruitful results in the various fields of medicine.

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II

THE PATHOGENESIS OF HUMAN PULMONARY CONSUMPTION[1]

The conception of allergy, which was at first essentially clinical and under the influence of studies in anaphylaxis developed along humoral-serological lines, tends now to become more and more morphological. Better said, cellular pathology is coming into its own in so far as one attempts more and more to correlate the particular periods of diminished and increased resistance such as one sees in nearly all infectious diseases, with the altered powers of reaction of the tissues and their associated cells. This phase has been sufficiently covered in the chapter on the reticulo-endothelial system in relation to its behavior in inflammatory reactions.

That the secretions of the cells also participate in the changed reactivity is self-understood. Future investigations will have to determine what rôle is played in the individual case by the altered resistance of the tissues themselves and by their secretions. At any rate, the tissues should not be neglected in favor of the secretions. We must agree with Hajek that the immunity studies in the domain of pulmonary consumption, which have been predominantly along clinical and humoral-serological lines, furnished the keystones for modern investigations. No less a person than Koch himself discovered the increased resistance of animals injected with the bacillus of phthisis, against reinfection. Many researches have been made with the idea of producing a state of immunity in animals, and also in human beings, through the injection of quantitatively or qualitatively weakened phthisical infectious material. The basic experiments of von Behring and Römer as well as Baumgarten have shown that such an immunity, in the sheep for example, can be achieved, but only up to a certain point. At any rate,

[1] Edward G. Janeway Lecture.

the reaction in animals infected while young is different from that observed after reinoculation in later life. The experiences gained in animal experimentation naturally spurred the investigator to carry over such work to the human being. Behring made the first step in this direction in 1904, and declared that pulmonary consumption in man was the end state of an infection experienced in childhood. That as a result the incorrect conception arose, that infection with the bovine tubercle bacillus by way of milk played the most important rôle, and that the source of all later manifestations of consumption was to be traced to the infection of childhood, does not enter into our discussion. It is more important for us to correlate the later forms of adults' phthisis, particularly of the lungs, with the renewed infection of a respective organ, for example the lungs, in an organism already infected in youth. The erroneous view that the endogenous mass infection arising from a focus acquired in youth was looked upon as the sole or the principal source need be only briefly noted.

At any rate, it was from this work that all subsequent research in immunity in the field of chronic consumption took its inspiration. One had to get away from the idea that consumption of the lungs which arises suddenly in the adult was an autogenous disease. It was likewise impossible to explain the differences between the phthisis in adults and that in children, from the anatomical changes seen in the lungs of adults alone, as I myself had at first tried. One was gradually forced to connect the phthisis of the adult with perhaps earlier infection. The clinical method of systematically testing with tuberculin paved the way for this. These investigations showed for a fact that the infection of infancy and childhood played a very important rôle. One arrived more and more at the conviction that analogously to syphilis it was possible to subdivide the course of consumption in man into various periods, and that consumption of the lungs was nothing else than an endogenous or exogenous recidive of tuberculosis. (Hamburger 1908.) Whether this conception was correct or not, it was possible to establish only through morphologic-histologic studies of individual cases. It was therefore necessary, just as in syphilis, to fix certain definite

pictures as corresponding to the reactions manifested at various periods in phthisis.

Thus it appears that this infectious disease occurs as a preeminently chronic affliction, which commences in childhood and may be prolonged in its various phases throughout an entire life. The more we realize that every period of this disease has its own peculiar clinical and anatomical characteristics, the less is it permissible to name it tuberculosis from the symptoms of only one period, namely the tubercle formation, for example, as an indication of the progressive immunization. One might as well call syphilis gumma disease; we know however that the characteristic gumma develops in the tertiary period of syphilis. The term "phthisis" is over two thousand years old and has been employed by the Greeks, in contradistinction to the atrophy seen in malnutrition and cachexia of cancerous disease, as an indication of a disease accompanied by general loss of body weight, which they described as follows:[1] "The third and by far the most terrible form of emaciation (*tabes*) is that which the Greeks call phthisis. It usually arises in the head and thence spreads to the lungs. On top of this, ulceration occurs (*exulceratio*) and a slowly creeping fever, which at times disappears and at other times reappears." Here Celsus speaks of an *exulceratio* of the lungs, but nowhere does he call this process in the lungs phthisis. I have found the expression nowhere in the study of available Greek and Roman literature (Hippocrates, Celsus, Galenus, Aretäus, Alexander von Tralles, Caelius Aurelianus).

In this chapter I speak of the variously described but etiologically identical disease picture, phthisis, in the same sense as our clinicians were accustomed to until the middle of the last century. The discovery of the tubercle was the occasion for differentiation of the tuberculous from the non-tuberculous forms, the so-called scrofulous. It did not, however, lead to the identification of these tuberculous forms with phthisis directly. In England, on the other hand, we see that the prominent clinicians—I mention Addison for example—retained the conception of pneumonic phthisis, tuberculopneumonic phthisis and tubercular phthisis. It was

[1] Celsus. De re Medica. Lib. III, Chap. xxii.

only gradually, especially since the discovery of the exciting agent by Koch, who named his organism the tubercle bacillus, that the fashion of employing the word tuberculosis, instead of phthisis, came into general use. It is about time that we should again employ the name phthisis for this disease entity. Then we shall see that tuberculosis is only a special reaction form in the course of phthisis.

How does the course of phthisis manifest itself? To understand this we must examine the newer pathological anatomical investigations which form the groundwork of the entire concept. The first beginnings lie very far back. The French clinician, Parrot, had already stressed the remarkable picture of the primary infection of childhood. We owe a great deal to his pupil, Kuss, an Alsatian, for an excellent description of the so-called primary affect. Unfortunately this work, at any rate its morphological side, was entirely forgotten. One can therefore speak of a really new discovery of the primary "affect" of phthisis by the German-Austrian investigators, H. Albrecht and Ghon. The latter, particularly, has described the anatomical picture in such a classical manner, and confirmed it again and again on such exceptionally rich material, that now this concept has become fully accepted by the scientific world. His studies round out in a valuable and indispensable manner the clinical conclusions arrived at by Hamburger, which we have noted before and for which we find in Ghon's work a firm support. It is also on the basis of the investigations of Ghon that Ranke brings the clinician and pathologist together. Following out the studies already made by him in 1910, he attempts to correlate on the basis of combined clinical and pathologic-histologic observations, the further development of consumption. Starting with the primary infection, through the period of generalization to the tertiary period, and in agreement with the criteria established through immunological studies he endeavors to give a unified picture to the entire problem of phthisis. According to him chronic phthisis, especially pulmonary, represents no other than the tertiary stage of the infection, in which the further extension of the phthisical process becomes restrained on account of the previously intervening increased resistance of the individual,

and only slowly affects the involved organ through tubular invasion. Thus there appeared to be available a rather far-reaching comparison with syphilis, which, characterized by the varying histologic pictures, namely that of the primary lesion, secondary (anaphylactic) period of metastasis and finally that of increased resistance, found its analogue in organic phthisis. Out of these arose a general law that in contrast to the anaphylactic period, where the exudative processes predominate, following the increasing resistance during the third period, the productive forms, that is to say the tuberculous processes in the strictly histologic sense, appeared in the foreground. In this so-called tertiary period the lungs occupy a preeminent place. According to Ranke, their involvement should also arise as a form of metastasis from the primary infection, just like the metastatizing phthisis of other organs (bone, brain, kidney, genital organs, etc.). It would then be a question of an infection of endogenous origin which had for a second time attacked the lung, in other words an endogenous reinfection. It is impossible, however, as far as this particular organ is concerned, to exclude absolutely the possibility of a new infection from the outside. It would then be a question of exogenous infection.

That for the origin of chronic pulmonary phthisis a new infection, a sort of reinfection in an already immunized body, plays a rôle, was established by Orth from a pathological-anatomical standpoint in 1907 and vigorously defended by Kretz in repeated communications. Orth could readily demonstrate by the presence of two types of tubercle bacilli, the human and the bovine, that this reinfection in certain cases could not be of endogenous, but was of exogenous origin. In recent times Beitzke, in particular, was the strong exponent of the exogenous nature of the reinfection.

You will understand that it is of the greatest importance in the entire conception of phthisis, whether it depends upon an erstwhile infection which is effective throughout life, as is the rule in syphilis, or whether in phthisis more than one infection from the outside is possible, or indeed, the rule. Then phthisis in man would be in many instances a disease which is composed of independent periods, one of an exogenous primary infection and one of an exogenous

reinfection. Should one wish to solve this problem anatomically, one must first learn to differentiate between the various infections, namely the primary and the reinfection, as well as their method of healing, the stage of scar formation. For these come before us most frequently not in

FIG. 1. Primary infection in a child. Caseous bronchopneumonic focus in the lower lobe. Caseous focus in the related bronchial lymph node.

their fresh state, but in an advanced stage of healing and cicatrization. The existing differences were made particularly clear in 1922, by Puhl, who was able to show that the primary infections of childhood have not only the distinctive picture described by Ghon, but that they are capable of producing a typical form of scarring. Not only do they calcify but they have a marked tendency to ossification. If this

ossification should also occur in a reinfection, it remains such a rarity that in spite of it the presence of bony foci in the lung and lymph-nodes is to be regarded as representing the healed primary infection. These teachings of Puhl have recently been confirmed through the observations of Schmorl.

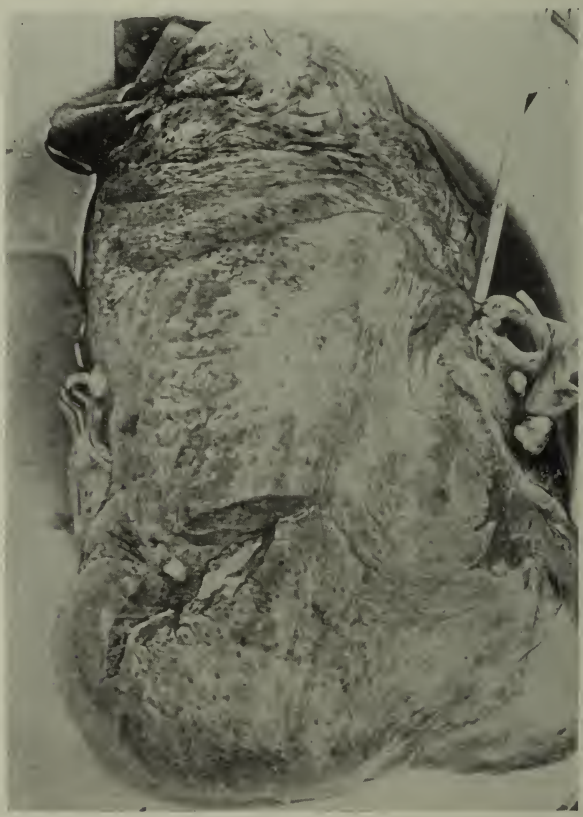

Fig. 2. Scar of primary infection. Bone-containing scar in the lower lobe and in the related lymph nodes.

It is easy from a large mass of material to establish the difference between the primary infection and the reinfection. The primary infection, as Kuss and recently Ghon have shown, may occur in various parts of the lung, but the upper lobes, and especially the right, are sites of predilection. Still the middle and lower lobes are also often affected. The primary

infection almost invariably lies immediately under the pleura. As a rule there is only one primary affect to be found. It consists of an exudative, rapidly caseating bronchopneumonic focus, which is sharply delimited from the rest of the lung. It is always accompanied by a somewhat larger caseous focus in the related lymph node. About both foci there develops a specific granulation tissue which gradually becomes

Fig. 3. Reinfection—fresh. Acinous nodose phthisis of the apex.

transformed into a hyalinized fibrous-tissue scar and builds a so-called specific cicatricial tissue capsule whose outside circumference is surrounded by the usual fibrous scar tissue of unspecific nature. The encapsuled, caseous, chalk-like masses become gradually absorbed by invading connective tissue which builds typical bone. This likewise has fat-containing marrow, which is practically free of myeloid elements, but rich in so-called anthracophores, that is to say,

carbon-laden wandering cells. These arise in the vicinity of the focus.

The reinfection, in contrast to the primary infection, may be multiple. It occurs essentially at the apex of the lung, less frequently in other locations. It is situated more often within the substance of the lung than subpleurally, so that when it heals it causes contraction of the surface of the lung

Fig. 4. Reinfection—scarred. Calcified form. No bone formation focus.

in the process of cicatrization. These contractions comprise the apical changes described earlier as primary infections which have been discussed especially by Birch-Hirschfeld, Schmorl and Abrikossoff. The reinfection induces a productive phthisical focus in the vicinity of a small dividing lobular bronchus, which is made up of a number of adjacent acini (acinous-productive or acinous-nodose phthisical focus). The acinus of the lung of the older authors embraces, as the newer work of Nicol, Loeschke and Husten has shown, a definite specially constructed area of respiratory tissue, which is

supplied by a bronchiolus respiratorius of the first order. In this last unit of pulmonary tissue, the phthisical granulation tissue, composed of epithelioid cells, giant cells and round cells, which is consequent upon the reinfection of the bronchus by the tubercle bacillus, localizes itself. These acinous-nodose foci also finally caseate and calcify, but only rarely do they build bone. The reinfection becomes encapsuled by a very much more extensive scar, which stretches out into the surrounding area: thence the radiations and inequalities in the borders. Especially characteristic is the freedom from involvement of the related lymph node.

On the basis of this knowledge there develops the following morphological picture in the pathogenesis of consumption of the lungs. In youth, very often even in infancy or in prepuberty, the individual acquires his phthisical primary affect. This is as a rule to be found in the lungs (aspiration), occasionally in the intestine, the middle ear or the skin, very seldom in the ocular conjunctiva. The primary infection heals completely in the large majority of people. One can establish its scar in over 90 per cent of adults. Only in a certain number, not as yet definitely known, of children and youths, does the primary affect go over to the stage of generalization or metastasizing phthisis. In such cases the process manifests itself not so much in the lungs as in the lymph nodes.

Here we enter upon the so-called anaphylactic period of phthisis. This is histologically characterized by the very active exudative and emigrative reaction, marked lymphocytic proliferation and rapid caseation. There arises the well-known diffuse swelling and caseation of the tracheobronchial lymph nodes which is no longer limited to the nodes corresponding to the primary focus of the lung, but embraces the entire so-called hilus nodes, which call forth the familiar shadow seen in the roentgen-ray picture. Later, however, when we find new foci occurring in the lung, especially in the upper lobe, we get the impression that the phthisis arising from the lymph nodes traveled towards the lung. We now know that this interpretation is incorrect. The new foci in the apex of the lung arise not from diseased lymph nodes but, as we shall soon learn, from reinfections.

The diseased, markedly enlarged lymph nodes have a tendency to caseation. Thence arises the picture which has also been designated as scrofula. Naturally this marked caseation and simultaneous softening of the lymph nodes during this so-called anaphylactic period is not without its effects on the organism. There arises the great danger that the caseating tracheobronchial lymph nodes can become responsible for the invasion of caseous masses into the air passages and bring about the familiar, rapidly caseating aspiration pneumonias of the lower lobes, that so frequently are the cause of death in children. We must likewise remember that the primary infection of the lung also progresses in this period and can bring about extensive caseation. Here the exudative or the mixed, productive-exudative processes predominate. That is to say, the clear, sharply circumscribed node formation, the so-called gray tubercles, are practically not to be seen.

While these processes go on in the lung, on the one hand, we see on the other, in consequence of the progressive caseation of the tracheobronchial lymph nodes, a sudden breaking into the blood stream of the virus, which wrenches open the barriers. Now the metastasis arises, and dependent apparently upon the physiological rate of development of the individual organs we may see for example involvement of the adrenals (which undergo physiological involution in the first year of life and may serve as the origin for Addison's disease in later life) or the brain (which attains its increased growth in the first year of existence) the bones (which develop in the second period of growth, namely the prepuberty stage) or the urogenital apparatus (during the period of puberty). The skin also, as well as mucous membranes with their related lymph nodes, participates in the reaction during this period of generalization. (Here we see the tuberculides of the skin [Ranke], the scrofula.)

The type of metastasizing phthisis that overcomes the individual seems to be dependent in part on the time of life during which the primary infection occurs and the period of its generalization.

It would not be out of place at this point to say a few words about the scrofulous diseases. I have already discussed

the rapidly caseating processes of the tracheobronchial lymph nodes as they appear in the anaphylactic period in conjunction with the primary affect of the lung. We know however that such scrofula, that is to say, the rapidly caseating and readily softening lymph nodes, may also occur in the anterior and posterior cervical regions, the mesentery, retroperitoneum and so on. These so-called scrofulous lymph-node involvements are very often associated with the signs of an exudative diathesis, namely, eczematous changes in the region of the mouth, the alae nasi, with phlyctenular conjunctivitis and purulent otitis media. That a retrograde infection of the jugular and higher chains of lymph nodes can occasionally arise from the scrofulous involvements of the tracheobronchial nodes, cannot be denied. And yet through the careful work of Ghon, Harbitz, Beitzke and others, it has been established that as a rule the disease of the anterior and posterior cervical nodes proceeds from above down and not from below up. One has to conclude therefore, that the involvement of these nodes takes its origin from areas above, that is, the middle ear, skin, mucous membrane of the nose, and the oral and pharyngeal cavities. It lies, however, within the realm of possibilities, that in all this we may be dealing, especially in children and young individuals, with exogenous reinfections, arising from the same source of infection as does the primary affect of the lung. Thus the scrofulous manifestations would be regarded as reinfections in the sensitization or anaphylactic period, as reinfections moreover with the *identical* virus. It is obvious of course that at this point endogenous infections of the skin, for example by way of the blood, may also play a part. Of particular interest in this connection is the question of the so-called phlyctenulae which we often see develop in the middle of the cornea immediately beneath the epithelium. Here also the possibility of a new infection from filth from the outside must be taken into consideration. This may arise either from the old source of infection which is already responsible for the primary affect; or the carrier of the primary affect itself, when it by chance deposits infectious material in some place or other, may come into question.

At any rate, we believe that the variegated pictures of scrofula represent an essentially stormy reaction of the

sensitized organism against exogenous or endogenous infection with *the same virus*. Scrofula is thus only a single evidence of the anaphylactic period, which serves as a prelude in the processes of generalization and metastasis of the infection in the various organs. Let us again return to the subject of these metastases which are responsible for the phthisical processes in the different organs. In such organs we see everywhere that the fresher the process, the more rapidly does the picture of progressive caseation dominate the situation. Only gradually do actual tubercles develop in the various organs (kidney, testes, etc.) evidences of an increased resistence or immunity. In this way arise the well-known, chronic, slowly progressing disruptions in the individual organs which we know under the name of organic phthisis.

At this stage you may perhaps justly bring up the question of the hitherto unmentioned form of phthisis, the so-called *miliary tuberculosis*, which is found in infancy and characterized by typically gray tubercles in all the organs. We are in the habit of employing this as an example of an especially rapid form of dissemination of the tuberculous virus in the young unprotected organism. This however is an entirely erroneous conception. At first it must be noted that not all types of miliary tuberculosis look alike. There are those which present the preeminently characteristic gray tubercle; others, however, have a more washed-out appearance due to actually caseating nodules that permeate the entire lungs and various organs. These are indeed fine distinctions in the type of reaction between virus and organism. The fact however that the organism finds time, in spite of such apparently tremendous blood invasion, to produce local reaction, is evidence that it must have attained a certain amount of immunity. Were this not the case, the body would succumb to a phthisis bacillus sepsis. Such cases, with practically no reaction, likewise occur. When we are forced to conceive of miliary tuberculosis as a bacillary infection in a more or less immunized body, then we must look for the focus of origin. And here we know that especially in children we almost always find a so-called intima tubercle in the pulmonary vein, or the veins of the adrenal, the ductus thoracicus, or some other place. From this it follows that miliary tuberculosis should not be regarded in the same

light as other disseminations which occur in the period of generalization, but as a particular form, which owes its derivation to intimal phthisis. This is to be placed in the same category as the metastasizing organ phthisis of the kidney, bone and brain.

The course of events is somewhat as follows: At first a limited organ phthisis arises, for example in the vascular system, which manifests itself in the form of the intima tubercle and is an expression of a more or less existing immunity which renders possible this shunting off of the invader, and calling forth of a local reaction. Next begins the multiplication of the bacilli in this intimal focus which may reach such a grade that, given an opportune moment, they can break into the circulation. Thus arises the particular danger of intimal in contrast to all other organ phthisis. One deals here with a relatively rapid dissemination through the blood stream of comparatively large masses of the infectious agent, in a body that is more or less markedly immunized. The greater the acquired resistance, the more clearly does the picture of true disseminated tubercle formation occur.

After this digression into the problem of miliary tuberculosis, let us return to the *generalization stage of phthisis.* Here we find that during this period a certain proportion of affected infants and young individuals die. In other cases, the metastasizing process comes to a halt, but the local infection, the so-called organ phthisis, goes on. Thus develops the picture of the brain tubercle, the chronic bone, joint and urogenital phthisis. This has also been named as the tertiary stage of phthisis. It is a very striking fact, however, that just in these very cases the lungs remain remarkably unaffected for relatively long periods, or altogether free of phthisical involvements. From this we must conclude that it is not possible to place chronic pulmonary phthisis in the category of the hematogenous metastasis, as we do chronic organ phthisis. Otherwise, the combination of pulmonary and other organ phthisis ought to be more frequent. Unfortunately statistical corroboration in this connection is as yet unavailable. To go on, however, it might be conceived that the chronic pulmonary consumption might still owe its origin to a generalization of a primary affect, because the lung would presumably be the first organ to retain the seed

which reaches the blood stream via the lymphatics. It is known from the investigations of Ghon and his coworkers that there is occasionally a possibility that such cases arise as the result of hematogenous, endogenous reinfection. If that were the usual event we would expect that such pulmonary reinfections would, on the average, be as old or older than the metastatic infections of the bone, kidneys, genital systems, etc. As a rule however these last date back, as autopsy material shows, to early puberty, or puberty itself, or even to the earliest infancy. The reinfections in the lung, on the other hand, as far as we can conclude from our autopsy findings, seem to arise in later puberty, or the adult stage of life. Just this very difference in the time element was the main reason for causing Puhl to attribute the reinfection in the lung not to an endogenous metastasis of the generalization period, but to a later, exogenous reinfection. He based his conclusions on the results of the clinical material of Romberg and Haedicke. The method of extension of the reinfection along the course of division of the smaller bronchi is also in support of his point of view, a fact which could scarcely be explained on the basis of a hematogenous distribution. Remarkable also in this connection, although not regularly found, is the mutual exclusion of the simultaneous occurrence of chronic pulmonary phthisis on the one hand and the chronic phthisis of the rest of the organs on the other. For this there is also a certain explanation. The more markedly a chronic organ phthisis develops in connection with the generalization period, and the longer it exists, granting the presence of a sufficient amount of resistance in the individual, the more thorough will be the immunization and the more difficult it will be for the exogenous infection to engraft itself upon the lungs or, if it occurs, the less rapid will be its progress. Should the individual skip the generalization stage, or the metastatic spread come to a rapid termination, then the immunization process will be broken off prematurely. The reinfection will take hold more readily and will lead more quickly to a progressive chronic phthisis. Naturally the consequences of an exogenous reinfection depend not only on the amount of acquired resistance of the individual, but also on the quantity and quality of the new invader, the

general state of nutrition and intercurrent infections like grip, pregnancy and so on. From the above-mentioned facts, it is obvious that a comparison with syphilis, if it can be attempted at all, can only be applied to the primary infection, the generalization period and the chronic organ phthisis. That the chronic pulmonary phthisis can be included within this scheme, is out of the question. We ought to classify phthisis as altogether different from syphilis. It should be divided into a primary, exogenous-infection period (with its primary affect and its associated generalization and chronic organ phthisis) and a period of exogenous reinfection (with its consequent pulmonary phthisis).

The best proof that the usual chronic pulmonary phthisis (which in all civilized countries, for the present generation at least, represents the most common and serious of all human contagions) presupposes a previous immunization through a primary infection acquired in youth, is from the observations of Metchnikoff, Westenhöffer and others. They could establish, as is now known, the fact that among the uncivilized people who live under more natural circumstances, such as the Kalmicks, inhabitants of China, phthisis in adults, whenever they in any way come in contact with the infection, runs through a most virulent course. The World War has given us sufficient opportunity to enter upon this question anew. I, myself, have observed most serious cases of infection in a very large number of autopsies of Anatolian peasants, who came from small mountain villages, and in whom it was impossible to find any traces of previous phthisis. Here we found pictures like those usually seen in children during the stage of generalization. Similar findings have been reported by Gruber among the black troops in the occupied territories on the Rhine. And finally, the very careful new work of Pasteur which deals with very exact military statistics of the diseases of the French colonial troops during the war, also comes to conclusions similar to those of Metchnikoff, Westenhöffer and us. Unfortunately, at the time that I was stationed as army prosector in Turkey, I had no knowledge of the histological structure of the primary affect. In future investigations of such material, it will behoove us to pay particular attention to the occurrence of the primary infection, so as to

dismiss the criticism that the remarkable course of phthisis in such individuals is to be attributed not to the absence of the primary infection in infancy, but to the peculiarities of the race. That among the more cultivated communities there also occur cases in adults which present the pictures of phthisis seen in youth, and similar to those seen in the most primitive peoples who have not been immunized in the early years of life, must also be emphasized. In all probability, by mere chance, these individuals escaped the primary infection of infancy. We know that such primary infections most frequently occur in the first five years of life, then in decreasing number in childhood, only to increase again in prepuberty, to a certain extent in the puberty period, and even somewhat later. Puhl found such a case of true primary infection in an individual of about forty years. It is comprehensible that such people, like the children, instead of going through a stage of rapid healing, may experience a progressive disease of the lymph nodes with generalization. As a rule the number of such cases appears to be small, but still we not infrequently see, and especially during the period of puberty, in individuals who carry an old primary infection, the sudden appearance of a progressive inflammation of the lymph nodes with extensive caseation, in short, a replica of the complex seen in childhood. These we have designated the phthisis of puberty. In young pregnant women, one may often observe similar pictures. Here also one sees rapidly extending processes in the lung. In this connection we must look for the cause either in the remarkable changes which are associated with the age of puberty and the state of pregnancy, which perhaps may lead to a flaring-up of the original primary infection, or in a new exogenous reinfection which may overwhelm an organism whose powers of immunity have been so greatly depleted that the infection runs a course similar to that seen in the virgin state. For the occurrence of the phthisis of puberty, the question of the duration of the survival of virulent phthisis bacilli in a primary affect is naturally most important. One would imagine that a semiosseous primary affect would be devoid of living bacilli. Yet the latest investigations of Koenigsfeld and Puhl have shown that in just such ossified primary infections of the lung, which one must assume had occurred

many years, perhaps many decades, earlier, virulent bacilli are still to be found, as proved by guinea-pig inoculations. It is therefore within the realm of possibilities that in adults also, metastatic infections may arise from bacteria derived from apparently fully obsolete foci, which have escaped into the blood stream. That is to say, we must assume, although the principal generalization period of youth is terminated, that the possibility of a smoldering infection being prolonged into old age, without any new exogenous reinfection having occurred, may exist. Under such circumstances it is readily understood that certain metastatic forms of phthisis, as for example, phthisical iridocyclitis, may be seen in individuals in the fourth and fifth decades of life, as has been communicated to me by my colleague, Professor Axenfeld. In the future we shall have done our duty properly only when we have carefully examined the autopsy material of cases which during life were free of pulmonary findings, in order to ascertain in what state the primary affect exists: whether it still contains infectious material, or whether, besides the primary affect, a reinfection is to be found. Such investigations as have already been made by Puhl enable us to make the following observations:

TABLE I

STATISTICS OF PRIMARY INFECTIONS IN PULMONARY TUBERCULOSIS

(According to Puhl)

Among 122 patients with lungs showing signs of phthisic infection 109 cases of *primary infection* were found = 90 per cent.

Of these 109 cases

76 showed full primary infection of lung and lymph nodes.

17 showed only primary infection of the lung.

19 showed only primary infection of lymph nodes.

1 showed full primary infection of the intestine.

Among the 109 cases there were 35 cases of so-called tertiary advancing phthisis of the lung: of these 29 showed primary infection = 83 per cent.

Of the 87 arrested cases 43 showed *reinfection*. This suggests that in all the 35 cases of tertiary phthisis of the lung primary infection was existing, upon which later on a reinfection had been grafted.

109 cases of primary infection showed 25 plus 53 = 78 cases or 71.5 per cent of reinfection.

Of these 78 cases with reinfection 35 or about 50 per cent developed advancing phthisis.

About two thirds of individuals who have had a primary infection, and that comprises over 90 per cent of all living, develop a reinfection. Whether an explanation of this fact is to be found in the imperfect immunization by the primary infection, or whether unfavorable outer or inner circumstances play the important rôles, is until this day unestablished. Half of the number of those reinfected get absolutely well. Only in a small proportion does the exogenous phthisis (seldom endogenous) develop into a progressive disease of the lungs. It is as yet impossible for us to separate the individual factors, the summation of which leads to a successful invasion by the agent of consumption. It makes very little difference for us how they assert themselves in the activation of the phthisical process. This is not the place for a disquisition on the subject. That belongs to the study of disposition and constitution, not to the field of morphological pathogenesis.

The pathologic-anatomic picture of progressive pulmonary phthisis is familiar. The extension of the process follows from the reinfection of the apex of the upper lobe. The phthisis, so to speak, seeds the lung craniocaudally. The manner and course of the process varies between two extremes of reaction with numerous transition forms. On the one hand, one has to deal with marked chronic cases with a definite tendency to healing through the formation of hyalinized fibrous tissue in the individual foci. These are favorably influenced by physical therapy, especially the *x*-ray. Here the productive character of the reaction characterized by the occurrence of granulation tissue with its histocytic elements (the so-called epithelioid cells), the giant-cells, lymphocytes and plasma-cells, predominates. This avascular tissue caseates slowly. It either becomes surrounded by a hyalin ring, or else goes over to a specific hyalin scar, without caseation. Such a productive reaction is to a certain extent characteristic of a special state of tissue immunity, and is a token of increased resistance. On the other hand, one deals with cases which run a more acute or subacute course following their reinfection. Here, within the respiratory passages, the characteristic exudative reaction is mostly in evidence. This is composed of large exudative cells (alveolar epithelium, wandering histiocytes)

and a marked amount of fibrin containing varying numbers of leucocytes, which has a tendency to rapid caseation and softening. Encapsulation and healing meet with difficulties. The exudative reaction is a sign of lowered resistance, a rapidly progressive destruction of the organism. Physical therapy fails, or may indeed hasten the destructive processes, unless resorted to with the greatest of caution. Between these two main forms there are numerous combinations. With the occurrence of softening, which, in the productive types is wont to come on slowly, and in the exudative, more rapidly, the picture becomes more variegated. Thence arise the motley appearances characterized by ulceration and cavitation with their accompanying consequences.

The changing picture of phthisis is dependent not only on the different forms of reaction but also on the varied localization of the process within the lung and the method of its spread. You all know that, based upon the location of the tuberculous processes, it was and still is the rule to talk about a bronchitis tuberculosa, peribronchitis tuberculosa, lymphangitis tuberculosa peribronchialis, intra-alveolar tuberculosis and so on. I believe that this very often confusing nomenclature is based upon a false interpretation of the histologic pictures. At any rate, for the understanding of the correct localization of the phthisical-tubercular foci, it is important to have a proper knowledge of the normal histology of the lung. Since the work of Miller, as far as I know, there have been no complete histologic studies of the lung carried out. Only recently has interest in this question been revived. Very careful studies have been made by Loeshcke, Husten and Baltisberger. From these we learn that the pulmonary respiratory tissue proper is made up of a final unit, namely the acinus. By the term acinus I understand that pulmonary area which is associated with a so-called bronchiolus respiratorius of the first order. The bronchiolus respiratorius of the first order is distinguished by the occurrence of sporadic alveoli within its wall. It arises in its turn from the bronchiolus terminalis, which is the narrowest portion of the entire bronchial system, and divides dichotomously into the bronchioli of the second and third order, which are recognized by the progressively

increasing number of alveoli within their walls. The bronchiolus respiratorius of the third order finally divides into three or more parts, the so-called alveolar passages, which in turn terminate in alveolar sacs. I believe that the entire structure of this system, as has been depicted, is of the utmost importance in the explanation of the normal function of the lung. It has deen established by the investigations of Husten and Baltisberger that not only the bronchioli of the first, second and third order, but also the alveolar passages at the free ends of the so-called alveolar pillars are well provided with smooth muscles, and only the alveolar sacs are devoid of them. You can readily see therefrom that even in the immobility of the lung, through the contraction of the muscles in the alveolar passages, the movement of the air current into the alveolar sacs is still possible. At any rate, on the physiological side these independent intrapulmonary exchanges of air should receive more attention. As to the significance of this musculature in disease processes, especially in stasis lungs, repeated observations have already been made, and yet we lack a thorough knowledge of the physiology and pathology of this muscle system. Dr. Harkavy of Mount Sinai Hospital has occupied himself intimately with this question. He has been able from various histological studies to establish the predominating passivity of the alveolar sacs in contrast to the activity of the alveolar passages.

Besides these physiological and pathological important minutiae in the structure of the acinus, the acinus as a whole plays an important rôle in the pathology of the lung. This is readily shown by the fact that all fresh infections which come in contact with the pulmonary tissue in their passage through the lung lodge within the acinus, particularly in the bronchioli respiratorii and at the points of their transition into the alveolar passages. The physical factors, characterized by the marked slowing of the air stream, the formation of currents and the biological factors, such as the replacement of ciliated epithelium by ordinary cylindrical or the flat epithelium of the alveoli, must favor the settling of foreign bodies, living or otherwise, within this territory. The phthisis bacillus likewise finds this area the site of predilection and, on settling, calls forth the characteristic

reaction in the surrounding tissue, be it of exudative or productive nature. If the productive inflammation ensues, the phthisical granulation tissue spreads within the acinus and to the naked eye, depending upon whether it is a longitudinal or a cross section, it appears either as a rounded tubercle-like nodule or an elongated oval, or a dichotomously branching, irregular, sac-like nodule, which subsequently through caseation may naturally assume a different aspect. These very fresh foci of phthisical-tubercular involvement of productive type represent an acinous focus. One may designate this as *acinous-productive phthisis*. Should such a focus spread extensively over the entire surface of the lung, or perhaps through aspiration reach the lower lobes, there results a picture which closely resembles hematogenous miliary tuberculosis. The difference however lies in the fact that whereas the latter in its productive form lies more interstitially, the spread of the acinous-productive phthisis as seen through the microscope is intra-acinous. As a rule however it is very easy to diagnose the bronchogenic acinous-productive phthisis because of the tendency of one diseased acinus to interlock with its neighboring second or third. Thus a conglomerate, grayish, nodular mass ensues, which may reach the size of a pea or a cherry. This represents the type of so-called *acinous-nodose phthisis*. The older, central portions of such foci shrink, as a rule, and assume a slate-colored appearance. If one examines them more closely, one notes that he is dealing here with a collapse induration of the alveolar sacs which have remained unscathed in the tubercular process. At the moment that the alveolar passages of the individual acini become filled with the phthisical granulation tissue, there arises a spontaneous collapse of the alveolar sacs, provided they are not in the meantime filled by a perifocal inflammatory edema or exudate. When such atelectatic or carnified areas of induration become infiltrated with carbon, the characteristic, black-pigmented centers of the acinous-nodose foci ensue. When these interlocked foci finally fuse, and induration processes set in within and about them, there follows a hyalin fibrous transformation of the foci involved, and the characteristic reparative stage which

we designate as *cirrhotic phthisis* comes into being. Thus we see that the entire process can be traced back in its fundamental development to the acinous foci, and with that all the complicated and for the most part erroneous characterizations, such as peribronchitis tuberculosa, bronchiolitis tuberculosa, etc., fall to the ground. It is a question, not of the disease of the bronchioli and the peribronchial tissue, but of primary disease of the acini.

Quite the same rules hold for the localization of the exudative processes. Here too the phthisical exudate begins within the acinus. Here also arises an acinous-exudative focus. This is macroscopically and especially microscopically distinguished from the acinous productive focus by the washed-out borders and the tendency to more rapid caseation, so that we are most apt to talk of an *acinous-caseous phthisis*. As a result of a rapid confluence of these acinous-exudative foci, entire lobuli, and finally whole lobes, become invaded, whence the terms *lobular-caseous*, and *lobar-caseous phthisis*.

When we finally become accustomed to refer all phthisical pulmonary processes to the final unit, the acinus, then it is possible, in spite of the apparently complicated pictures, to classify almost every case of chronic pulmonary phthisis which follows a reinfection, in accordance with the predominating character of the reaction, and thus decide upon the prognosis and therapy.

Today we recognize in accordance with Eugen Albrecht and Albert Fraenkel, depending upon the type of the reaction on the one hand, and the localization as well as extension on the other:

I. Productive phthisis
   (a) Acinous-productive phthisis
   (b) Acinous-nodose phthisis (through the fusion of individual acinous foci, to the size of a cherry, or still larger nodules)
   (c) Cirrhotic phthisis (more widely confluent acinous-nodose foci with diffuse shrinking of entire cicatricial lung areas)

II. Exudative phthisis
  (a) Acinous-exudative processes
  (b) Lobular-caseous phthisis
  (c) Lobar-caseous phthisis

The origin of (a) and (b) under exudative phthisis is similar to that of (a) and (b) under the productive form, namely through fusion of acinous foci. Besides these come the pictures of phthisical caseous bronchitis and the complica-

FIG. 5. Progressive phthisis of the lung. At left acinous nodose phthisis (productive form); at right lobular caseous phthisis (exudative form).

tions arising from the softening of caseous masses, especially within the bronchial tree, such as the acute ulcerous and chronic cavernous phthisis.

According to the site, we speak of apical, cranial or caudal localization and designate a case as apical-cavernous, cranial acinous-nodose, or caudal acinous-productive phthisis.

That these various forms are readily diagnosable during life, particularly by the roentgen plate, has been shown by the investigations of Gräff and Küpferle, who published their findings in atlas form. The prognostic value of such classifica-

tions from a clinical point of view has been particularly stressed by A. Fraenkel and von Hajek. We stand face to face with new problems in the pathogenesis of phthisis. The fact that consumption in infancy has not diminished in proportion to that of the adult (Gottstein) makes us pause. We must reconsider whether we have fought with equal vigor both periods in the development of consumption, namely that of the primary infection and that of reinfection, or whether through our social hygiene we have merely dammed back the reinfection. We must, however, remember that with the prevention of the primary infection in childhood the adult is sent forth into life unprotected against this disease, which will then attack him with infinitely greater virulence than the usual familial infection, so to speak, in infancy. Absolute prophylaxis against infantile infection will be desirable, then, only when we shall be able to replace the naturally induced immunity by an artificial one, or else completely get rid of the most serious infection of later life. It would be well worth while in our battle against phthisis if we could at least induce a limited artificial infection on top of the primary infection, and thus dam back the metastasizing process. We shall, however, understand the clinical and autopsy material more correctly and be able to evaluate from the point of view of its genesis, prophylaxis and therapeusis, only when we learn to differentiate the primary infection period with its consequences from the reinfection period with its consequences.

NOTE. The lantern slides used in this lecture may be ordered through The Bildarchiv, Freiburgi. Br.

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The full references are given in

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III

CONCEPT OF INFLAMMATION

Life is characterized by the so-called vital processes which present themselves in the form of morphological change, metabolic processes and energy exchange. We can study these three fundamental types of vital processes in each living organism. They serve to support the biological existence of the living organism. As long as they satisfactorily fulfill their functions the vital processes or vital functions are considered *healthy or normal* and the state of the respective organism is designated as *health*. The organism seems to be adapted to the given vital conditons. We know, however, that these external vital relations are extremely variable, the meteorologic conditions, the temperature and moistness of the atmosphere and the constitution of the diet undergoing continual change. In order to maintain the necessary constancy of isotonicity, hydrogen ion concentration and temperature essential to its existence, the organism must maintain a continuous regulation of the vital processes by the diminution or increase of the individual factors. The organism must therefore be equipped with certain regulatory mechanisms in order to insure its biological existence. *A healthy organism* is one possessing complete powers of adaptability toward the natural exchange of external vital conditions. It is self-evident that correspondingly healthy or normal organs are essential for the possession of such perfect adaptability, for which the term "healthy constitution" is generally applied. We can thus characterize *a healthy life* as one possessing the capacity for adaptation.

The great question of what disease signifies has occupied the attention of human beings from time immemorial. We know today that it is nothing but life under altered conditions. Disease has no autonomous existence, but depends on disturbances of the normal vital functions.

But where shall we draw the line between health and disease? The first to give a clear answer to this question was Virchow, when he linked the conception of *endangering the organism* with that of disease. Accordingly, a disease process may be defined as a disorder of the processes as a result of which *the biological existence of the organism is endangered,* i.e., no longer adapted to the given vital conditions. *Taking sick* is a disturbance of the state of health endangering biological existence. It is self-evident that the capacity for adaptation toward the various external vital relations can be exhausted even in the healthy organism if the disturbing factors reach an extreme degree. Thus a healthy individual is powerless against excessive deprivation of fluid and solid nutritive material, or an extreme reduction of the oxygen content of the surrounding atmosphere, and so on. In the presence of such unusual conditions the biological existence of even healthy organisms is endangered, i.e., the *organism becomes diseased.* We designate causes of disease arising from changes in the external vital conditions as *causae externae* or external causes of disease. Medical experience shows, however, that the biological existence of all individuals is not endangered with equal ease by the external vital conditions. Certain individuals take sick when the deviations in the latter are so slight as not to affect the great majority of living beings. Under these conditions it is necessary to assume a reduced adaptability to the natural exchange of external vital relations. We designate those organisms which possess diminished power of adaptability as *weakened organisms.* This reduced adaptability is not infrequently due to a pre-existing disease process. It is well-known that disease, however insignificant, is really never followed by complete *restitutio ad integram.* In practically every instance, disease leaves its mark on the organism in variable degree. A familiar illustration of this type is observed in rheumatic disease of the heart valves. Experience teaches us that a relatively large percentage of cases is followed by more or less pronounced thickening and distortion of the valves and chordae tendineae, agglutination and shortening of these structures, changes which definitely interfere with the functional power of the heart. If the

permanent damage to the heart valves is not very severe, the individual is able to meet the ordinary demands of life, engage in mental work and perform slight bodily exertion without complaint, and his biological existence *appears* to be secure. But this state of health is only *apparent* and is limited in degree. More violent bodily exertion, though it cause no ill effects in healthy individuals, is at once followed by serious disturbances of cardiac function, indicating that the heart no longer possesses the normal adaptability toward the natural exchange of external vital relations. We speak of an *organ defect*, e.g., of a cardiac defect in the pathological anatomical sense, or of an *organic disorder*, e.g., cardiac disorder in the clinical sense. An organism with reduced powers of adaptability possesses, as we shall term it, a *weakened constitution*. A diseased or ailing organism whose powers of adaptation to the natural environment are limited possesses only a *relative state of health*. Such a diseased existence in contrast to the healthy state does not represent an intermediate stage between the two, but one which lies on the borderline of adaptability. It is easily understood that the limits of adaptability in such an ailing organism are easily overstepped. The cause, however, is not to be found in the external factors of an extraordinary nature but in the reduced adaptability of the individual, in his weakened, i.e., abnormal, constitution. Where the cause of a particular disease is to be sought for essentially in the abnormal constitution of the individual, we speak of the *internal causes* of disease.

These brief definitions of healthy and diseased life, of the healthy and diseased organism, make clear the great significance of the capacity for adaptation. On analysis the latter is found to consist in turn of a diversity of regulatory mechanisms relating to the individual vital processes. It therefore appears to me to be both interesting and of importance in the construction of a system of general pathology, to consider the phenomena of life during health and disease from the point of view of the regulatory mechanisms.

Let us first consider the healthy organism. Its functions are activated and sustained by the natural vital stimuli which are due chiefly to the physical environment, the

atmospheric temperature, the chemical constitution of the atmosphere and the fluid and solid nutritive materials. We designate those regulations which compensate instantly for the fluctuations in the external temperature, alterations in the humidity of the air, and the excessive fluid intake with the food by changes in the bodily production, by diminished or increased heat dissipation and increased water output by kidneys and sweat glands, as the *compensatory or balancing regulations*. They are of the utmost importance to the life of the organism. We must marvel at the exactness with which the blood maintains its hydrogen ion concentration, its content of Na, K, and Ca ions, and its temperature. We are aware of the complexity of those mechanisms which subserve the balancing functions. They include the glands of internal secretion and the nervous system. In connection with the balancing regulations which serve to ward off certain harmful factors arising from the external world, I mention by way of illustration the desquamation of the skin by which the latter is repeatedly cleansed of foreign bodies, microorganisms and plant parasites, unfortunately however without permanent results. I may also mention the lid reflex, the ciliary movements in the tracheal and bronchial epithelium, the increased secretion of the nasal mucosa, and the desquamation of the alveolar epithelium with the formation of the so-called "dust cells." All these phenomena serve to prevent the contamination of the organism or to ward off direct injury to the latter. Although these regulatory mechanisms occasionally fail in their function their usefulness to the organism is unmistakable. When I speak of usefulness, I do so in its relation to the organism, for we must regard all the vital processes from the standpoint of the organism as a whole. This conception naturally is of value only to the biologist and hence the physician, who at all times deals with the personality as a whole. This biological conception can be subordinated by the anatomist and the physiologist, being replaced by the purely scientific viewpoint concerning the physicochemical structure of the cells or the colloid-chemical, purely chemical and electrical factors in cellular activity. But this purely scientific or causal method of investigation does not lead to concepts of totality and organization. For

the analysis of the latter we cannot dispense with the viewpoint of the organism as illustrated in the conception of self-preservation, propagation and accommodation.

In mentioning only the balancing and prophylactic regulations in human beings I am well aware of the important rôle played in animals by still other regulations, especially those pertaining to metamorphoses and alterations in form. To illustrate I may mention the involution of the tail and gills in the metamorphoses of tadpoles, the marked solution of body tissue in fish prior to the spawning period, the transformation of insects, etc. In human beings, too, we find similar metamorphoses, but of much lesser degree, e.g., the involution of the adrenal cortex immediately after birth, the involution of the thymus at the beginning of puberty, the development of the secondary sex characteristics under the influence of the gonads, etc.

Under what special conditions can the adaptability of the normal organism be overtaxed through external influences, that is, *how can the biological existence of the organism be endangered and the latter diseased?* In contrast to the natural or adequate vital stimuli which maintain health, we are confronted by unnatural or inadequate vital stimuli which cause disease. Each disease-producing stimulus leads to a change in the given organism, which we designate as an *affection.*

Depending upon the type of vital function predominantly involved by the disorder in question, we distinguish three types of affections corresponding to the three types of vital functions. First of all, there are the disorders of *form*, especially those concerned with development and growth, which we generally term *dysplasias.* In the category of the latter are included the large group of malformations and the neoplasms. A second group comprises the disorders of metabolism and nutrition, termed the *dystrophies.* Another group includes the disturbances of energy exchange, heat production and electromagnetic force, termed the *dysergies,* which play an important part in febrile states. In the more highly organized animals in which the individual provinces of the organism are closely interconnected by a highly developed vascular and nervous system, there arise circulatory disorders

TABLE I

HEALTH AND DISEASE REGARDED FROM THE VIEWPOINT OF THE REGULATORY MECHANISMS

- **Vita sana (Orthology)**
  - *Sanitas*—requires vital stimuli
    - Balancing (compensatory) regulations
    - Prohibitory (preventive) regulations
    - Metamorphotic regulations
  - Absolute health
  - Absolutely healthy organism
- **Vita aegra (Pathobiology)**
  - *Morbus* (Nosology) *νόσος* calls forth in
    - A. *Simple*, purely *functional* affections—*recreative* reactions
      - Recreatio
      - Involutio
      - (Resorptio)
      - Compensatio
    - B. *Material* affections
      - 1. *Deficiency* affections—*regenerative* reactions
        - Regeneratio
        - Compensatory hypertrophy
      - 2. *Destructive* affections—*reparative* reactions
        - Resolutio
        - Remotio
        - Granulatio
        - Organisatio
        - Demarcatio
      - 3. *Infectious* affections—*defensive* reactions
        - Repulsio
        - Adsorptio
        - Digestio
        - (Lysis, Phagocytosis)
        - Immunisatio, etc.
  - *Passio* (Pathology) *πάθος*
    - Dysplasias
    - Dystrophies
    - Dyshemias
    - Dysergias
    - Dystonias
    - *Indirectly* called forth in consequence of a demonstrable effective reaction—morbus (Passiones indirectae)
    - *Directly* produced without demonstrable or with poorly developed reaction (Passiones directae)
  - Relative health
  - Relatively healthy (i.e. ailing, diseased)

or *dyshemias*, and disturbances involving the conduction and tension of the nervous system, termed *dystonias*.

These are the five main groups of disturbances of the vital functions which are united under the term *affections*. How the organism behaves in the presence of these different affections, what *reactions* set in, depends not so much on the localization of the affection, i.e., of the vital function primarily involved, as on the nature of the affection and the disease-producing stimulus. The simplest form of affections followed by reactive processes are those which overtax the potential energy of the organism without visibly altering its *material* substratum or cellular construction. I designate this group as simple or purely *functional affections*. Familiar illustrations are mental or bodily overexertion, states of undernutrition and one-sided feeding, and artificial conditions of bodily constraint. The organism possesses but limited adaptability toward such purely functional affections. Thus, though the body during hunger maintains for a relatively long time the function of the more important organs at the expense of the less vital ones, ultimately this power fails. The organism can recover only if supplied with the materials required for the storage of new potential energy. The body can then rebuild more or less rapidly the necessary substitution material. We designate this type of activity as *recreative* reaction. It is self-evident that in undernutrition of a more advanced degree in which actual material losses are sustained, the organism can still continue its existence. Thus, during the war it was possible to observe many cases of severe hunger anemia, osteoporosis and edema arising from hunger.

But in such cases too, we deal more with functional exhaustion, e.g., of the hematopoietic system, the isotonic condition of the skin and subcutaneous tissue, the calcium-binding capacity of the endothelial cement substance, than with material disorders in the strict sense. As soon as the adequate diet is restored, the edema fluid is rapidly reabsorbed, and the osteoporotic bones strengthened by compensatory growth of new osseous tissue. The functional injury can be reversed and manifest itself in an accumulation of nutritive substances, e.g., fats, the disease process appearing as obesity.

Here too the body has very little power to arrest the process as long as the feeding continues; as soon as normal conditions are restored, however, the fat which has been stored in excessive quantities is again removed by a process of involution and the body relieved of its burden. All these phenomena are grouped as the *recreative* reactions.

The more or less purely functional affections contrast with those in which there are *material*, i.e., cellular or tissue alterations in the organism. Here too we can distinguish several groups. In the first of these are included the affections in which the organism sustains a macroscopic or microscopic defect. They are termed the *deficiency affections*. They are rarely observed in pure form in human beings because defects of this type are generally accompanied by destruction of the surrounding tissue. Pure defects occur much more commonly in the lower animals, particularly in the cold-blooded animals. We know that the body possesses highly-developed regeneratory powers which come into play when loss of substance is sustained, e.g., the loss of the tail in lizards. In human beings too, similar regenerative capacity may be observed almost in pure form, e.g., in surgical incisions. We know that this capacity is much more highly developed in animals lower in the scale of phylogeny than in the higher groups and that in the ontogenetic development of the latter, the earlier stages are likewise characterized by a greater regenerative capacity than at a later period. The skin, mucous membrane, connective tissue, periosteum, nerves, in part also the glands such as liver and kidneys possess excellent powers of regeneration, especially when the stroma is intact. On the other hand, the muscles, many glands of internal secretions and the nervous tissue of the cerebrospinal nervous system possess this power only to a very slight degree. The regenerative capacity even of the liver and kidneys is greatly diminished if the stroma, the actual framework of the organ, is also destroyed. In cases in which true regeneration is not possible, the organism attempts to compensate for the injury by the added growth of identical tissue, e.g., in the case of organs occurring in pairs by the enlargement of the opposite organ. Thus we speak of compensatory hypertrophy of the kidney, adrenal, testis, thyroid, etc. We

include all these phenomena under the term *regenerative reactions*. If such an equivalent organ is not available, the body endeavors to assist itself by other means.

Perhaps it is justifiable to include in this category the *metaplasias*, by which we understand certain adaptive phenomena manifested by certain tissues in the presence of abnormal influences which persist for a long time. Thus the mucous membrane of the exstrophic urinary bladder which at birth is clothed by simple transitional epithelium is converted into a membrane bearing goblet-cells and typical mucous glands so that the appearance of the rectal mucosa is closely simulated. In like manner the epithelium of the prolapsed vagina often assumes the structure of cornified pavement epithelium, and the delicate skin of the child's hand is transformed into the callous skin of the laborer. The marked hypertrophy of the cardiac muscle in outspoken heart-failure, the muscular hypertrophy of the trabeculated urinary bladder in prostatic enlargement, the hypertrophy of the elastic structures of the aorta in contracted kidneys, all these are instances of adaptive phenomena which can be included in the category of *regenerative-compensatory reactions*.

The conditions which obtain when the organism sustains a *destructive* affection are quite different. There results not only a structural defect, but the surrounding tissue is damaged to a variable degree. Before the true regenerative process can be instituted, the field of destruction must be cleared of the debris. The best illustration in human pathology is afforded by simple bone fractures. There is more or less splintering of the bone, tearing of the muscle and connective tissue, hemorrhage, and crushing of the fatty tissue. The vitality of the crushed tissues is more or less impaired and for the most part undergoes necrosis. The necrotic masses which lie partially between the broken ends of the bone must be removed before a new growth of bone can be instituted by the periosteum and the remaining regenerative processes executed by the connective tissue and musculature. These clearing processes are designated as *reparative reactions*. We include among the latter, resolution or the softening and solution of the coagulated masses of blood, the removal of which is accomplished

by intracellular digestion of the necrotic masses by histiocytic and fibrocytic elements. The more extensive the necrotic material, the more complete the development of a complex of cellular elements with its own vascular system which we generally speak of as granulation or organizing tissue.

We now know that the heterolytic ferments furnished by the histiocytes, the wandering cells of the connective tissue, play an important rôle in the solution of particularly resistant structures such as bone, cartilage, and tendinous tissue. The greater the solubility of the necrotic substances, i.e., the greater their content of blood corpuscles, fibrin, ordinary connective tissue, etc., the more readily they are digested by the action of the autolytic or heterolytic leucocytic ferments. It is thus evident that a great variety of cells is active in the solution of necrotic tissue (necrolysis), functioning according to the composition of the material to be digested. In addition, the plasmatic fluids of the body also play a significant rôle in these reparation and resolution phenomena. Wherever simple liquefaction of the necrotic substances does not occur, there is replacement by organizing or organized connective tissue which later, by a process of scarring, may more or less hinder actual regeneration. The more intense the disorganization, the more marked the bloody effusion, the less carefully the fracture in the illustration is handled, the less pains taken to remove the blood clots in the early stages, the greater the *reparation* task of the organism and the later actual *regeneration* can set in.

Both types of the aforementioned injuries in which there is loss of substance or even disorganization of marked degree and which are resolved by reparative and regenerative reactions, or as they might be termed *restitution reactions*, represent the so-called *traumatic diseases* in contrast to the non-material, purely functional injuries, which might also be designated the *insufficiency diseases*. As important as the insufficiency and traumatic diseases are, they are by no means as weighty from a clinical and therapeutic point of view as the members of the third group of disease processes. In this group, it is not a question merely of a single defect with or without disorganization of the structure of the organ by some external agent, e.g., simple injuries or fractures, but of the

invasion of the organism by pathogenic agents, i.e., infection. The disease-producing factor can be of an inanimate character, e.g., projectiles causing destruction and disorganization of the soft parts and bones and *remaining as foreign bodies*, or the causative agents can be living, such as animal or plant parasites, which directly or by means of another injury invade the organism where they multiply and cause further damage. This group of affections also includes those which are summoned into existence by bacterial toxins rather than by bacteria themselves. The same holds true for the inorganic poisons which gain entrance into the body and cause damage there. All those diseases in which the body is contaminated are termed *infectious-toxic diseases*, to distinguish them from the insufficiency and traumatic disease. The microorganisms play the dominant rôle in their causation.

What new task now devolves on the organism? In order to compensate for the injury incurred by a given affection, the body must make an effort to render the living or non-living invader innocuous. By one means or another, the harmful agent must be metabolized, digested, destroyed, detoxicated, or excreted. In short, the organism must protect itself against the further inroads of the invading foreign substance and rid itself of the latter. We term those reactions which accomplish this function the *defensive or expurgatory reactions*. What means are available to the organism in the accomplishment of this task? As an illustration we may consider a simple infection due to one of the pyogenic bacteria, e.g., furuncle. As in any of the specific infections, such as pneumonia, typhoid fever, scarlet fever, measles, etc., the local reaction, however insignificant, is practically always accompanied by a *general defense* reaction. Frequently the picture is first dominated by the latter. They develop slowly and often precede the local manifestations. They usher in the disease, as it were, and are therefore designated the incubation period or prodromal stage. We now know that such general reactions can manifest themselves by changes in the blood, before the appearance of symptoms of a special character, with the single exception of fever. We shall later discuss the importance of the blood cells in local defense reactions. In the meantime, we may speak of a general mobilization of the

organism, a general state of excitation. The change in the blood picture which may consist of an absolute increase in the polymorphonuclear leucocytes or lymphocytes, or in a transitory diminution of both types of cells or a change in the differential formula is accompanied by a quantitative increase in the normal immune bodies in the circulating blood. The general mobilization becomes very pronounced when the usual febrile reaction sets in. The intensity of the general defense reaction is extremely variable. The higher the temperature, the more violent the general reactions are as a rule. The local reactions may be completely overshadowed. In other instances, as in the furuncle of our illustration, the general reactions are often insignificant as compared with the local reaction, at the site of which the actual battle between the host and the invading microorganisms is waged. Under favorable circumstances it is possible to observe a prompt mobilization or even solution of the invading parasites by fluids exuding from the blood capillaries. These phenomena are described as agglutination and bacteriolysis. In addition to restraining forces of this character, other cellular reactions enter into play. These are concerned with the activities of the leucocytes, the macrophages of Metchnikoff, which, having emigrated from the capillaries, aid in the destruction of bacteria by phagocyting them. Extracellular and intracellular digestive phenomena also play an important part. The reactive processes, however, include more than the arrest of the invaders and the digestive activities of the leucocytes. Under certain conditions, especially in the excretion of toxic substances, the parenchymatous cells also participate in their detoxication. Of greater importance, especially in the infections running a protracted course, are the proliferative changes in the stroma which complete the picture of the local defense reactions. In the case of the more resistant infectious agents, the Koch bacillus, lepra bacillus, the ray fungus, it is found that the wandering cells of the connective tissue, the so-called histiocytes, play a most important rôle. These cells construct a protective capsule about the given exciting agent, especially in phthisis, in which they form the minute nodules or tubercles. The latter consist of epithelial-like or epithelioid cells arranged in more or less radiate fashion, the

cells in question being essentially altered histiocytes. One of these cells, when it engulfs the Koch bacillus becomes converted into a typical giant cell. The bacilli undergo destruction within the body of the latter. In like manner, the lepra bacillus is taken up by lepra cells, the so-called leproma; the sporothrese, by the large cells of the sporotrichoma, and as far as possible destroyed. On the other hand, it is possible for the cells to be destroyed by the fungus, or for the fungus to continue its existence within the cell body in symbiosis with the latter. In any event, it is clear that the organism employs a great variety of means for overpowering the invader. The methods of defense are indeed varied. In certain instances, the dominant rôle is played by the exudation of coagulable substances, i.e., fibrin. I shall mention only the membrane formation of diphtheria which gives the impression of serving to remove the diphtheria bacilli from the surface of the mucous membrane where the bacteria are harbored to permit the fibrin net to absorb the bacterial toxins. It should be noted that these defense or expurgation reactions do not always accomplish their purpose; the organism may be overcome by the invader. Nevertheless, it is necessary to consider these processes in the nature of defense mechanisms from the point of view of their significance to the organism as a whole, inasmuch as they generally accomplish the favorable result of rendering innocuous the harmful agents which have threatened the welfare of the organism. The reparative process is not instituted until the general and local defense reactions have subsided. Every defense reaction is accompanied by extensive disorganization and solution of tissues, by the deposition of exudative material, destruction of numerous cells, apart from the accumulation of dying and decomposing microorganisms. The field of battle must be cleared and freed of all useless material before the last phase of the disease process, the restoration of the original structures, can be instituted.

If we pause to review the various groups of diseases which we have differentiated, we observe that the simpler the affection (*affectio*), the simpler the reaction (*reactio*), as a rule. In the insufficiency diseases, the recreative reaction is initiated promptly after the onset of the affection, that is if an opportunity is given for the reaction to set in. In the

infectious diseases we observe first a defense reaction, then a reparative reaction, and finally a regenerative and, if required, a recreative reaction. In each infectious disease, we distinguish an incubation period, in which the general defensive processes prepare for action, the acme of the disease in which the local reaction dominates the picture, the convalescent period with its accompanying reparative and regenerative reactions, and finally, the period of recovery attended by the recreative reactions. Dealing as we are with the same organism all the time, inasmuch as the latter must accomplish its various tasks with the same fluids and cells, it is clear that there can be no sharp lines of demarcation between the various reactions. Thus the process of cellular proliferation in the defense reaction gradually merges into the cellular proliferation of repair, and these in turn into processes of a regenerative character. The contention might therefore be made that nothing is gained by such a classification of affections. But in our therapeutic efforts, it is not a matter of indifference whether the organism must be supported during the stage of defense reaction or during the period of the reparative, regenerative or restitution reactions. In the defense reactions various types of specific processes come into play to combat the infection, phenomena which are altogether wanting in the restitution reactions or are present only to a negligible degree. But even in conditions in which the specificity of the defensive processes is not so marked, e.g., in tubercle, sporotrichoma, leproma, etc., careful analysis of the entire morbid process reveals the true character of the reaction. All reactions which are directed against exogenous noxa should be designated as defensive, and all reactions to endogenous damage arising from the body cells should be termed reparative, whereas the term regenerative reactions should be employed in discussing the processes involved in the simple replacement of lost tissue. In the absence of material alteration in the cellular structures, the term recreative reaction is the appropriate one. It must be admitted, however, that the reparative and regenerative reactions are often difficult to distinguish because the one frequently merges into the other. On the other hand, the two types of endogenous reaction much more commonly remain distinct

from the exogenous defense reactions. For this reason we proposed to unite the former under the single designation *restitution reactions* as opposed to the *defense reactions*.

Unfortunately the reactions of the diseased organism almost never lead to complete *restitutio ad integram*. Naturally this is most easily accomplished in the least damaging affections, the functional ones. Nevertheless, even the slightest change in the organism leaves behind some permanent change in the organism which may be easy or may be extremely difficult to recognize. This is particularly true of the infectious processes. Although a certain number develop a sort of immunity against the disease in question, it is not known whether it is gained at the cost of diminished resistance in another direction. But of far greater importance is the fact that if such protection develops at all, it persists only for a limited period in the great majority of cases, and often enough the organism is reinfected over and over again by the same infectious agent. The various organs involved in the disease process are left with permanent anatomical changes which result in a diminution of the powers of adaptation of the corresponding organ or tissue. This is well illustrated by the endocardial changes following rheumatic fever, the kidneys following nephritis, the brain following encephalitis and the lungs and pleura following pneumopleuritis. Every undue strain imposed on the previously diseased organ can lead to renewed functional disturbances, so that one might speak of a disposition toward repeated injury. Every disease leaves behind a pathological condition; every *nosos* has as its consequence a *pathos*, however slight. The permanent change resulting from the disease process affects in turn the various vital functions to a varied degree. Thus depending on the type of pathological process, we are confronted with developmental disturbances, e.g., the stunted growth of the extremities following acute anterior poliomyelitis, metabolic disorders, e.g., diabetes following inflammatory diseases of the pancreas, or circulatory disturbances following endocarditis. We designate those pathological states which follow in the wake of a particular disease as indirectly acquired ailments, as opposed to those arising directly without discernible reaction from external causes.

Thus we obtain a general view of the various types of affections involving the most important vital functions, their character depending upon the point of attack of the pathogenic agent, and of the various reactions of the human organism, the type of which is in turn determined by the nature of the disease factor. General pathology is nothing more than the study of the morbid affections and of the reactions instituted by the organism to maintain or restore health. It may surprise you that in this classification of the scope of general pathology no place has been set aside for the chapter on *inflammation*. A great controversy concerning the latter has arisen in Germany and I feel constrained to present to you the salient facts. Considering that so much space is devoted to inflammation in all textbooks of pathology, it must surprise many that such distinguished pathologists as Andral, Thoma and Ricker advocate that the concept of inflammation be struck from its pages. The well-known hematologist Naegeli once expressed himself as follows: "It is a sure indication of the undeveloped state of a science if the logical concepts with which it deals are not fixed, when multiple meanings are assigned to the same term." In my opinion this statement justly applies to our own field of knowledge with respect to inflammation. We too, assign to it a variety of meanings, and as a result controversy arises. The term inflammation (phlogos) was coined more than 2000 years ago to indicate nothing more than a clinical symptom-complex. Wherever the symptom-complex of a *rubor*, *tumor*, *calor* and *dolor* was found, it was permissible to speak of inflammation. But not if one or particularly several symptoms of the complex were wanting. How has the concept of inflammation altered since that time? With the resumption of anatomical methods of investigation and especially with the initiation of histological methods, the clinical symptom-complex was gradually replaced by a morphological one. Inasmuch as the two most important clinical criteria of inflammation, *rubor* and *calor*, and especially the relatively unimportant symptom *dolor*, were no longer present in the corpse, the histologist could study only the inflammatory *tumor*. In the last century controversy raged concerning the latter and the conditions of its develop-

ment. The phenomena of the inflammatory circulatory disturbances as such were too much neglected even where it was possible to study them in the living animal. Nowadays we regard the problem of the genesis of the inflammatory tumor as essentially solved. We know that together with the fluid exudation the cellular accumulations play the chief rôle and that among the latter we can differentiate better than previously the hematogenous wandering cells, including the leucocytes and lymphocytes, from the histiocytic wandering cells, the histiocytes, the fibroblasts and the angioblasts. We know that depending upon the type of infectious agent these various cells can participate in diversified form in the development of the inflammatory tumor. Inasmuch as the *alteration in the vascular system*, the exudation and emigration generally occupy the most prominent position in all these processes, a few authors believed that this phenomenon was the only suitable criterion of the inflammatory reaction. They asserted that it was not permissible to speak of inflammation in the absence of leucocytic emigration. Thus the conception of inflammation, or rather the symptom-complex of inflammation, was arbitrarily restricted.

On the other hand, many authors regarded the demonstration of active cellular proliferation, e.g., in tubercle formation, as sufficient evidence for the presence of inflammation, although there can be no question here of any well-marked hyperemia or heat production. Indeed we have become accustomed to speak of "cold abscess" in which the most important clinical criterion of inflammation, heat, is absent. It is thus clear that morphological criteria by no means coincide with the clinical ones. As a result the definition of inflammation has become very uncertain. This uncertainty and indefiniteness has become more pronounced with the increasing prominence accorded to the microparasitic causes of the infectious diseases. Inasmuch as the clinical inflammatory phenomena *rubor*, *calor*, *tumor* and *dolor* on the one hand, and *exudatio*, *emigratio* and *proliferatio* on the other, appear in full-blown form in the infectious diseases, at least in the majority of the latter, clinicians and especially surgeons and gynecologists become accustomed

to define inflammatory diseases as infectious diseases, i.e., to identify inflammatory reactions with reactions against infection. It is obvious therefore that the surgeon and the gynecologist recognize only an infectious peritonitis following aseptic laparotomy. When they inquire of the pathological anatomist whether signs of peritonitis were found at autopsy, they refer to signs of infection. The pathologist, however, who studies the histological criteria, namely exudation, emigration and proliferation, and not the etiology, must admit that every abdominal operation and every surgical wound incision, however aseptically performed, shows signs of inflammation. It is not infection, however, but trauma which has provoked the reaction observed by the pathologist. These reactions, though reparative, show pictures of hyperemia, emigration and proliferation which are very similar to those seen in defensive reactions. The histological findings in the skin about the wound and in the peritoneum necessitate the diagnosis of dermatitis and peritonitis, respectively. But these lesions are not necessarily of infectious origin. They may represent merely reparative reactions due to trauma. Similar considerations apply to the inflammatory processes of the knee-joint. There too it is possible to have traumatic inflammation in addition to that caused by infection, the former showing the same *clinical* signs of inflammation as the latter. Similar illustrations are offered by the brain. In addition to typical abscess formation we recognize atherosclerotic and traumatic foci of softening about which are found reactions of lesser degree but similar in character to those in brain abscess. But the neurologist is just as reluctant to speak of encephalitis or myelitis in the absence of infection as the surgeon or gynecologist is to regard non-infectious reactions of the peritoneum as peritonitis. Similarly, no clinician is willing to designate the organization in a renal infarct as nephritis, although the same morphological signs of inflammation are present.

How can we reconcile these contradictory views? In my opinion there are but two ways. The one is to discard completely the inflammatory concept and speak only of regenerative, reparative and defensive reactions. But the term

inflammation is too well established to be eliminated for the present from the physician's vocabulary. If the term is retained, it should be defined neither by the clinical nor the morphological criteria because there are too many contradictions between them. We must seek a clearer definition in order to reach an agreement between the clinician and the morphologist. This is possible only if we choose in place of the purely descriptive definition one which takes into account the significance of the entire process to the organism. I have designated this definition as the *functional definition*. If the question is now asked what inflammation signifies, it is evident from the choice of the word "inflammation" that the ancients understood by it a special type of excitation and agitation. The term inflammation signifies in a word a state of excitation of the organism. Inasmuch as all reactions, or at least those which are precipitated by material injury, represent a state of excitation of the organism, all materially produced states of excitability may be designated as inflammatory reactions, i.e., inflammation may be identified with a state of reactivity. We would then have to distinguish between regenerative, reparative and defensive inflammation, depending on the exciting cause or the functional effect, which comes to the same thing. According to this nomenclature, the process of regeneration with active cellular proliferation following the section of a nerve would be termed regenerative neuritis, the organization of a renal infarct and the resorptive phenomena following softening of the brain would be designated reparative nephritis and encephalitis, respectively, and the suppuration of the bone marrow resulting from a staphylococcus infection, defensive osteomyelitis. At any rate, by the addition of the appropriate adjective the clinician can recognize at once what type of inflammatory reaction is meant. Thus the physician will know when he inquires concerning the abdominal operation that a reparative-regenerative peritonitis was found and not a defensive peritonitis.

The objection might be raised, however, that the reactive processes in regeneration and repair seldom reach the degree of intensity commonly found in the defensive reactions, and that for this reason the extension of the concept of inflam-

mation to include reparative and regenerative reactions is unjustified. To a certain extent this objection is valid. It is true that the clinical phenomena of inflammation are best developed in the defensive processes. The clinician can continue to employ the term inflammation as a convenient designation for that type of reaction which results from infection, i.e., the defensive reaction. I believe that we can all agree on this point. We must bear in mind, however, that the defense reactions do not always present the classical histological picture of functional hyperemia, exudation, emigration and proliferation. We must remember that the term inflammation only signifies a reaction of special intensity. Inasmuch as this degree of reactive intensity is attained with great frequency and in fact almost regularly in the defense reactions, it appears quite feasible to identify in customary language the inflammatory reactions with the defensive reactions.

We must not forget, however, that under certain circumstances the reparative and regenerative reactions may become sufficiently well marked to present all the characteristic morphological and even clinical signs of inflammation, e.g., in traumatic joint affections or in severe fractures. In such cases too we are justified in speaking of inflammation, but to avoid misunderstanding we should speak of a reparative arthritis or reparative osteoperiostitis so that the clinician knows that we do not refer to defense reactions caused by infection.

From the above remarks it is evident that we must express ourselves more clearly in scientific discussions concerning the inflammatory or non-inflammatory nature of a particular affection, for *inflammation is only a concept of intensity*. In discussing the inflammatory or non-inflammatory character of a given process we are interested less in the intensity attained by the latter than in its character, its significance and its functions. We wish to know whether the process is defensive or regenerative-reparative. This we can decide as a rule from a knowledge of the causative factor, the infection or trauma. Where the etiological factor is unknown and the clinical picture and anamnesis offers no help, the decision cannot be made or we can only suspect the true character

of the reaction and assume that if the process has reached a certain degree of intensity the reaction is defensive in character. I believe these functional considerations of the events in question may permit us to settle the old and ever-recurring controversy concerning the concept of inflammation. In the course of the centuries the formulation of questions concerning inflammation has changed, and likewise the answers. We no longer inquire whether a given process is inflammatory or not, but what its significance to the organism is. In this way we have included the concept of inflammation with the functional consideration of all pathological processes. We see that there are five principal groups of functional injuries and four main groups of functional reactions. It is possible to describe all the known pathological processes in terms of these factors.

It would be desirable to sketch rapidly these nine principal chapters of general pathology to obtain a general view of the essential content of this realm of knowledge. But space is too limited and it is necessary to consider a few more definitions to which too varied meanings are ascribed, frequently leading to error. These definitions pertain to the subject of affections (*affectiones*).

The disorders of form, energy exchange, circulation and nervous conduction require no special discussion. A few words must be said, however, concerning the metabolic disturbances which we shall discuss more fully in succeeding lectures. Such expressions as passive processes, regressive nutritive disturbances and degeneration are still employed in discussions of metabolic disorders. Since I am of the opinion that the term degeneration, e.g., as employed in the study of fatty changes, has lead to great error, I deem it necessary to elucidate certain of the concepts before discussing the metabolic disturbances in greater detail. It is to be noted that many of the terms employed originate in departments of study in which the vital processes and their essential vital stimuli are regarded from an altogether different viewpoint from that of the pathologist or clinician. From a physiological standpoint we can classify the vital stimuli into three large groups.

TABLE II

TYPES OF STIMULI

I. Physiological, adequate stimuli
   1. Immediate (actual) stimuli = functional stimuli = investigative field of physiologist
      Potential and kinetic energy—*actio et passio*
   2. Periodic stimuli = nutritive stimuli = investigative field of physiological chemist
      Metabolism—*assimilatio-dissimilatio*
   3. Continuous stimuli = formative stimuli = investigative field of anatomist
      Growth—*progressio-regressio*
      Development—*evolutio-degeneratio*
II. Pathological, inadequate stimuli = disease producing stimuli = investigative field of pathologist
   Health-disease—*affectio-reactio*

First, there are the *actual or functional stimuli* which are studied mainly by the physiologist. He devotes his attention to the conversion of potential energy into the kinetic form. A stimulus provokes activity, i.e., an action, or as the physiologist is wont to say, a reaction. The latter term, however, is used in an altogether different sense from that employed by the pathologist. A reacting organ is an active organ as opposed to a resting or passive one. It would avoid much confusion if the physiologist spoke of actions instead of reactions and the pathologist of affections and reactions, avoiding the terms active and passive.

A second group of stimuli comprises the *periodic or nutritive stimuli.* These concern mainly the physiological chemist. He deals with the chemical and colloid-chemical problems of metabolism. The vital processes have only a negative or positive value for him. He recognizes assimilation and dissimilation, hydration and syneresis. He does not employ the terms active and passive. In so far as he is also a physiologist he knows that "actions" are linked essentially with dissimilative processes; therefore the function effects a nutritive stimulus in that it acts indirectly by assimilation.

The third group consists of the *continuous* or *formative stimuli.* These comprise the investigative field of the morphologist. The involution and solution of living tissue

represent the catabiotic or regressive processes, and their converse, the building up of new tissue, represents the bioplastic or progressive processes. Inasmuch as the growth of new tissue cannot take place without an increased supply of nutritive substances and the increased metabolic processes cannot proceed without increased functional stimulation from without, it is clear that functional, nutritive and formative stimuli are very closely interrelated. The pathologist does not deal primarily with any of these groups of stimuli. His chief interest is not in the active or passive state, assimilation and dissimilation, building up or breaking down of living tissue, but in the question whether the given process is healthy or unhealthy for the organism—whether it insures or endangers its biological existence. He investigates the vital stimuli from the point of view of whether they maintain or impair the health of the organism. He speaks, therefore, of adequate and inadequate stimuli and he also designates the *latter as effective* stimuli because they give rise to affections in the organism. The pathologist in considering the diseased organism deals above all with *affections* and *reactions*. It is fundamentally false to employ terms for the pathological processes which arise from fields of study in which the viewpoint is different from that of the pathologist. For this reason we should avoid speaking of regressive or passive nutritive disorders because such terms are misleading when applied to the conditions in the sick organism. It is true that there may be regressive phenomena, i.e., involutions of the Wolffian body, the thymus, the female gonads, belonging to the category of the physiological, the useful and the healthy. The term "degeneration" is similarly inappropriate. This term is also taken from a field of study in which a different viewpoint is taken, and signifies nothing more than diminished worth. Virchow, too, at first employed it in this purely functional sense of diminished worth. But as Virchow gradually carried over the term into the field of morphology, it finally developed a morphological significance so that ultimately almost all of the metabolic disorders were included among the "degenerative" process. It was believed that the protoplasm and cells or remaining tissue components were transformed by a process of gradual

disintegration, i.e., so-called metamorphosis, into the chemical substances in question, e.g., fat, glycogen.

In this sense the terms "fatty degeneration," "glycogen degeneration" and "amyloid degeneration" were used, and it was the general opinion that all these substances arose by a transformation of protoplasmic structures. The studies of the last decade have taught us, however, that this conception is false, at any rate one-sided, and that a protoplasmic metamorphosis plays no part at all in the majority of so-called degenerative processes. For this reason it appears more accurate to eliminate this term from the descriptions of metabolic disorders. It is sufficient for all purposes to speak of metabolic disturbances, dystrophies, pathological fat content, pathological glycogen content, etc. These terms, however, give no indication of the manner by which these affections arise. In another chapter we shall see that this point of view will lead us to a clearer understanding of pathological fat metabolism, which is still incorrectly spoken of as fatty degeneration.

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IV

PATHOLOGICAL FATTY CHANGES[1]

If at the present time we are to consider the question of pathological fat deposits we must first determine what is to be included under the term fat. The Greek word *lipos* includes all of the vegetable oils, for which reason the term is now restricted to neutral fats and other saponifiable substances. We also know that in addition to the lipoid substances present in both animals and man, there are other fat-like or lipoid substances which do not belong to the group of neutral fats. The term lipoid was first proposed by Kletzinsky, ("Biochemie," Wien, 1858) to the not easily saponifiable extractives of the cell which were soluble in boiling alcohol and ether, and latterly Overton has again used the term in the same sense. The term lipoid was more strictly defined by Bang to include all lipoids in such a combination that they are soluble in organic solvents such as ether, alcohol, chloroform, benzine, etc.

The lipoids of the human body may be grouped into four categories. The *first group*, the so-called phosphatides, is characterized by the presence of nitrogen and phosphorus. In this group there are:

(*a*) The monophosphatides or the so-called lecithins. The latter are glycero-phosphoric acid esters of two fatty acids with cholin (Trimethylaethylenhydrinammoniumhydrate). The acid lecithins are also called myelins.

(*b*) The monoamidodiphosphatides, the so-called cephalins, which contain another base besides cholin.

(*c*) The diamidomonophosphatides, the so-called sphingomyelins.

The *second group* comprises P-free and N-containing substances, the so-called cerebrosides. They contain galactose.

[1] Lane Lecture.

A mixture of lecithin and cerebrosin may also be called *Protagon*.

To the *third group* belong the P- and N-free substances, among which we find:

Cholesterin,

The fatty acids (oleic, palmitic, stearic),

Cholesterin fats, combinations of the fatty acids with cholesterin,

Neutral fats, combinations of fatty acid and glycerin, and soaps (that is, the sodium, potassium and calcium compounds of the fatty acids).

The last or *fourth group* comprises the so-called lipochromes and other fat-containing pigments, for example lipofuscine. Inasmuch as they play no important rôle in fat metabolism and their chemical nature has not been sufficiently investigated, we will not consider them.

From this tabulation it is evident that the fatty substances of the human organism are chemical bodies varying greatly in character, the nature of which has been accurately determined only within the past decade. It is readily understood therefore that such terms as myelin and protagon, so frequently found in the earlier literature, are disappearing more and more, for these names for certain mixtures of fatty substances were arrived at as a result of external or accidental characteristics. It must be our endeavor, therefore, to substitute for these obscure ones, terms which express as clearly as possible the type of fatty deposit encountered. This would be simple if the various fatty substances occurred in the human or animal organism in pure form. Unfortunately, this is the case with only a few; most of them are so complex that a careful chemical analysis is necessary in order to establish their composition. Nevertheless various large groups of fatty substances can be distinguished from one another by their macroscopic and microscopic appearances.

One is accustomed, therefore, to recognize the following main groups of lipoid bodies:

1. Lipoids (in the strict sense). Here we place the nitrogenous phosphatides, those containing phosphorus, and also the cerebrosides in their various forms. The collective term "lipoids in the strict sense" appears justified because these

substances are practically never found pure, but almost always in combination with others of their own group or with bodies belonging to other groups. The term phosphatides is often used to designate this group, because the phosphatides represent the main mass of the lipoids in the strict sense. In cases in which the products of fatty deposit are primarily lipoids, one speaks of lipoid degeneration or liposteatosis (*lipoidosis*).

2. The cholesterin esters or cholesterin fats. Fatty deposit of this type is called cholesterinsteatosis or *steatosis*.

3. The glycerin esters or neutral fats. This process is called glycerinsteatosis or *liposis*.

The differentiation just described can, however, especially as regards the three main groups of fats, be achieved only with difficulty by the unaided eye. To make the diagnosis certain, microchemical methods must be resorted to. These morphological methods were originally very primitive and were confined either to the demonstration of the solubility of the substance in alcohol, ether, chloroform, etc., or to its resistance to weak acids or alkalies (acetic acid, potassium hydroxide). We all know that the usual fixing and embedding methods with alcohol, chloroform, celloidin and paraffin do not preserve the fats. We find in place of the fat only hollow structures which no longer contain fat, because it has been dissolved. Thus further differentiation is impossible. The tests with acids and alkalies are equally unsatisfactory and do not tell us anything about the exact character of the fat under consideration. In order to analyze the various fats of the body, other methods are necessary. Of these we must mention first of all, the polarization microscope. It was a German physician, Mettenheimer, who was the first to call attention to the peculiar double refraction of certain fatty substances, then still called myelins. That was in 1858. Even then F. W. Beneke, professor of pathology at Marburg, presumed that these substances were cholesterin compounds. This versatile pathologist, the founder of constitutional pathology, whose centenary we are to celebrate this year, was the first research worker to point out the great importance of cholesterin in the animal organism. But his and Mettenheimer's observations sank into oblivion.

It was not until the rediscovery of the double refracting myelins by Kaiserling and Orgler that renewed chemical research of these substances was undertaken. After physicists, especially Lehmann, had pointed out double refraction as the characteristic property of fluid crystals and that certain cholesterin compounds formed fluid or so-called sphaero-crystals, the idea of producing cholesterin compounds artificially and comparing them with the double-refracting fat bodies of the body, was brought forward. Adami and I succeeded in ascertaining that certain cholesterin esters, among them such as occur in the animal organism, were actually like the so-called myelins in all their physical and staining properties; or speaking inversely, that an entire definite group of fats were not neutral fats but cholesterin fats. Besides optical methods, other more modern chemical and physical procedures for the differentiation of fats were brought into play. Today the methods for differentiating fats are almost innumerable. To describe all of them would only lead to confusion. I shall therefore confine myself to mentioning the most important ones as tabulated above. I must preface further remarks by stating that we use the term "myelinformation" in reference to the ability to swell, so clearly possessed by fatty substances, and to their tendency to form so-called myelin figures. We all know these figures from our experience with brain softening, in which the medullary sheaths or myelin sheaths swell up into peculiar double-contoured, sausage-like, clubbed, or other bizarre forms.

If we take up the four previously mentioned main groups of fatty substances, and examine them according to their physical and staining properties, the following characteristic differences are manifest:

(*a*) The phosphatides show positive myelin formation, and in part, double refraction. With sudan they stain a yellow red; with Nile blue a dark blue; and with natural red, they become reddish.

(*b*) Cholesterin fats show no myelin formation, but marked double refraction. They stain yellowish red with sudan, red with Nile blue, and not at all with neutral red.

(*c*) Glycerin fats show neither myelin formation nor double refraction. They stain a bright red with sudan, with Nile blue reddish, and with neutral red not at all.

(*d*) Fatty acids do not form myelin and are crystalline. With sudan they become yellow, with Nile blue, blue, and with neutral red, red.

(*e*) Soaps swell up, are as a rule crystalline, are yellow with sudan, blue with Nile blue, and red with neutral red.

(*f*) Cholesterin does not swell up and shows definite table-formed crystals with broken corners, which take on a blue violet color with iodine and sulphuric acid.

I would add to this that the common sodium and calcium soaps formed by the breaking down of peripancreatic fat or otherwise, can with calcium salicylate be converted into calcium soaps, which are not soluble. When treated with copper sulphate, these calcium soaps become copper salts of fatty acids, which when stained in the usual way with hematoxylin stand out very clearly in the preparation. Inasmuch as the sodium calcium soaps are soluble with relative ease, one can distinguish them by their solubility from the pure fatty acids, of which only the insoluble crystallize out.

Having thus obtained a general idea of the macroscopic and microscopic behavior of the various forms of fat, we will take up the question of where they occur physiologically and how they present themselves in the microscopic picture (on the microscopic slide).

The phosphatides are found primarily in the brain, and also to a great extent in the cortex of the adrenals. They are as well, an important constituent of the fatty substances found in the organs of internal secretion (thyroid, hypophysis, corpus luteum, ovary, interstitial cells of the testicles, thymus).

Cholesterin fats occur principally in the cortex of the adrenals; also in the glands of internal secretion, in the epithelium of the gall-bladder, into which they are probably absorbed from the bile.

The glycerin fats form the main bulk of the fatty tissues of the body, make up the so-called stable fat, such as occurs also in cartilage, and the unstable fat of the liver cells, which

is intended for combustion. Mixed with cholesterin fats we find them in the mammary glands; in the sebaceous glands they are mixed with lipoids.

Fatty acids and soaps are found in the normal intestinal contents.

Cholesterin occasionally crystallizes out in bile, in the feces, and in the sebaceous matter of the skin.

When the various types of fat do not occur as plate-like or needle-like crystals, as do cholesterin and the fatty acids, they appear usually as droplets. Even physiologically we are able to distinguish fat consisting of fine droplets, as for instance, in the adrenals, where after extraction of the fat the cells appear as a fine alveolar structure, of medium-sized droplets in the liver cells, and of large droplets in fatty tissue where the entire cell body is taken up by one drop of fat.

We now turn to the question as to how these droplets are produced within the cell. From the well-known researches of von Recklinghausen, Arnold and others, we must conclude that the cells have the ability to build up the different fats from substances brought to them in the blood and body fluids. That ability rests undoubtedly on the aid of intracellular ferments. Just as there are fat-splitting enzymes, so there may be enzymes reversible in their reaction, capable of synthetizing fats. A much more difficult question to answer is, where these ferments are localized within the cell. After the work of Arnold and Altman, one becomes convinced more and more that the so-called chondriosomes play a part in building up the fat droplets; at any rate there can be no doubt that when fat first becomes visible it is in the form of very fine droplets, which we also call microsomes or liposomes. Whether these really correspond to the chondriosomes is another question. Today one inclines to the view that the building up of fat within the cell is a more diffuse process. The formation of finer and coarser droplets, one looks upon as secondary condensation processes. The more lipoids formed in a cell, the coarser the droplets, until finally from the confluence of droplets a large drop is produced. Naturally the type of lipoid on the one hand and the consistency of the surrounding protoplasm on the other, have an influence on the process. From these remarks, we see that the physio-

logical presence of fat in the cell is looked upon as a storing-up process. Of course this view is not an old one and is very closely connected with the theory of pathological fatty processes. The latter we must now take up in detail.

Pathological fatty changes, which even today are still called fatty degeneration, form one of the most important and one of the most discussed chapters of general pathology. As early as Virchow's time, it was definitely stated by Virchow, who really was the first to study the subject more thoroughly, that the fats occurring in the cells could be derived from various sources:

1. Forced into the cell from without (infiltration).
2. Pre-existing in the cell and set free by some process at present not understood.
3. Formed through metamorphosis.

Virchow was of the opinion that with a true infiltration as observed physiologically in fat and liver cells, the formation of large droplets was characteristic and that pathological fat deposits were characterized by small droplets. On this basis he denied the pathological character of a fatty infiltration. Today, however, we know that this view is incorrect, for small drop physiological fat deposits also occur, as, for example, in the adrenal, where alterations of the protoplasm are not in question and where we can experimentally demonstrate that the fat content of the cell is the same as the fat content of the surrounding tissue juices, a proof that the process is one of infiltration. Since Virchow could not see his way clear to accept infiltration as pathological, he attempted to explain pathological fat formation in two ways. He believed that there were in the protoplasm of the cell fat-like substances, such as fatty acids and soaps, which were in combination with the proteins and which in disease of the protoplasm might be set free. This, however, was not sufficient to explain the volume which fat deposits at times assumed; and to cover this he offered the explanation of a metamorphosis or transformation, the latter in his opinion being the chief source of all pathological fat deposits. That fats might be formed from proteins and carbohydrates was at that time unknown.

Virchow's free use of the term fatty degeneration so as to include not only fatty metamorphosis but also fatty destructive processes in the cell, as well as functional substitution, as, for example, the ingrowth of areolar tissue into the musculature of the heart, has led to confusion. A clear terminology is necessary for clear understanding, for which reason I would suggest the following:

1. Fatty *infiltration*, under which I would place the storage of fat within the cell following the supply of the fats themselves or their component parts. The formation of fat occurs, then, through the action of the ferments. Infiltration can only occur as long as the cell is alive.

2. Fatty *decomposition*. Under this term I would include those processes in which there is a destruction of the protoplasm of the cell, particularly of the lipoid containing chromatin, whereby fatty substances become visible.

3. Fatty *transformation*, under which I would include the transformation of the carbohydrate or protein reserve of the cells into fats.

Which of these three possibilities plays the most important rôle in pathological changes? It is interesting to observe that as morphological and chemical studies become more and more exact, the drift of opinion is more and more to the importance of fatty infiltration and less to the other two possibilities; in other words, directly the opposite of the opinion held by Virchow. This change is comprehensible since in contradistinction to the earlier view of Virchow the physiological chemist denied the possibility of transformation of protein or carbohydrates into fat. Up to fifteen years ago it could be asserted that fatty deposits were explainable, most often on a basis of infiltration, less often as decomposition processes and never as transformation processes. This viewpoint has not been altered even at the present time. In a majority of pathological fat deposits the mechanism is so similar to physiological processes, that infiltration must be accepted. This opinion is reinforced by physiochemical examinations which show, for example, in dogs fed with mutton fat, and then poisoned with phosphorus, that the liver fat is derived from the ingested mutton fat. The liver cell must therefore have been fed from without. Fat decom-

position occurs only in dead or dying tissue and arises because of decomposition of the complex lipoids, that is, the phosphatides, which are derived from the nuclear substance. Because these substances show their derivation by their tendency to form myelin figures, one also speaks of this type of decomposition as *myelinosis*.

What is the mechanism of fat transformation? Though it has previously been denied, the more recent work in physiological chemistry by Neuberg and Knoop has shown that proteins and carbohydrates may be used to synthesize fats. The change is aided by the condensation of the lower fatty acids (so-called aldol condensation). This condensation commences with pyroracemic and oxbutyric acids, both of which are decomposition products of the carbohydrates and proteins. Since the possibility of the synthesis of fat from carbohydrates and proteins within the organism has been shown, we must see how far this occurs in experimental investigation. Shortly before the late war, an article by Gross and Vorpahl appeared, coming from the clinic of Morawitz. The authors asserted that they had discovered proof of a fatty transformation. They perfused the living kidney in living condition with Ringer's solution and during this manipulation demonstrated the formation of fat droplets in the kidney epithelium morphologically. In addition a chemical increase in the lipoids present was also demonstrable. Since these changes could not be attributed to fatty decomposition of dying cells, the only explanation possible was a new formation of fat derived from the protein and carbohydrates of the kidney epithelium. These investigators believed that their experiments furnished proof of the occurrence of fat transformation, particularly since the addition of glycerin to the Ringer's solution increased the fat formation. Their results were so surprising and so contrary to previous knowledge that they necessitated confirmation, and a repetition of the experiments was undertaken by Dr. Maurice Goldberg of New York. He showed that the results obtained by the previous investigators were not correct, a fallacy being introduced in making their fat determinations on dried tissue. Long washing with Ringer's solution containing glycerin resulted in the solution and removal of all sorts of

soluble substances, which loss invalidated the value of the subsequent computations. The increase noted was therefore apparent, not actual. The *weight of the fresh tissue* must be considered, and if we consider it, there is not a gain, but a loss in the weight of lipoid substances.

Histological examination of the perfused kidney by Gross and Vorpahl also seemed to indicate a new formation of fat; upon reexamination, however, this conclusion was shown to be in error. We have repeated their work; and while it is true that the lipoids which are present become more visible, we have not been able to demonstrate that they increase. Of particular interest are the *in vitro* culture experiments of Goldberg. He planted rabbit kidney epithelium in plasma and in Ringer's solution and found that both transplants showed fat formation at the periphery of the cells more plainly visible in the plasma plants than in the plants placed in Ringer's solution. In the tissue placed in Ringer's solution, it was found that the fat formation always commenced a little distance from the cell wall, the extreme periphery of the cell showing commencing destruction. One must therefore conclude that the observed change was also an infiltration process in which the lipoids are derived either from the plasma or from the zone of protoplasmic destruction. Neither by chemical nor histological examination is there any definite proof that new fat formation occurs under the conditions just stated.

It appears therefore that even if fat transformation actually does occur in the pathological processes of man, it must play a very minor rôle. Since fatty decomposition is either post-mortem or necrobiotic in origin, we have to consider that pathological fat deposits can only occur in consequence of fatty infiltration which has its origin in the surrounding cell juices. Therefore in the human organism fatty deposits, whether pathological or physiological, occur in the same manner.

If this is kept in mind we can consider how these deposits of fat are best grouped.

I would like to point out in advance that fat deposits are called steatoses and are subdivided into cholesterinsteatosis, glycerinsteatosis, or phosphatidesteatosis, according to the

type of fat present. (It should not be forgotten that these three forms are also known under other names: the phosphatides group are also termed lipoidose, the glycerin group lipose, the term steatosis being reserved exclusively for those of the cholesterin group. When I speak of the different types of steatosis I mean the glycerinsteatosis or lipose, though the same statements are also applicable to those derived from cholesterinsteatosis and to a slight extent to one rare type, lipoidsteatosis. The following scheme applies therefore directly to the glycerin ester steatosis; if others come into the discussion I shall mention them specifically.)

I deem it of some use to divide the pathological steatoses in two chief groups, each of which may be subdivided as follows:

I. The cellular steatoses. . (collections of fat in the cell protoplasm)
- 1. Extracellular origin:
  - (*a*) Steatosis saginativa.
  - (*b*) Steatosis dyscrasia.
  - (*c*) Steatosis transportativa.
  - (*d*) Steatosis resorptiva.
  - (*e*) Steatosis retentiva.
- 2. Intracellular origin:
  - (*a*) Steatosis progressiva.
  - (*b*) Steatosis regressiva.

II. The interstitial steatoses (fat deposits occurring in intercellular substance)

I. The first group can be subdivided into two classes: (1) those where the fat deposits are due to excessive amounts of fat, arising from any cause, being forced upon the cell from without, and (2) those where the cell cannot metabolize the normal amount of fat brought to it.

(*a*) The first group of this fat deposit is obesity (*steatosis saginativa*).

We may speak of a general obesity as it is observed in the capon, and in man when the individual eats too much and is muscularly inactive. If the food be unusually rich in cholesterin, there is not alone a glycerinsteatosis, but also a cholesterinsteatosis. In animals a cholesterinsteatosis can be induced by the administration of cholesterin and choles-

terin esters. The cholesterin is dissolved in oil and oral administration has been found to be the most effective; intraperitoneal and subcutaneous injections less so. Latterly, Dr. Benjamin Sacks of Mount Sinai Hospital, New York, as had Dewey before him, prepared a very finely suspended emulsion of cholesterin which can be administered intravenously in animals. His experiments have shown that the cholesterin is deposited in the reticulo-endothelial system; in other words, cholesterin is deposited in a different location than are the glycerin esters, showing that there is a difference in the metabolism of the two substances. The cholesterin deposits of the cells of the reticulo-endothelial system are in closest relation to the cholesterin esters of the blood and body juices. In addition to general obesity, there is also a local obesity. Wherever an exceptional blood supply develops, local fat deposits can be observed. As an example, we see in every long-continued defense reaction hyperemia, a deposition of fat in the inflamed region. The invading leucocytes of a defense reaction are also rich in fat and the characteristic yellow color of pus is due to the fat content. At the edge of an anemic infarct of the kidney, spleen or other organs we see adjacent to the hyperemia of the collateral circulation, an increasing fat deposit which invades the edge of the infarct. As a rule these deposits are glycerin esters, though as experience shows, in all long-continued reactive hyperemias, cholesterin esters are also present to a greater or less extent in the more richly nourished tissues. In previous years there was much discussion as to the origin of this deposit. Today we believe that the fat has its origin in the larger amounts of plasma which are brought to the part, following which a fatty infiltration occurs. The former opinion was that the fat was derived from a fatty decomposition of the infarcted tissue. The fact that these defensive and reparative fat deposits consist, not of lipoids but of neutral fats, speaks against a fatty decomposition as their origin, which, as has been stated, was the opinion in previous years. I was able to show through the work of Griesser that small pieces of kidney rendered fat-free by ether extraction and then placed in the peritoneal cavity of other animals, also showed fat deposits. In this instance the fat could not have been derived from the

implanted fragment but must have come from the surrounding parts; in other words, was an infiltration.

Many fat deposits are particularly rich in cholesterin esters. This is particularly true in the so-called chronic edema of the lung, Buehl's desquamative pneumonia. In this condition there must be a particular tendency of the alveolar epithelium to store the double-refractive lipoids, for even in the gross, the cut surface of the lung has a spotted yellow appearance, such as is found in chronic atelectatic edema with chronic pulmonary tuberculosis.

(*b*) A second type of fat deposit occurs because of metabolic or hormonal changes (*steatosis dyscrasia seu hormonalis*). As is well known, it occurs after ablation of the gonads and is then termed castration obesity. The obesity which follows disease of the posterior lobe of the pituitary gland is also well known. In these instances there is without doubt disturbance of hormone function.

In other instances the obesity is a more indirect effect of hormone disturbance. As it occurs in Basedow's disease and pancreatic diabetes, there is a marked increase of the lipoid content of the blood, so-called cholesteremia or cholesterinesteremia. It is not surprising that with this cholesteremia there occur abnormal fat deposits in the cortex of the adrenals and kidney, in the muscles, etc. In diabetes the cholesterinester infiltration of the stellate cells of Kupffer are especially characteristic, the liver cells themselves being free of fat. Here again is an instance of the affinity of the reticulo-endothelial system for cholesterin. In certain cases of diabetes, chronic jaundice and cirrhosis of the kidney we can have in addition to general increase of blood lipoids, also localized collections of cholesterin esters. Such localized deposits occur particularly in the skin as so-called xanthelasmata. In this lesion there is a lumpy thickening of the skin, characterized by a more or less yellow color, particularly on the extensor surfaces of the joints. Microscopically, the lesions consist of large cells containing a fine foam-like protoplasm. The foam-like character of the protoplasm is due to the deposition of minute droplets of doubly refracting lipoids, cholesterin esters. Since these cells simulate the cells of the true xanthomata, as seen about the eyelids, they are

termed pseudoxanthomata. They are, however, nothing more than wandering connective tissue cells (histiocytes) with a large amount of fat deposit.

(*c*) Another type of cellular fat deposit is that which follows transportation (*steatosis transportativa*). One example of this is a post-traumatic fat embolus which occurs particularly in the pulmonary capillaries. From previous investigations, particularly those of the younger Beneke, we know that the endothelium of the lung capillaries plays an active part in the reabsorption of the fat. A prettier demonstration is given by the fat-filled muscle fibers in the heart surrounding a capillary which has been closed by fat. The fat of the subcutaneous tissues can be mobilized in much larger masses by chemical action than by physical trauma, as is shown in phosphorus poisoning, acute yellow atrophy and after poisoning by certain mushrooms. It can be demonstrated in such cases that the fat found in the parenchymatous organs, chiefly in the liver, kidney and heart muscle, is not derived from these organs but is actually transported from the subcutaneous tissues. There are physicochemical investigations which substantiate this, but in my opinion they should be confirmed. I am not in a position to say whether or not this has been done by any American investigator either during or since the past war.

(*d*) The next question is that of the reabsorption fat deposits (*steatosis resorptiva*). This is an important process, particularly in liquefaction, for example, in the brain. Whereever brain or spinal-cord tissue *disintegrates*, the lipoids and simpler fats which have become free are taken up and stored by certain cells. This is particularly true of the glia cells which assume the power of ameboid motion, ingest the fat and become the so-called fat granule cells. Whenever we encounter such a fat granule cell in the nervous system of an adult we can be certain that there has been an antecedent destruction of nerve tissue. The exception is only in the newborn, in whom these fat granule cells are so frequent that for a long period they were viewed as physiological, being interpreted as an intermediary state in the myelinization of the nerve fibers. In the last ten years, however, this view has, in Germany, been vigorously opposed. The more recent opinion

is that such cells are pathological, for they are more frequently associated with recent or old hemorrhages or even extensive areas of softening. I believe that both opinions are correct. On the basis of personal investigations I must assert that in the more mature fetuses and in the newborn the process is physiological and has nothing to do with reabsorption processes, but is a phase of the development of nerve tissue. However, there are in every newly born child as soon as it has lived a few days, larger and smaller areas of softening, consequences of the trauma of birth. The frequency of these birth traumata is surprising. They occur as small hemorrhages and are most frequent in those portions of the brain over which the soft tissues are most swollen. The hemorrhages, which are purely mechanical, result in a softening of the brain substance with subsequent formation of fat granule cells. There is also a physiological fat granule cell formation in the newborn due to local fat deposits with subsequent reabsorption and the development of fat granule cells.

Extensive fat reabsorption also occurs in chronic suppuration. The fat and lipoids liberated by the destruction of the leucocytes are slowly reabsorbed out of the surrounding granulation tissue. For this reason it is in the most chronic type of suppuration, as for example, gonorrhea of the Fallopian tube, that we get the most extensive fat deposits in the pyogenic membrane. These deposits appear in the gross as sulphur-colored areas, and are exceptionally rich in the previously described pseudoxanthomatous cells. The deposit is a cholesterin steatosis. Similar infiltrations with a doubly refracting fat are present in chronic inflammatory processes of organs, particularly the kidney. Loehlein has pointed out that in chronic glomerular tubular nephritis, after the destruction of the fat-storing kidney epithelium, part of the fat is reabsorbed into and precipitated into the cells of the interstitial tissue.

(*e*) A final type of cellular fat deposit is that which follows retention (*steatosis retentiva*). This is particularly well illustrated in the liver in such instances as where the organism is no longer in a position completely to burn up liver fat. If one ascertains the iodine value of the fatty acids

in the different organs, as has been done by Beatson and Duncan, Hartley and Imbery, and Goldberg, it is found that the liver fat has an average index of 115–135, and subcutaneous fat tissue 1–62, approximately one-half that of the liver. There are certain wasting diseases, as for example, tuberculosis and neoplasms, where, in spite of marked loss of body weight, the liver is very fatty. In such instances one may speak of a cachectic fat deposit. As Goldberg has shown in tuberculosis, the more marked the fat deposit, the lower the iodine value of the fat until the iodine figure of subcutaneous fat is approached. We must conclude therefore that the liver fat is gradually used up and replaced by the transportation of subcutaneous fat, which however, cannot be burned, but remains behind in the liver. Similar retention fat deposits can be demonstrated in the adrenals in starvation; in this instance the fats are not glycerin fats but cholesterin fats.

With these remarks the chapter on fatty charge brought about by extracellular conditions is closed. There are a few words to be said on fatty changes produced by intracellular conditions. Here the reason for fat deposit is to be found not without the cell, but due to some change *within the cell* itself. In any event, the differentiation of fatty changes caused by extracellular or intracellular conditions cannot always be sharply drawn. We would differentiate the fatty changes produced by intracellular conditions as two types:

1. Progressive obesity (*steatosis progressiva*). A classical example is the inherited obesity, so-called idiopathic obesity. Possibly the obesity of pregnancy belongs in part to this group. Certain invasions of old organs by areolar tissue are also to be placed here.

2. Regressive fat deposits (*steatosis regressiva*), fat deposits occurring because of cell weakness. Here the cell, in consequence of some injury, has lost the power of burning up or further manipulating the absorbed fat. In necrobiotic processes, for example, in tumors, such fat deposits are not infrequent and are looked upon by certain authorities as degenerative fat deposits which, however, means something quite different from fatty degeneration and which should under no condition be confused with fatty degeneration.

With this I have said all there is to be said about fat deposits within the cell.

II. Let us now turn to a consideration of the second main group, namely, *interstitial* fat deposits. Is there really any such process? Until the beginning of the present century such a process was unknown; at least it was not described. Only in the present century has it claimed the increasing interest of the investigator. The classical instance of so-called interstitial fat deposit is the atheromatous fat deposit in the intima of the blood vessels. Microscopic examination shows that we have to do not so much with a fat deposit within the cell as with a deposition of the smallest fat droplets between the cells in the region of the intercellular substance, as was first demonstrated by Jores and Torhorst. Where do these fat droplets lie? Are they found in the fibrillae of the connective and elastic tissue or are they in the cement substance which binds the fibrils together? My own investigations lead me to believe that for the most part they occur as a precipitation in the ground substance in those locations where the cement substance is either more or less viscous than the surrounding areas. In such localities condensation and absorption processes occur more readily. It is noteworthy that only the cholesterin esters have an affinity for this tissue. There must be some physicochemical reason for this. The entire process is termed atheromatous fatty deposit; and at another time in the discussion of atherosclerosis I shall return to this question.

We have still to consider the *fate* of fat collections.

A portion of the fat leaves the body in physiological processes in the body fluids, as for example bile, milk, sebaceous secretion. Traces are also found in the urine, where upon occasion it gives rise to lipuria. The investigations of Anitschkow are of particular interest at this point, for he found that in rodents certain skin glands excrete neutral fats; others however, excrete cholesterin fats. After the administration and absorption of cholesterin the most marked changes are found in the liver where a marked fat deposit in the epithelium of the bile-ducts can be microscopically demonstrated.

Another portion of the fat is burned up in the body, and this is particularly true of liver fat. It can be shown that cholesterin fats intentionally introduced into the body, gradually disappear; how this occurs is still to be demonstrated.

Another portion of the fat, particularly such portions as follow the liberation of fat through protoplasmic destruction, are reabsorbed and used elsewhere in the body. When large masses of fat undergo necrosis, as in fat necrosis associated with pancreatic disease, the liberated glycerin, because of its easy solubility, is reabsorbed. The fatty acids crystallize out or unite to form soaps with sodium potassium or calcium. These soaps are particularly important in the destruction of atheromatous patches in blood-vessel walls. The fatty acids are transformed into fatty acid soaps, as Klotz has shown. The calcium fatty acid soaps are gradually changed to phosphoric acid calcium combinations and thus bring about the picture of calcification. There is no doubt in my mind that these fatty soaps take a more frequent intermediary part in the process of calcification than we have hitherto believed.

Though I have tried to present the picture of pathological fat deposits in a somewhat set form, I am aware that in nature there are no sharp borders, that there are all sorts of mixtures and overlappings of the various processes, and that one process may substitute for another, or through reversible processes, recede. I beg of you to consider the presentation as a scheme which is not final but which has been planned so as to stimulate further investigation.

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V

THE NORMAL AND PATHOLOGICAL MORPHOLOGY OF THE SUPRARENALS[1]

During the World War there appeared in Germany a morphological-physiological study on the suprarenal cortex by Max Landau, first assistant in the Freiburg Pathological Institute. He was a victim of the war, and did not himself live to see his work appear. This work, however, gives so important a summary of what we know today about the function of the suprarenal cortex that I feel myself in duty bound to report to you briefly on the contents of this and other works similarly directed. I confine myself to morphological work and only touch the physiological in so far as it concerns the suprarenal cortex, for the medulla of the suprarenal gland with its typical hormone epinephrin is sufficiently well known and surely has been discussed often enough in your circles.

One might believe that the *development, normal anatomy* and *histology* of the human suprarenal would have been sufficiently studied and known in view of the great interest which has been accorded this organ from the pharmacological and clinical sides. Unfortunately, this is only true to a certain extent. We know, to summarize briefly the whole, that in the lower vertebrates—the fishes—the interrenal organ growing from the epithelium of the coelom and the suprarenal organ growing from the anlage of the sympathetic are completely separated and remain apart. Only when we reach the amphibia does the union of the two anlagen begin, this being still more plain in reptiles and birds. Finally, in the mammalia the nervous suprarenal organ is placed completely within the cortical interrenal organ, forming the so-called medullary substance. The anlage of the cortex starts from the coelom epithelium as a closed epithelial body.

[1] Lane Lecture.

In man, beginning with the third month of embryonal life the sympathetic formative cells, the so-called sympathogonia, grow into the epithelial anlage and form the first anlage of the medullary substance, from which there first develop the phaeochromoblasts and later the phaeochromocytes. This inwandering of the sympathetic cells everywhere occurs from the surface toward the center of the cortical anlage. While these processes are common to all the higher mammalia, there occurs in man in the last months of embryonal life a further process of transformation, which is completely lacking in the closely related species of apes. This transformation consists in an especial formation of folds and a process of invagination, as the result of which a particular main fold, the so-called central fold which includes the central vein, and numerous similar and finer folds, are formed. On a cross section through the suprarenal, the cortex, therefore, appears invaginated deep into the interior in many places; especially, however, along the large central vein. We thus find even in the newborn, but better marked in the adult, that the central vein is almost entirely surrounded by cortical substances. One might speak of an external and internal cortex, between which the medullary substance is pushed. Landau has compared this peculiar folding process, characteristic of man only, with the infolding of the central nervous system. He believes that we may regard this formation of folds as being for the purpose of forming the largest possible surface of contact between the medulla and the cortex of the suprarenal. To what extent this conception is supported by other structural relations of the suprarenal will be seen later.

The *development* of the suprarenal which has just been described reaches its *maximum* just before the birth of the child. At this time the suprarenal still has a very impressive weight when compared to the kidney. It amounts to about one-third of that of the kidney. As is well known, this relation changes in the adult so strongly in favor of the kidney that the relation of the suprarenal to the kidney is 1:28. But this displacement does not take place solely through a varying difference in the speed of growth, as is the case with most of the other organs of the body, but rather suddenly

through a peculiar process of absorption of the cortex of the suprarenal (first described by Thoma and confirmed by Kern, Elliott, Pappenheimer and Lewis) which usually starts in immediately after birth and continues to the end of the second month of extrauterine life. As the result of this process of absorption, the originally very voluminous organ becomes so contracted that in infants of the age of several months the suprarenal is represented only by a very thin yellow-colored lamina on the upper pole of the kidney. How does this peculiar process of absorption take place, and what does it mean? As is shown by histological investigations of suprarenals of newborn infants who have died in the first days of life, there occurs during birth or immediately afterwards a tremendous hyperemia of the cortex of the suprarenal. This hyperemia of birth or of the newborn does not, however, involve equally the entire cortex of the suprarenal, but predominantly the middle and internal layers, while the external layer remains recognizable by its lesser hyperemia and darker coloring. In the next days and weeks there starts an increasing fatty change in the cortex. Here occurs, as was shown by Kawamura, an infiltration of particularly coarse drops of isotropic fats, while the most external layer of the cortex usually shows a finely granular fatty change. With this the nuclei of the cells containing coarse drops of fat are gradually destroyed by various degenerative phenomena. During these necrobiotic processes the inner layers assume, instead of the original perpendicular arrangement, an order which is parallel to that of the medullary substance of the kidney. In the course of some two months this necrobiotic fatty change leads to a more or less wide-spread disappearance of the inner layers of the entire suprarenal cortex, so that only the glomerular layer remains as a so-called layer of growth, from which there occurs a regeneration of the suprarenal cortex.

This process of *regeneration* is completed quite slowly and is finished only at the end of the second year of life. During this time the medullary substance has also markedly developed. The absorption layer lying between the two disappears gradually, and finally there exists a widespread contact between the medullary substance and the cortical substance,

which is all the greater because, as the two parts of the organ gradually grow into one another, islands of cortical tissue are isolated in the medullary substance. With this the organ is completely formed, but continues to grow parallel with the growth of the body. This period may be designated as the childhood period of suprarenal life. It represents the termination of the newborn period and a sort of reproduction of the fetal condition.

To these three periods—the fetal period, the newborn period and the childhood period—there is now added with the beginning of prepuberty a *new and more marked period of growth.* It is characterized by the obvious differentiation of the cortex and a peculiar storing of fat in this part. Through this process the growth of the suprarenal is so great that it becomes twice as heavy as the testicle, but later the relation is reversed so that the testicle is twice to three times as heavy as the suprarenal. The cortex of a suprarenal during puberty shows a very characteristic distribution of lipoid substance. As is known, we differentiate three layers of the suprarenal cortex, the so-called glomerular, fascicular and reticular layers. The glomerular layer passes as a so-called neogenous zone from which the other two zones are formed. One may also designate it as the resting zone or germinal layer, while the two other zones would be conceived of as the functional layers. This difference follows not only from the structure but also from the distribution of the lipoid substances. In general, in a healthy person, the glomerular layer is usually quite poor in lipoids; but this varies somewhat according to the general condition of nutrition. These lipoids are distributed in the glomerular layer in the form of fine droplets and consist predominantly of lipoids in the narrower sense. In contradistinction to the glomerular layer, the functioning layers of the suprarenals, particularly the fascicular layer, are very rich in fat. The outer portion of the fascicular layer shows normally a veritable overloading with coarse and fine drops of fat, the first of which consist predominantly of cholesterin esters, the others of lipoids in the narrower sense. With these there exist all sorts of mixtures of the two substances and also solutions of cholesterin in the other lipoids. In contradistinction to the fatty fascicular layer, the reticular

layer also shows a regression of fat; it here occurs predominantly in the form of fine drops. It is striking that also the endothelial cells of the blood capillaries within the reticular layer may show a storage of fine drops of fat. Besides the different distribution of the fat, the occurrence of a pecular pigment is characteristic of the reticular layer. The earliest period at which this pigment usually occurs is the second decennium. With increasing age this pigment becomes more and more evident, so that we are accustomed to designate the reticular layer also as the pigment zone. At the acme of life there is, at least in the male sex, a sharp division of the cortex into three parts: (1) the glomerular layer, poor in lipoids and with fine droplets of fat, (2) the fascicular layer, rich in lipoids and with both large and small fat droplets, and (3) the reticular layer containing pigment and fine droplets of fat.

Formerly there existed a lively dispute about the nature of this pigment. It was believed to be a melanin-like type, i.e., a true pigment, as is peculiar to the cells of the skin. Indeed, it was even believed that there exist certain relations between the quantity of skin pigment and the amount of pigment in the reticular layer of the suprarenal. The investigations of Tuczek, however, have shown that this is erroneous. Schief, also, was unable to find any such relations. Although the conditions in Addison's disease show that there are actually connections between the suprarenals and the pigment of the skin, yet according to Tuczek the pigment of the reticular layer has nothing to do with the pigmentation of the skin. Rather, we are here concerned, according to all available characteristics, with the so-called lipofuscin, i.e., the wear-and-tear pigment with which we are acquainted in the heart muscle, the liver cells, the ganglion cells, etc.[1] Since these wear-and-tear pigments become more marked with age it is comprehensible that the reticular layer in adults is much more darkly colored than in younger individuals. But it must be emphasized that this deposition of pigment, just as in the heart muscle and liver cells, does not begin in the declining period of life, but starts very early, apparently immediately after the completion of the reticular layer; we

[1] According to Kutschera, it is melanin surrounded with a layer of lipoid.

can microscopically recognize this pigment at the end of the second decennium. These are the cortical relations in the male. In woman, the glomerular layer is on the average more markedly developed, especially in those women who have had children. The glomerular layer of the suprarenal cortex stands, as a so-called germinal layer, in close connection to the generative periods of woman. During each menstruation especially, and at each pregnancy, the suprarenal cortex enlarges (Gayesse). During the menstrual period the glomerular layer swells, and it increases during pregnancy to a gravidity-hypertrophy (Landau, whose statements are confirmed by the findings of Watsin and Verdossi). During this stage, the glomerular layer stores up a strikingly large amount of lipoid substance, so that, contrary to the relationship in the male, it becomes a layer very rich in lipoids, which can be hardly differentiated from the fascicular layer. This can all the less be done, because from the proliferating glomerular layer there apparently occurs a growth of the fascicular layer. After the end of pregnancy there occurs during the puerperium a puerperal involution of the suprarenal cortex. However, this never leads to a complete regression of the newly formed cortical parts. The entire cortex, especially the glomerular layer, remains wider than before. The average weight of the entire suprarenal becomes greater in woman than in man. The glomerular layer is, on the average, richer in fat in the female than in the male. Therefore, there here exist differences between man and woman entirely akin to those found in the hypophysis. According to Watsin, the pregnancy hyperplasia of the suprarenal cortex is due to the placenta and not to the fetus.

Between the fortieth and fiftieth year of life the suprarenal cortex has attained the *height of its development*. Then it gradually undergoes a senile involution. This shows itself especially in the glomerular layer, more in the male, less in the female. It consists in a diminution in the size of the glomerular layer with greater prominence of the supporting substance, which before was only very delicately developed. One may speak of a veritable senile sclerosis of the glomerular zone of the male suprarenal. This must naturally be very sharply differentiated from infectious-toxic sclerosis, espe-

cially syphilitic. The latter may attain a much greater degree in congenital syphilis. In the female, senile atrophy is not so striking because the glomerular layer has grown to a greater breadth. In contradistinction to the atrophic glomerular layer, the fasicular layer, in consequence of greater storage of fat, seems to increase in volume in older individuals. This occurs mostly in a very irregular form as foci or islands. Between the parts which have stored a large quantity of fat there frequently lie quite atrophic thin cords of cells. These have been spoken of as atherosclerotic atrophies with compensatory hypertrophies. To what extent this is true I do not venture to decide. The reticularis finally shows a well-marked atrophy with striking loosening and marked pigmentation of the interstitial substance, which is especially characteristic of the senile suprarenal. With this we have covered the development of the suprarenal cortex—in the fetal period, in infancy, in the period of pre-puberty, at the height of life and in the senium. It is seen that hardly another organ undergoes so marked a change as the suprarenal cortex, this change making itself especially notable in the process of absorption after birth and the sudden development of the cortex in pre-puberty.

Before we describe the function and pathology of the suprarenal cortex, we must briefly survey the medulla. We have heard that at the end of the second year of life the medullary substance is again proximal to the cortex. The chromaffin property of the cells becomes very obvious and there disappear the peculiar round-cell infiltrates that we usually find in the suprarenal medulla during fetal life and also after birth, and about which we know that they are in part immature sympathetic formative cells and in part foci of hematopoiesis. During the following period the medullary substance grows quite markedly, especially during the period of puberty, becoming macroscopically recognizable and microscopically a well-delineated organ within the cortex. The structure of the medullary substance is very peculiar. The chromaffin cells, which are especially beautifully brought out with the Ogata silver method, are quite irregularly arranged, confused systems of cords, without any special arrangement like that of the cortex being recognizable. What

is, however, especially characteristic of the medullary substance is the strikingly rich content of the supporting substance in elastic fibers. One might compare the medullary substance with a sponge made up of elastic fibrillae, which is further penetrated by the central vein and its broad branches. Only the medullary substance possesses a large venous system, while in the cortex and capsule only a relatively small venous system can be demonstrated. The main mass of the blood of the suprarenal, therefore, is led through the medullary substance into the vein. The arterial supply is entirely different. The more recent experiments of Krawkow, who, in artificial perfusion of the surviving suprarenal, was able after days and weeks to obtain pharmacologically active substances, have again called attention to the different arterial system of the cortex and the medullary substance. In the cow and horse an arterial system of the cortex and an arterial system of the medullary substance can be very clearly distinguished. If one injects into the one system a red-colored and into the other a blue-colored mass, the cortex is colored blue and the medullary substance red, and vice versa. To be sure, very much depends upon the pressure with which the injection is carried out. If this is not entirely equal, there very readily occurs a penetration of the injection mass from one vascular area into the other. Krafkow was able to show that perfusion of the medullary artery yields an epinephrin-like, and that of the cortex a cholin-like, substance, which agrees with the statements of previous authors. Since the cortical substance has no considerable venous system of its own, the cortical arteries must go over into the capillary network of the medullary arteries, so that here the blood of both regions is carried into the venous system of the medullary substance. It can be shown that this transition occurs in the region of the reticular layer. Here is found an exceedingly fine capillary system with very narrow meshes, each mesh of which appears to surround a single cell. If, however, this fine network really consists of closed capillaries or of unwalled spaces, it is difficult to say. It is striking that just the suprarenal capillaries, especially in the cortex, behave on vital staining like the reticulo-endothelial cells of the spleen, the liver, the bone marrow and lymph nodes.

In all of these organs there lie strikingly loosely built or interrupted capillary systems. The same must be assumed for the reticular layer of the suprarenal cortex.

Besides this circulation of the suprarenal, in which the blood, reaching the cortex and the medullary substance by means of two arterial systems, is removed through the venous system of the medulla, there is a second variety of circulation in which the blood that flows into the cortex and medulla can partially flow out through the much more delicately developed so-called capsular veins. Through more recent investigations of Kutschera and Aichberger it has been determined that this venous system of the capsule, especially of the left suprarenal, communicates with branches of the portal vein, and does so through branches of the splenic and pancreatic veins. In the case of the right, collateral communications with the portal vein system, i.e., with the veins of Glisson's capsule, could not be demonstrated with certainty, but they were not excluded. For the function of the suprarenal, the demonstration of a sort of double circulation of the suprarenal and communications with the portal vein system is, however, important.

The extraordinarily great muscular content of the suprarenal veins is striking. This musculature has been considered as a sort of closing muscle (Materna) which serves to block the departing blood of the suprarenal and, so to speak, to reverse the circulation of the suprarenal. That, however, a true reversal of the circulation of the suprarenal is possible, in the sense that the main mass of the blood, instead of leaving through the central vein, departs through the capsular veins, is very questionable. However, the vein may serve as a regulator of the departing flow. Perhaps the powerful musculature only amounts to a support of the pumping and sucking work of the caval system, into which the epinephrin substance must be poured.

Nothing especial is known about true senile changes of the medullary substance. On the other hand, it is probable that the medullary substance also participates in the gestation processes of the female sex. A pregnancy hypertrophy of the medullary substance is therefore spoken of. Other physiological changes of the medullary substance are not

known. The medullary substance is, therefore, in contradistinction to the cortical substance, more of a resting organ.

Now that we have learned the structure of the suprarenal, we will turn to the *function* of this organ, as far as this can be given a morphological basis. We begin with the medullary substance because this has been best investigated with regard to *epinephrin formation.* It is certain that the chromaffin property of the medullary cells depends on their content in epinephrinogenous substance. By the intensity of the brown-staining with chrome salts, one can approximately estimate the epinephrin content of the medullary substance. As already mentioned, the silver method of Ogata is also a good method for its demonstration. Personally, I have had especially good service from the cresyl-violet method on tissues hardened in chrome solutions.[1]

In suprarenals of the horse examined quite shortly after death, the drop-like epinephrin formation in the medullary cells could be very plainly demonstrated. Aside from this the entire supporting substance of the suprarenal medulla also, when fixed as soon after death as possible, was found to be permeated with green-staining epinephrin substance. One may say that the medullary substance was literally soaked like a sponge with epinephrin substance. This epinephrin substance was not only found in all the smaller and the larger veins, but also in the crevices of the connective tissue surrounding the larger arteries, the nerve branches, etc. By means of Magnus' hydrogen peroxide method we tried, without success, to demonstrate the lymph-vessel system. We did not succeed because the entire venous system also immediately fills. Dr. Tammann, who carried out these investigations, had the impression that all these crevices of the medullary substances are smaller veins which then empty into the larger venous system of the central vein. These small veins collect, so to speak, the epinephrin substance, which itself saturates the tissue, and thereby lead it from the suprarenal medullary substance. Since in

[1] I will not here go more deeply into the question of how far the chromaffin and silver reactions are identical (Kutschera, Aichberger). I have no personal experience with the osmium method.

the central vein, which empties directly into the inferior vena cava, a negative pressure may at any time occur, which acts as a sucking force, we can completely understand the building of the elastic tissue into the medullary substance.

Certain as is, therefore, the histochemical demonstration of the passage of epinephrin substance into the venous system, very questionable do the relations to the nervous system appear. As is known, it was Lichtwitz who advanced the conception that epinephrin is led away less through the blood stream than through the sympathetic nervous system. Older investigations of Dewinsky, and newer ones by Tammann have, however, been able to bring no histological proof of this. In the nerve branches that run through the cortical substance, and even in the nerves of the medulla, no epinephrin could be demonstrated by the usual staining methods; but epinephrin is found very richly in the connective-tissue sheaths of the nerves, especially in the smaller branches of the medullary substance, which appear to be literally bathed in epinephrin substance. In this general saturation of the medullary substance with epinephrin substance, it appears to us that an influence by epinephrin substance on the sympathetic nervous system within the medullary substance of the suprarenal itself is quite possible. If one removes a suprarenal, this epinephrin stimulus for the splanchnic area of the side in question is removed, and with it all local transformations occurring in this nerve area. It is, therefore, comprehensible that following extirpation of the suprarenal of one side, after healing of the wound, which takes several weeks, sugar puncture on the side of the extirpated suprarenal causes no glycogenolysis in the liver, while the other half of the liver gives up its glycogen.

To be sure, all these considerations hold only if we may assume that such a saturation of the entire medullary substance with epinephrin also occurs intra vitam. As yet, all our attempts to fix the material as soon after death as possible have led to the same result. Therefore, one may assume that this epinephrin saturation is actually a vital process. This would also retain its validity even if it should be found that in the short time between the killing of the animal and fixation of the suprarenal a certain diffu-

sion of the epinephrin substance increases the appearance of saturation.[1]

While in the case of the medullary substance we have a relatively good idea of its function in so far as the formation of *epinephrin* is concerned, and can also speak from a morphological standpoint, the situation is entirely different in the case of the cortex. *What function has the cortex?*

Here, two subordinate questions must be asked, namely, what function has the suprarenal in the newborn? *What does the remarkable process of absorption mean?* Secondly, what function has the suprarenal cortex of the adult? I believe that we will come to greater clarity if we attempt to answer the last question first. Then it will be seen that this is most intimately connected with the physiological and

[1] I must not omit to say that with the chrome and silver reactions the relations are not so unequivocal, especially when one examines human material. In this case the passage of the epinephrin substance into the blood cannot be so clearly demonstrated, but this is probably due to the especial difficulties of fixation, etc. Yet it is remarkable that with the silver method also an especial relation of the capillary system at the border of the cortex and medulla may be discovered, inasmuch as here the content of the capillaries not uncommonly gives the epinephrin reaction. Therefore, the mixture of cortical and medullary blood occurs here. The occasional occurrence of epinephrin substance in the more peripheral capillary system of the cortical substance is probably to be attributed to post-mortem processes or to an involuntary squeezing of the suprarenal when removing it (Tammann), and at all events furnishes no proof of transport of the epinephrin substance through the capillary system to the cortex. There are, however, authors who assume that a greater passage of epinephrin in the capillary system of the suprarenal cortex, and above all into the venous system leaving the cortex, does occur. If this epinephrin transport through the so-called capsular veins were demonstrated with certainty, it would have to be taken into consideration in all experiments on suprarenals. Especially important would be the flowing of the epinephrin through a part of the capsular veins into the portal vein system. In this manner epinephrin might work directly on the sugar metabolism of the liver (Kutschera, Aichberger) without the necessity of a simultaneous pouring of epinephrin into the greater circulation, the blood pressure therefore remaining unchanged. In that event there would be two humoral ways in which epinephrin influences the organs. On the one hand, a rise in tonus in the arterial system when epinephrin is discharged through the medullary veins, and on the other hand, an influencing of the sugar metabolism when the epinephrin is poured into the capsular veins. Whether epinephrin flows continually or only periodically, or whether it reaches the inferior vena cava at all, are questions which cannot be decided by morphology, and into which I cannot enter here, in view of the great controversies among the pathologists and pharmacologists.

pathological storage of fat. While the medullary substance of the suprarenal was formerly looked upon as an organ essential to life, we now see, especially through the investigations of Landau, that the cortical substance also is of the greatest significance for the organism. Briefly expressed, it forms the most essential regulatory organ for cholesterin-fat metabolism. I have already brought out that the suprarenal cortex of adults is extraordinarily rich in cholesterin esters, as well as in other lipoids, and also in free cholesterin. Since in the human organism we know essentially only processes of fat storage and no transformative fatty change, one might also assume for the suprarenal cortex that it is concerned with especial processes of storage of lipoids. The question is only if these lipoids, especially the cholesterin esters which make up the main mass of the fats of the suprarenal cortex, are first formed in the suprarenal, or if the suprarenal cortex is rather a storage and regulatory organ of the suprarenal gland. As is known, Chauffard and Rigaud have advanced the view that in the suprarenal cortex cholesterin is formed and also esterified. The cholesterin formed in the suprarenal cortex and its cholesterin esters are then secreted by the suprarenal cortex into the blood according as they are needed. On the contrary, Landau has stated that the suprarenal cortex is essentially an organ of storage for cholesterin and cholesterin esters preformed in the blood, from which the blood, again according to need, removes the necessary masses of lipoid. Both parties have sought to support their conceptions through experiments. Rigaud was able to determine that after unilateral extirpation of the suprarenal the total cholesterin content of the blood gradually rises, and referred this to a compensatory hypertrophy of the suprarenal. The re-investigations of Dr. Marcus Rothschild of New York did, in fact, show that the blood cholesterin increases very quickly after removal of one suprarenal, then sinks and gradually rises again, reaching a maximum on the twelfth day after the operation. Then the cholesterin content sinks to a minimum on the seventeenth day, again attaining the average value after three weeks. Corresponding variations occur in the cholesterin content of the cortex of the intact suprarenal. Although these changes

appear to lag somewhat behind the changes in the blood, yet no definite conclusion could be drawn from these experiments. Only the extirpation of both suprarenals by Marcus Rothschild under the direction of Landau furnished unequivocal results. It was found that here, also, despite the removal of both suprarenals, a hypercholesterinemia sets in. Examination by the method of Windaus showed that here free cholesterin as well as cholesterin esters are increased. Therefore the formation of cholesterin and its esterification must take place outside of the suprarenals occurring in the blood. One has the impression that through the removal of the suprarenals, i.e., the removal of the regulatory storage organ for cholesterin fats, the rest of the organism loses its ability to retain its cholesterin fats. It pours them recklessly into the blood, from which they are removed through the liver by the bile. The animals, died, so to speak, from a cholesterin flow through the bile. As is known, the bile of the rabbit contains normally no cholesterin, or only a trace of it. If this conception of Landau's is correct, the life of the animals without suprarenals should be lengthened by artificial feeding of cholesterin and cholesterin esters, which was actually possible. Similarly, all circumstances which lead to a greater cholesterin content of the body before extirpation of the suprarenals, or which diminish the cholesterin-ester flow after suprarenal extirpation so that any accessory suprarenal cortical tissue may take over the function of the lost suprarenals by hypertrophy, must delay or prevent the death of the animal. This is also true. The pregnant animals with a high cholesterin content of the body in consequence of gravidity survive suprarenal extirpation longer. Rats (in which accessory suprarenals are very common) that are kept warm and fed a diet rich in meat and milk may completely survive the operation and even become pregnant.[1] This all speaks for the view of Landau that the *suprarenal cortex* represents essentially a *storage organ for cholesterin*

[1] The exact question, why some sorts of animals survive longer than others, is however not settled (Stewart, S. N., *Physiol. Review*, 1924, IV, 2). In my opinion the whole metabolic process in the normal animal must be regarded, before there can be said anything about the influence of the extirpation of the suprarenals on the special sort of animal.

fats, as the liver is a storage organ for neutral fats. This view of Landau was further supported by the well-known attempts to bring about changes in the suprarenals by feeding cholesterin. Here I name above all the work of Wacker and Hueck, Chalatow, Anitschkow, Sternberg, etc. All these authors agree in the result that a cholesterin-rich diet may cause a considerable increase in the cholesterin and cholesterin-ester content of the suprarenal cortex. But here there is a remarkable difference from pregnancy. In the fatty change of pregnancy, it not only comes to a fat storage in the glomerular layer, but also to a true hypertrophy in this layer. In the fatty change following a fat-rich diet there is also a fat storage in the glomerular layer, but true hypertrophy does not occur. I want particularly to emphasize that different results are obtained in different animals. On the whole, however, all experiments speak unequivocally in favor of the suprarenal cortex being a storage organ for lipoids. Also remarkable is the fact that the suprarenals at the end of pregnancy gain much in weight, while at the same time there begins a myelinization of the nerves (Cazzaniga). According to Chauffard the suprarenals of the newborn have a cholesterin content of 15 gms. per kilo, the liver and kidney only 2.5 gms. per kilo.

If this really exhausts the entire *significance of the suprarenal cortex* may be questioned. If the suprarenal cortex were only a storage organ for lipoids which are given up to the blood according to need, one could not understand the spatially close relations of the suprarenal cortex to the medullary substance. Also speaking for some co-working of the suprarenal cortex and medullary substance are the intimate connection of the arterial system of the cortex with the arterial system of this medullary substance, and the common flow of both bloods into the medullary vein. It has been thought that the suprarenal cortex forms a precursor of epinephrin from which epinephrin is first formed in the medullary substance. But for chemical reasons, this is not to be considered. Also the fact that apparently the blood of the cortex does not flow at all through the true medullary substance, but, after being mixed with the arterial blood of the medullary substance within

the reticular layer, flows directly into the venous system, speaks for the co-action with epinephrin within the blood itself. Landau constructed the somewhat peculiar hypothesis that the lipoids of the cortex have some significance for the sympathetic nerve branches of the medullary substance, just as the lipoids of the medullary sheaths have for the nervous elements of the central nervous system. But one can, as I brought out above, determine a connection of epinephrin and the nervous elements, but no such connection of the cortical lipoids to them. Therefore, this theory does not appear to me to have enough basis. Finally, it has been thought that the suprarenal cortex, in consequence of its greater lipoid content, has a local detoxifying action on the blood, so that the medullary substance is protected from some poisonous effects. This assumption, however, appears to me to be erroneous, since the medullary substance is not only supplied with blood by the cortex but also by its own arteries, and so in any case must be exposed to the danger of poisoning. It must be openly admitted that from the morphological standpoint we still have no valid idea of the co-working of the cortex and medulla. However, I believe from histological findings that we must assume that the union of the cortical substances with the medullary substance occurs in the region of the reticular layer, and that from here both substances pass in common into the departing veins. Whether, however, this intimate union of the medulla and cortex is indeed chemically or pharmacologically necessary, or whether this *building together* has arisen because of entirely different grounds, perhaps from economy, in order to allow the passage into the blood in approximately equal concentration (through the sucking action of the inferior vena cava) of two substances of unusual importance for the blood, namely, epinephrin on the one hand and the lipoids on the other hand, is yet an unsolved problem. We will later return to this briefly.

Besides the suprarenal medulla and cortex, the *reticulo-endothelial apparatus of the suprarenal capillary system* is yet to be mentioned. That it has similar functions to those which it carries out in the spleen, liver, etc., seems to be certain from the morphological pictures. This furnishes the final

justification for terming the suprarenal, at all events the cortex, as a storage and digestive organ. However, thorough investigations on this subject are as yet lacking. Stephan could not cause any alteration of blood pressure by radiation of the suprarenal, but did bring about changes in the blood picture. Since he states that only the cortex was destroyed, while the medulla remained intact, one must blame the loss of the cortex for the disturbance of blood formation. The suprarenal cortex produces hemolysins, which are said, however, to become effective only in the spleen.

We now turn to the question of the *significance of the suprarenal cortex of the newborn*. What meaning has the peculiar process of absorption of the suprarenal cortex following birth? What function does it fulfill? It must first be stated that this process of absorption apparently occurs only in humans, but not in the ordinary species of apes. The higher apes are not as yet exhaustively enough investigated.[1] If we hold to the conception that the suprarenal cortex is a storage organ for lipoids, and if we see that these lipoid-containing tissue constituents are absorbed to a great extent, the impression is involuntarily obtained that the human organism, for some reason, needs these cortical substances in an especially great quantity during the first weeks of life. The next thought is naturally of a connection with the processes of growth of the brain, but as yet this has not been supported in any way. Only one fact is very striking: under well-defined circumstances the physiological process of absorption of the suprarenal cortex does not occur. This occurs in so-called hemi- or anencephaly, i.e., in those malformations where the larger part of the brain, and indeed of the fore-brain, is not formed or has regressed. In such cases it is noticed that uncommonly small suprarenals are found, or there is even so-called absence of these organs, which is, however, not proven with certainty. It was formerly believed that this smallness of the suprarenals must be attributed to a lack of nervous anlage. It was believed that in this case there exist multiple defects in the nervous anlage. Microscopic examination, however, shows

[1] In the case of the white rat Jackson has described a prenatal process of absorption.

that in these suprarenals there exists tolerably well-developed medullary substance and that it is predominantly the cortex which is poorly developed. But the latter also is already completely partitioned, as if it had undergone the process of absorption during fetal life. It is, so to speak, the suprarenal of the adult on a smaller scale. Here we see, therefore, very striking connections between the cortex of the suprarenal and that of cerebral development. It will, therefore, be the task of future investigation to connect the absorption of the suprarenal of the new-born with the process of growth of the brain, and also with the process of growth in the other organs. Such a high degree of tissue absorption must have some meaning for the organism. Very remarkable are the observations of Ceni, who claims to have observed, after extirpation of parts of the cerebral hemispheres, a hypertrophy of the suprarenal, and indeed of the medulla and cortex, which increased with the size of the defect. With this went atrophy of the testicle and proliferation of the interstitial cells. This exhausts what there is to say about the function of the suprarenal of the new-born, and indeed all that we know from the morphological standpoint about the cortex and medulla.

We now turn to the *pathology of the suprarenals*, in which I will again emphasize the suprarenal cortex, because as the regulatory organ of cholesterin metabolism it interests us most in connection with our main theme. But I must occasionally go into diseases of the entire suprarenal. It will be best also here in the question of pathology that we separate the individual periods of life from one another.

In so far as the *suprarenal of the newborn* is concerned, we know that it may be hard hit by one particular event. That is the so-called suprarenal apoplexy, *hematoma formation*, or total infarction of the entire suprarenal. If both suprarenals are thus affected the natural result is the death of the individual. We know that also in later life, hemorrhages, and even infarctions, of the suprarenal may occur, but in the newly born they are relatively frequent and especially well developed. If we recall that just after birth, perhaps during birth, the so-called hyperemia of the cortical substance of the newborn occurs, we will understand that in

the face of unfavorable efforts at resuscitation, the uncommonly delicate and hyperemic tissue of the suprarenal cortex may tear and give rise to severe hemorrhages. Naturally, secondary thromboses of the suprarenal veins are also conceivable, which may be propagated into the renal veins or vena cava. Certain obliterative processes of the suprarenal or renal veins, or even of the inferior vena cava, found in later life, may have some relation with such pathological processes in the suprarenal of the newborn.

After the rebuilding of the suprarenal cortex at the end of the second year of life there follows a certain *period of rest* for the suprarenal, which is only occasionally disturbed by pathological influences. These are diseases of childhood, especially diphtheria and scarlet fever, in which the suprarenals are also involved. We know, through the investigations of Thomas, that in these instances the medullary substance does not suffer any severe changes. Thus, the chromaffin property is often strikingly well preserved even in severe cases of diphtheria, and occasionally somewhat more markedly diminished in cases of scarlet fever and sepsis. The medullary cells occasionally show hyaline droplet inclusions, but this is all that is to be found. On the contrary, the cortex is much more sensitive. In the various infectious diseases, especially in diphtheria, there occurs very evident vacuole formation in the protoplasm. This formation of vacuoles is accompanied by a loss of lipoid substance of which we will speak again in connection with the suprarenal of adults. These changes can also be artificially produced in the suprarenal cortex by diphtheria toxin. In scarlet fever, especially in the septic forms, there occurs, aside from this, a well-marked edema of the suprarenal cortex, which may be especially notable in the outer third of the fascicular layer. Here the compact cell cords of the fascicular layer may be pressed apart by an exudate accumulating between them, and form veritable gland-like structures in whose seeming lumen edematous fluid lies. Although these processes in themselves indicate that the suprarenal cortex is a very sensitive reagent for all sorts of infectious-toxic processes, this is only well shown in the *suprarenal of the adult.* The large number of septic infections which was furnished

us by the World War gave us an opportunity to study more exactly the relations of the suprarenal cortex to these infections. Dietrich called attention to the fact that, as in childhood, but to a much more marked extent, every septic infection lasting a long time is followed by an edema of the suprarenal cortex. Besides the edema, changes in the lipoid substances play a very important rôle; especially affected are the outer layers of the fascicular zone and the glomerular zone, and to a less extent, the reticular layer. The more severe the septic process, the more diffuse are the changes. These consist mainly in the progressive disappearance of the lipoid depositions. This disappearance first affects the depositions in the form of fine droplets, while the medium and large droplet lipoids are preserved a longer time. But they also diminish visibly, so that instead of the fats in the form of various-sized drops one later finds only fine drops. Fatty degeneration of the cortical cells has been spoken of in this connection, but here also we are only dealing with infiltrated fat, disintegrated under the influence of the sepsis. This disintegration may go so far that one may speak of a complete disappearance of the cortical lipoids. This disappearance of lipoids is followed by vacuolization processes of the cells up to necrosis, and by complete destruction of the cells. During this, it may also come to reactive proliferation of the vascular connective tissue of the cortex; but in septic-toxic processes these reactions, hemorrhage and migration of leucocytes, play no great part. It is somewhat different in the metastatic septic processes where it comes to a deposition of microorganisms in the capillaries of the cortex. In this event there may occur large necroses, hemorrhages, leucocytic emigrations and abscess formation.

These changes in the cortex occur in all possible infections, especially in the so-called septic, i.e., the streptococcic infections; also in infections with gas bacilli, such a disappearance of the lipoids is reported (Dietrich, Goormaghtigh). I have not been able to observe this to such an extent. On the other hand, the great disappearance of lipoids in peritonitic infections is extraordinarily characteristic. Deutscher has also been able to show experimentally that acute peritonitis leads much more rapidly and to a much greater degree

to a disappearance of the lipoids in the cortex than do the hematogenous septic intoxications. Here direct action of the toxins from the abdominal cavity on the suprarenal cortex may play a certain rôle. To what extent the severe changes in the suprarenal cortex are connected with the death of the individual is a question in itself. While formerly only the suprarenal medulla was looked upon as essential to life and the loss of epinephrin resulting from the destruction of the suprarenal was looked upon as the true cause of death, nowadays there is a tendency to the error of exaggeration in the other direction by ascribing those functions essential to life to the cortex and looking on its injury as the cause of death. Lacassagne and Samsonow have indeed been able completely to destroy the medulla by intensive radiation with radium, while the cortex is said to have remained preserved. Under such circumstances they claim to have observed no disturbance in the vital functions of the animals. Also the important investigations of David Marine and his coworkers on the relations of the suprarenals to heat formation in the organism with or without the help of the thyroid, show that the suprarenal cortex has, at least in this direction, a greater significance than the medulla. He was able to eliminate the suprarenal cortex by shorter or longer freezing of the suprarenals. By histological investigations it was determined that only the suprarenal cortex, and not the medullary substance, was injured. Such animals in which the cortex was extensively injured while the medullary substance was shown to be preserved, showed a fatal disturbance of heat production. Marine and his coworkers conclude from these experiments, with a certain degree of justice, that the suprarenal cortex is the most important constituent of the suprarenal gland, and the one most essential to life. To be sure, one must consider that in these experiments the nerves of the suprarenal glands are frozen and injured. If epinephrin is really removed by way of the nerves and not via the blood stream, these experiments would, to be sure, not be decisive. But I have pointed out before that morphological investigations speak for the fact that the principal manner of removal of epinephbrin is through the blood stream. Houssay and Lewis removed one suprarenal and destroyed the medulla

of the other. The animals remained alive. They, therefore, viewed the cortex as the organ essential to life. Similarly, Stewart, because of the marked fluctuations of the cortex in all sorts of diseases, has the same view. But this does not prove anything against the significance of the medulla. On the contrary, the circumstance brought out by Stewart, that dogs that have no accessory suprarenals die after extirpation of the suprarenals, while rats mostly live, speaks for the significance of the cortex.

One may naturally ask the question: just what is the function of the suprarenal cortex in septic processes? It must be recalled in this connection that also in simple poisonings, e.g., with saponin, a high degree of disappearance of the lipoid substances of the suprarenals occurs. It seems very plausible that the expulsion of lipoids from the suprarenal cortex signifies a detoxifying process, the cholesterin and cholesterin esters contributing in some manner to the saturation or inactivation of the poisons or bacterial toxins (Leupold and Bogendörfer). Since this process cannot be followed further morphologically, I will not here go into it any more; but I must point out that this impoverishing of the cortex in lipoids occurs not only in the exogenous but also in the endogenous formation of poison. It has been described as especially characteristic in death due to burning, but this holds only for the cases with a somewhat slower course. In these cases the blood is evidently poor in cholesterin and the lipoids of the suprarenal cortex disappear. The more one inclines to look on subacute death from burning as the consequence of endogenous toxicosis, the more reasonable it seems to connect the disappearance of lipoids from the suprarenal cortex with processes of poison formation. But these questions need an especial investigation, particularly the question as to what extent in such cases of subacute death from burning, the death itself is to be attributed to the impoverishment of the suprarenal cortex in lipoids.

Besides the infectious processes, metabolic disturbances have an extraordinarily important rôle in the pathology of the suprarenal cortex. It is here that the significance of the cortex as a storage or regulatory organ for the entire lipoid

metabolism becomes especially clear, and we understand the difficulty of obtaining precise weights of the suprarenals in entirely healthy people. The weight of the suprarenal is said to bear a particular relation to the height of the body (Schief). Materna found, after the war, that the average weight of both suprarenals was hardly 10 gms. We have to differentiate, on the one hand, a diminution in lipoids: on the other, an increase in the same substances. Such a diminution in lipoids we find in sudden bodily overexertion in pernicious anemia and in some forms of diabetes. We cannot at present say to what extent this disappearance of lipoids from the suprarenal cortex in pernicious anemia is due to toxic effects or to the anemia itself. In the different forms of diabetes it is known that the lipoid content of the blood fluctuates within very wide limits, and the complications of the individual cases of diabetes are so different that it is comprehensible why the lipoid content of the suprarenal cortex is diminished in some cases of diabetes and increased in others.

At all events, increase of the lipoids of the suprarenal cortex plays a much greater rôle in metabolic disturbances, viewed from a morphological standpoint, than does diminution. We have pointed out before that by artificial cholesterin feeding the cholesterin content of the suprarenal cortex can be increased. This lipoid deposition first occurs in the fascicular layer, and only when the feeding is protracted, in the glomerular layer. Conversely, when the cholesterin feeding is stopped there is first a diminution of lipoids in the reticular layer, while the fat storage in the glomerular layer usually lasts a longer time. From the demonstration of a glomerular layer rich in lipoids one may draw the quite certain conclusion that a particular period of lipoid storage has preceded the period of lipoid impoverishment which is beginning again. Quite similar relations hold for pregnancy, which is only to be differentiated from true fattening as the result of feeding by the simultaneous hypertrophy of the glomerular layer. It is therefore more or less possible to fill with lipoid the various layers of the suprarenal cortex by means of overfeeding, and to remove the lipoid by hunger periods.

In *chronic starvation* the relations are very peculiar. In this case one would expect a complete disappearance of the lipoids of the suprarenal cortex. The investigations of Landau and his pupils have shown that in protracted starvation, as well as in pedatrophy of infants, instead of the expected diminution, an increase of the lipoids of the suprarenal cortex takes place. These statements have been confirmed by the observations of Elliott, Stewart, Jackson, Prym and MacCarrison. It must be assumed that here, as in the case of the storage of neutral fat in the liver in the tuberculous, cancerous, etc., we are dealing with a sort of retention fatty change. While on the one hand, under the influence of hunger, a destruction of tissue takes place which also frees cholesterin and cholesterin esters and thereby increases the available quantity of these substances, on the other hand, the mass of lipoid which comes to be stored in the suprarenal cortex is no longer sufficient for metabolism and the building of new tissues. If this conception is true it is comprehensible that, just as in the case of phthisis and other destructive diseases, such an inanition or retention fatty change of the suprarenal cortex is observed. Whether this fatty change of the suprarenal cortex in the tuberculous goes parallel with fatty infiltration of the liver, requires more thorough histological and chemical investigation.

To be sure, there is a difference between the *fatty change of hunger* and the *fatty change of phthisis*. Thus in the first, cholesterin is increased in the suprarenal cortex—but not cholesterin esters; while in the phthisical fatty change both free cholesterin and cholesterin esters are increased, and indeed in approximately the ordinary proportions. This is a remarkable difference which is to be taken into consideration. Thus the newer morphological and chemical investigations on suprarenal changes in avitaminoses show that in scurvy there is an evident storage of lipoids in certain layers of the suprarenal cortex. Chemical investigation has shown that here, just as in the condition of hunger, we are dealing essentially with an increase in the ordinary neutral fats and lipoids in the narrower sense, but not in cholesterin esters. In this connection *scurvy* is to be designated as a sort of hunger condition; but it must be pointed out that between

true hunger conditions and scurvy there are considerable differences with respect to the manner of lipoid storage in the suprarenal cortex (Pfeiffer). To the group of inanition fatty change in the broader sense, belong, to a certain extent, the lipoid infiltrations of the suprarenal cortex in *cancerous* patients. To be sure, other causes also play a part here. As in phthisis, there is a lively lipoid formation, particularly of cholesterin esters, resulting from the involution of cancerous growths—regressive fatty changes as we have called them. In the later decomposition of the cancerous masses these lipoids are poured into the blood in great quantity, and may be stored in the suprarenal cortex. Therefore one may here speak of an overproduction of lipoids through cancerous growths.

The findings in the suprarenal cortex in mental diseases form a special chapter. According to Warilesco, the glomerular zone in maniac depressive insanity and hydrocephalus is better filled. Fewer lipoids are found in epilepsy, pellagra and dementia praecox; and more lipoids in paralysis. Total enlargement of the cortex was found in dementia praecox, epilepsy and general paralysis. All these statements can only be proved if the general nutritive condition of mental patients, which fluctuates so astonishingly, be taken into consideration.

These varieties of lipoid storage lead us to those cases of increased lipoid content of the suprarenal cortex to be found in ordinary metabolic disturbances or conditions of inanition. Here belongs, above all, the lipoid storage in the suprarenal cortex in atherosclerosis of the vessels. On the whole, a certain parallelism can be shown between the atheromatous fatty infiltration of the intima of the vessels and the fatty infiltration of the suprarenal cortex. The fatty change in the intima depends upon an abnormal deposition of cholesterin esters. It is therefore conceivable that in the cases of atheromatosis and of fatty storage in the suprarenal cortex, a common cause must be sought. This we believe we may assume to be an overloading of the blood or the tissue fluids with cholesterin esters. At all events, it is shown by experiment that by cholesterin feeding one can bring about, not only a high degree of fatty change of the suprarenal cortex,

but also a quite typical atheromatosis of the aorta. To be sure, the ease with which such fatty changes occur in the suprarenal cortex, the vascular system and other organs, especially where the reticulo-endothelial system enters, depends not only on the quantity of cholesterin fed, but also on the medium used to dissolve it when it is fed. In this connection the different oils play a decisive rôle. We may assume that, according to the nature of the oil, the emulsification and esterification processes of the cholesterin occur more quickly or slowly in the intestinal canal and on the other side of the intestinal wall in the lymph and blood. Not only the resorbability, but also the possibility of storage in the various organs, depends on the fineness of the disperse phase of the cholesterin or cholesterin-ester emulsion.

Since the mechanical moment of vascular overexertion doubtless plays a part in the atherosclerotic process in the vessels, one must also naturally pay attention to the blood pressure in the origin of atherosclerosis. But since this is in turn influenced by the epinephrin content of the blood, it has been attempted to connect the suprarenal as a whole with atherosclerosis. Wiesel and Schur believe that hypertrophy of the suprarenal medulla is to be looked on as the cause of atherosclerosis. Re-investigations by A. Cohn as well as other authors have, however, shown that such an hypertrophy of the medullary substance of the suprarenal is not the rule, but that the size varies individually very much. Also the assumption of Wiesel, that in atherosclerosis a proliferation of sympathetic formative cells occurs that leads to an increase of the epinephrin-forming tissue, has not been confirmed. Even if future investigations should render probable such an increase of the medullary substance of the suprarenal in atherosclerosis, we would not say that this hypertrophy of the suprarenal medulla is the cause of atherosclerosis. Rather, we might be dealing here with a secondary, or compensatory, process, inasmuch as the manifold softening and hardening process in the vascular system might require an increased formation for the maintenance of the necessary tension. However, inasmuch as an hypertrophy of the medullary substance is not demonstrated, it is useless to discuss its cause. On the contrary, an hypertrophy

of the cortex has been all the more plainly demonstrated. That this has no causal connection with atherosclerosis, but is only accompanying phenomena of the general lipoid increase of the organism, I have already remarked.

The situation is more complicated in another form of lipoid storage in the suprarenal cortex, which is found in certain contracted kidneys, especially the *arteriosclerotic contracted kidney*. We know that in the secondary contracted kidney, lipoid storage, and indeed cholesterin storage, in the epithelia of the tubules as well as in the cells of the supporting substance, is very frequent. That the kidney is indeed an excretory organ for lipoids is beyond doubt. This has been shown especially well in acute yellow atrophy, where, under the influence of the rich excretion of lipoids, the cortex of the kidney shows a striking storage of neutral fats, the medulla of the kidney a storage of fatty acids or soaps. In contracted kidneys there is apparently a greater excretion and simultaneous storage of cholesterin esters. As MacNee was able to show, and as I can confirm, in the majority of the so-called cholesterin-nephroses of the kidney, i.e., the cases of high-grade cholesterin infiltration of the kidney, we are not dealing with an independent disease, as Volhard assumes, but practically always with the consequences of a glomerulonephritis. If, however, the kidney shows such evident relations to the excretion of cholesterin esters, it is comprehensible that in progressive contraction the cholesterin metabolism of the organism suffers certain disturbances which may also be demonstrated by an increased cholesterin content of the suprarenal cortex. To be sure, the closer relations between renal contraction and suprarenal fatty infiltration are far from a closed book, since the increase in cholesterin or cholesterin-ester content of the blood which is really to be expected has not been regularly determined in contracted kidneys.

A final group of cases of fat storage in the suprarenal cortex is in so far connected with the contracted kidney as in it also circulatory disturbances play a rôle. This is the group of *cardiac failure*. In these cases one may often observe particularly striking lipoid storage in the suprarenal cortex. I believe that here the general plethora, with increase of the

entire cholesterin content of the blood, plays a part in the fatty infiltration of the suprarenal cortex.

Finally, we have to mention certain cases of diabetes, as well as of chronic jaundice. To be sure, there are here also, differences in the nature of the lipoids formed. In *diabetes* we are dealing with a cholesterinemia with deposition of the cholesterin esters in the suprarenal cortex. In *chronic jaundice* there is essentially a cholesterinemia, which has only a slight influence on the lipoid content of the suprarenals, and causes essentially an increase of cholesterin only.

This closes my remarks on the relations of the suprarenal cortex to general metabolism. They show very clearly how closely the suprarenal cortex is connected with the cholesterin metabolism of the body. It would be interesting to describe here a third group of changes in the suprarenal cortex. I refer to the changes connected with the other glands of internal secretion. But these relations are very complicated and having nothing to do with true fat metabolism, which forms our main theme. At most, the relations to the germinal glands come into consideration. It is striking that, for example, in pubertas praecox very frequently tumors of the suprarenal gland are found. Among the 12 cases collected by Leupold the female sex was affected eight times. In feminine pseudo-hermaphroditism, hypertrophy of the suprarenals has repeatedly been observed. After castration and in pregnancy there occurs an hypertrophy of the suprarenal cortex. Similar relations may also be demonstrated between the suprarenal cortex and the testicle. The development of the suprarenal cortex, to be sure, precedes the maturity of the testicle, as I pointed out above. In adults the testicle is characterized by the marked lipoid content, particularly in cholesterin esters, of the interstitial tissue. In certain individuals this lipoid content runs parallel, also in its composition, to that of the suprarenal cortex. But in the suprarenals the cholesterin esters predominate. In saponin poisoning the testicle also becomes poor in fat, and, just as in the suprarenal, the cholesterin esters disappear first. Under pathological conditions the manifest relations between the suprarenal cortex and the testicle change. Thus in cachetic diseases the testicle may become very atrophic, while the suprarenal cortex

even gains in weight by lipoid storage. Microscopically, however, it is seen that when the testicular substance disappears, the seminiferous and not the interstitial tissue is involved. This shows a rather similar fluctuation in lipoid content to that of the suprarenal cortex. The epithelium of the seminal tubules also contains, as is known, lipoids, but these show no definite relation to the lipoids of the suprarenal cortex. And yet this must in some way influence the development of the seminal epithelium. After extirpation of the suprarenals the seminal epithelia are destroyed (Leupold).

The relations of the thymus to the suprarenal and testicle are very striking. In the so-called status thymicolymphaticus there is a relatively small suprarenal cortex with a well-developed interstitial cell substance of the testicle. But this, like other interrelations, requires more thorough statistical study. The interrelations between the thyroid and the suprarenal recently play a great rôle. Morphologically, this is easily comprehensible. While Cramer, in feeding thyroid substance, found changes in the medullary substance of the suprarenal which recalled those resulting from the action of cold and injections (necroses), in the experiments of other authors (Herring, K. S. and Hoskins, E. R., Squier and Grabfield) enlargement of the cortex was demonstrated. This is nothing specific (Stewart) but occurs during feeding, blood injections, or after extirpation of one suprarenal (Gley, Carlson, Stewart). On the other hand, Rogers observed, when feeding suprarenal cortex to dogs, a rise of from 50 to 75 per cent in the iodine content of the thyroid. The feeding of epinephrin had no such effect. In the necrobiosis of the suprarenals of mice inoculated with cancer, Tokumitsu saw a parenchymatous enlargement of the thyroid gland. In Basedow's disease there is said to be a hypo-function of the suprarenal cortex (G. A. Friedman). Tokumitsu points out relations between the pancreas and the suprarenal cortex. On ligating the pancreatic duct he found hypertrophy of the suprarenal cortex. At all events, we see that between the lipoid content of the suprarenal cortex and the lipoid content of other glands of internal secretion there exist definite relations which fully justify us in designating the suprarenal, i.e., the suprarenal cortex, as an intermediary organ of choles-

terin metabolism. But this does not imply that the suprarenal cortex is the only organ that rules over cholesterin metabolism. Rather a great rôle as regulators is played by other organs, above all, by the germinal glands and also the liver. But there is no doubt that the suprarenal cortex is to be looked upon as the most important storage organ for certain lipoids, especially the cholesterin esters. If, therefore, we have differentiated a cholesterin-ester fatty change, a glycerin-ester fatty change and a lipoid fatty change in the narrowest sense, it will be the task of the future to define more definitely the regulating organ for each of these three varieties of fatty infiltration. In the case of the cholesterin fatty change we seem to have found the main organ in the suprarenal cortex.

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The other references are found in *Endocrinology.*

VI

ATHEROSCLEROSIS[1]

The expression "atherosclerosis" was first coined by Marchand to indicate the peculiar changes observed, especially in elderly individuals, in the intima of the aorta and large vessels of the elastic type, which are so characteristic of the clinical picture generally termed arteriosclerosis. Marchand desired to emphasize by this expression that, in addition to the sclerotic changes, the so-called "atheromatous" or "fatty changes" play a specific rôle. Since the fatty process, as we shall see, is of a unique nature and bears a definite relationship to the sclerotic process, particularly to calcification, the expression "atherosclerosis" is thoroughly justifiable. I hope to be able to show that this peculiar metabolic disturbance of the intercellular and connective tissue substance, nowadays termed "atherosclerosis," occurs not only in the vascular system but also in other organs. We shall concern ourselves at first, however, with atherosclerosis of the vascular system.

ATHEROSCLEROSIS OF THE VASCULAR SYSTEM

Our conception of atherosclerosis of the arterial system has, in the course of the last century, undergone a very remarkable transformation. We are indebted to Virchow for the first accurate histological description of the entire process. On the occasion of the centennial celebration of his birth, I indicated that Virchow's original presentation, which has gradually been forgotten, today again receives the honor and recognition which it deserves.

I consider it my duty to call attention again, at this time, to his ideas.

What is Virchow's interpretation of the atheromatous process? He thought the first change to be a "certain loosening of the connective-tissue ground substance" of which the arterial intima is for the most part composed. "This swelling of the ground substance, which, as I have mentioned, I am

[1] Lane Lecture.

compelled to conclude must be attributed in large measure to an increased imbibition of fluid elements from the passing blood stream, is recognized microscopically by the increased width and homogeneity of the connective-tissue spaces." Sometimes these areas of swelling have a gelatinous appearance which may be recognized macroscopically; at times they are cartilaginous. *Pari passu* with the thickening and transformation of the ground substance, the connective-tissue cells of the intima undergo changes. They enlarge in all dimensions, divide and form localized thickenings. "In this manner the process assumes an active character such as we have assumed for inflammatory processes in general." In pointing out the marked vascularization of the outer coats of the aorta, in addition to the intimal thickening, Virchow believed that he had sufficiently demonstrated the irritative nature of the process. When the thickening of the intima has advanced to a certain degree, fatty metamorphosis generally puts in an appearance. Only under certain conditions do these progress to true atheromatosis; that is, when the fatty process begins in the depths of the thickened intima and, becoming progressively softened, slowly extends to the surface. In other cases the fatty metamorphosis occurs directly in the most superficial layers. This Virchow termed *fettige Usur*, which may occur without an antecedent thickening of the intima. If we disregard this point for the present, then, according to Virchow, the entire atheromatous process represents a primary loosening of the intimal layer, due to the infiltration of blood plasma, which is accompanied or followed by a growth of intimal cells and a more marked vascularization of the media. Thus it is an active process, in which a fatty metamorphosis of the different layers may take place as well in an entirely passive manner. The *primum movens* of the entire irritative process is therefore a loosening of the internal coat. In what manner do these changes arise? Virchow discussed two possibilities, a humoral and a mechanical etiology. He rejected the former, which may be called arthritic and which is conceived as a primary exudation of the arterial intima, and clearly and definitely accepted the mechanical etiology. In a manner worthy of emulation, he briefly cited all the evidence afforded by the localization of the atheromatous patches. One cannot find a better expo-

nent than Virchow of the theory of the mechanical origin of atheromatosis. But it did not escape his keen perception that some dyscrasia must play a supplementary rôle.

Thus, what we know to-day as atheromatosis was essentially defined by him. Only after the lapse of half a century have we returned to this simple viewpoint that explains the entire process. A great part of the blame may be attributed to the name *endarteritis deformans*. Since pathologists unfortuntely have acquired the habit of viewing inflammation solely from the morphological aspect, while the clinicians interpret it etiologically, and understand under inflammation only processes of an infectious or toxic origin; so the endarteritis deformans of Virchow became something entirely different from the conception of the man who named it, that is, an infectious toxic process, in the origin of which the infectious diseases play the primary rôle. Virchow definitely rejects such a conception. He thought, not of a defensive endarteritis, but of a reparative endarteritis, which resulted from the primary injury to the intima determined by its mechanical loosening and the infiltration of the blood plasma. It is well known that Thoma places the primary injury in the media. He, too, considers the proliferative process in the intima as reparative. There should be no doubt as to the reparative nature of Virchow's *endarteritis deformans*. Of the greatest importance, it seems to me, is the fact that Virchow definitely called attention to the point that the changes occurring in the intima are initiated by invasion of the blood plasma. I have reached the same conclusion as a result of investigations which I carried out with Torhorst, and subsequently Ribbert independently expressed the same idea. In the light of newer histological and chemical investigations concerning the nature of the atheromatous fatty process, as, for instance, those of Adami, Windaus and myself, all of which led to the similar conclusion that this fatty process depends purely on a deposition of cholesterin esters, one may construct today, on the basis of Virchow's conception, an almost flawless picture of the atheromatous process in the aorta. I have called this conception of Virchow's the "imbibition theory," and in the light of this theory, I should like to trace for you the development of the atheromatous process.

VARYING MANIFESTATIONS OF DISEASE

In order to understand fully the varying aspects of atherosclerosis of the vascular system, we must first realize that the manifestation of disease in the different parts of the vascular system differs corresponding to the varying functional strains to which they are subjected. As you well know, we differentiate vessels which are especially adapted to withstand elastic strains (as, for example, the aorta, the carotids and the iliacs) as vessels of the elastic type, from such vessels in which muscular tension is the predominating factor (as in the peripheral arteries and those of the internal organs) which are classed as vessels of the muscular type. While the aorta is distinguished by the strong development of elastic lamellae in the media, in the femorals, brachials, etc., the musculature predominates and the elastic system is relatively unimportant. Since the so-called atheromatous changes appear most prominently in vessels of the elastic type, especially in the aorta, we shall devote our immediate attention to the aorta. But here, too, we must remember that its structure is not the same at all age periods. We must differentiate between an ascending period, a summit, and a descending period in the life of the vessel. The first is characterized by an equal increase of all the tissue elements of the vessel wall. In the second the artery retains its form more or less. In the third there commences the progressive dilatation of the vessel which increases with age, and which we term "senile ectasia." The ascending period in the life of the vessel ends with the thirty-third year; the summit from then to the forty-fifth year, which marks the commencement of the descending period. *Senile ectasis* is a disease of old age which no living individual escapes. The vessel becomes overstretched, not only in the transverse but in the longitudinal diameter as well, and so arise the characteristic widenings and tortuosities of the vessel. The dilatation of the aorta, which begins in the fourth decade, and later becomes much more marked, must always be borne in mind when one speaks of a normal, an abnormally narrow or an abnormally wide aorta. All three expressions are used freely in the literature but are not controlled by sufficient measurements and comparative figures. I wish to protest particularly against the expression "aorta angusta," which is used much too often. Indeed, there

still are some who see in the aorta angusta not only a stigma of a hypoplastic or asthenic constitutional weakness, but even the cause for severe heart disease and cardiac insufficiency. I do not wish to review the whole literature on aorta angusta at this point. I readily grant that in tuberculous individuals one is more apt to find delicate and elastic aortas than in individuals who are strong and capable of hard work. This seems to me to be a natural adaptation. A thin-walled aorta is not, however, synonymous with a narrow aorta. But especial importance has always been placed on the *narrowness* of the aorta. The attempt has repeatedly been made to determine the average size of the aorta at different periods of life by measuring a large series of bodies. I need mention only the work of Thoma, Beneke, Suter, Scheel and Kani. There can be no criticism of the accuracy of these investigations, especially of those of the last-named author. The only legitimate objection that might be raised is that they were dealing with material obtained during times of peace, when all kinds of chronic infections and wasting diseases play a significant rôle. Therefore, the large amount of material, mostly consisting of healthy men, placed at our disposal during the war, was of especial value in establishing a more reliable standard. Miss Kaufman, at my suggestion, has examined the war material of 685 autopsies. She arrived at the results delineated in the following table:

AVERAGES OF 685 MEASUREMENTS[1]

Age, years	Height, meters	Weight of heart (gms.)	Root of aorta	Thoracic aorta	Abdominal aorta
18–19	1.65 (33)	300 (19)	56.7 (44)	40.5 (35)	31.2 (35)
20–24	1.70 (176)	299 (133)	57.4 (187)	42.1 (173)	32.5 (164)
25–29	1.72 (121)	327 (102)	61.0 (147)	44.2 (119)	33.7 (118)
30–34	1.72 (105)	328 (85)	63.4 (116)	46.0 (95)	35.2 (80)
35–39	1.75 (60)	319 (65)	66.3 (91)	48.5 (83)	36.3 (81)
40–44	1.69 (68)	355 (45)	67.4 (72)	49.6 (64)	37.6 (47)
45–50	1.66 (23)	319 (19)	70.0 (28)	49.7 (22)	38.8 (21)

[1] The figures in parentheses give the total number of cases measured in each category.

In Miss Kaufman's table only the average figures are given. But it is very evident that the inner circumference of the aorta slowly increases from the eighteenth year on.

If, therefore, one desires to know whether any particular aorta is within the inner or outer limits of normal, one must take into consideration the variations above and below the average. We have done this in a particular way and in this manner have obtained the following table:

Age, years	Root		Thoracic aorta		Abdominal aorta	
	52.9		36.7		28.0	
18–19		56.7		40.5		31.2
	60.5		44.3		34.4	
	53.6		38.3		29.3	
20–24		57.4		42.1		32.5
	61.2		45.9		35.7	
	57.2		40.4		30.5	
25–29		61.0		44.2		33.7
	64.8		48.0		36.9	
	59.6		42.2		32.0	
30–34		63.4		46.0		35.2
	67.2		49.8		38.4	
	62.3		44.7		33.1	
35–39		66.3		48.5		36.3
	70.1		52.3		39.5	
	63.6		45.8		34.4	
40–44		67.4		49.6		37.6
	71.2		53.4		40.8	
	66.2		46.6		35.6	
45–50		70.0		50.4		38.8
	73.8		54.2		42.0	

In each age group are found the lowest and highest numerical values presenting the normal limits of that group. With this as a standard, one finds that the cases described as aorta angusta in the literature fall, practically without exception, within the limits of normal. We ourselves found, in our large war material, 11 cases in which the vessel was too narrow, and 6 in which it was too wide. The percentage of phthisis

was the same in both series. We could not determine any relationship between the size of the aorta and constitution. For details I refer to the paper of Kaufmann.

This senile overstretching physically can be attributed to a diminution in elasticity. As you know, in young individuals and in adults in their early twenties the aorta is under considerable elastic tension. If one frees the aorta from the vertebral column in such a manner that it is fixed only at its upper and lower ends, and then severs it in the middle, the cut ends will retract several centimeters. This is the best proof of the existing longitudinal tension. If one repeats the same experiment in adults of sixty or seventy, the edges do not move at all, or only very slightly. The great elasticity of the aorta is therefore entirely lost in the course of a lifetime. On the other hand, in old age there is apparently a marked increase in the elastic resistance. While the isolated aorta of a thirty-year-old adult can easily be stretched several centimeters, it is practically impossible to do this with the aorta of an individual in his sixth or seventh decade. Wherein lies the loss of this perfect elasticity and this striking increase of elastic resistance? The loss of perfect elasticity must be dependent on a physical alteration of the elastic tissue of the vessel. It is due to the change which the elastin undergoes with age, a phenomenon which is manifest wherever there is elastic tissue, in the bronchi, the skin, etc. The overstretching of the vessels under the continuous load of the circulating blood would probably be much greater, were it not for the fact that the intima of the aorta in particular, under constant longitudinal tension, becomes, with increasing age, invaded with more and more connective tissue. This connective tissue possesses very slight elasticity, but has, on the other hand, a great elastic resistance. This explains the fact that the strength of the vessel wall remains almost the same or even increases in spite of the progressive overstretching which it undergoes. It is the uniform thickening of the entire intima with connective tissue that is responsible for this. Here lies the explanation of a certain rigidity of the vascular tube which may be termed *simple or senile sclerosis*, which has, however, nothing to do with the condition generally referred to as atherosclerosis or destructive sclerosis.

DESTRUCTIVE SCLEROSIS

It is the latter which we shall now consider. I have already indicated that atheromatosis, or, as Virchow more correctly named it, "atherosis," precedes the sclerosis. The more carefully we examine the aorta at autopsy, the more evident does it become that atheromatosis is a disease which may be observed at all ages. It occurs in the ascending as well as in the descending period of life. We shall see, however, that atherosclerosis is observed only in the descending period. The atheromatous process, therefore, is the fundamental one, and the one we must first try to explain, if we wish to understand the further changes of later life. It follows therefore that atherosclerosis is no ordinary senile disease. Indeed, one frequently finds vessels with marked senile ectasia which show no trace of atherosclerosis. The latter is therefore an engrafted, or, at any rate, a very frequently associated or secondary disease of the aged aorta. Its origin will become clear to us only after we fully understand the origin of the atheromatosis which may commence in youth. Let us turn then to the study of atheromatosis of the ascending period of the life of the vessel. The World War afforded all nations sufficient opportunity to examine an enormous necropsy material composed of young people whose lives as a rule, had been snuffed out in the prime of health by the shells of the enemy. Here none of the diseases, such as tuberculosis, which in the ordinary peace-time material are held to be responsible for the accidental occurrence of atheromatous changes in youth, play a part. We all arrive at the surprising conviction that atheromatosis of the aortic intima occurs with striking frequency in youth. The following figures of Mönckeberg are illustrative:

Under 20 years—	14 cases, of which	5 show atherosclerosis	(35.7 per cent)
Under 25 years—	45 cases, of which	34 show atherosclerosis	(75.6 per cent)
Under 30 years—	20 cases, of which	18 show atherosclerosis	(90 per cent)
Under 35 years—	15 cases, of which	12 show atherosclerosis	(80 per cent)
Under 40 years—	16 cases, of which	16 show atherosclerosis	(100 per cent)
Under 45 years—	1 case, of which	1 shows atherosclerosis	(100 per cent)

Similar statistics were reported by other pathologists. In view of the fact that even in infancy atheromatous spots

may occur in the aorta at its root and still more often on the large aortic leaflet of the mitral valve (which, as our autopsy experience with children teaches, later disappears entirely), we must differentiate two periods of atheromatous change in the ascending period of the life of the vessel, namely, infantile atheromatosis and puberty atheromatosis. The atheromatosis of puberty can be followed to the prime of life, but, as I can show, it undergoes marked fluctuations. Other war pathologists besides myself have become convinced that, with the increasing duration of the war, the atheromatous spots on the aorta were observed less frequently. It follows from this that the atheromatous process, at least in infancy and childhood, must be a reversible process.

THE ATHEROMATOSIS OF PUBERTY

Let us leave at this point the atheromatosis of infancy and concern ourselves with the atheromatosis of puberty. Fundamentally, the former process is similar to the latter, except that in infancy the lesions are localized more generally on the heart valves than in the aorta. Puberty atheromatosis, or the atheromatosis of early adult life, under which I understand the period up to thirty-three, or at most, forty years, is characterized as follows: In the earliest stages, approximately between the ages of sixteen and twenty, there appear on the posterior wall of the aorta, especially along the lines of tension between the origins of the intercostal arteries, very fine yellow streaks or spots, which are opaque and not at all, or at best only slightly, elevated. The younger they are the more do they appear to lie within the intima itself. Only very gradually do they rise above the surface. The longer the process lasts, the more distinct do these streaked flecks become, until finally the whole posterior wall of the aorta, even the area between and on either side of the intercostal arteries, is involved. Other changes, such as a loss of substance which may be recognized macroscopically, are not to be seen. The aorta, unchanged in its elastic properties, shows no special ectasia and, in short, is otherwise normal. We have before us the picture presented by Virchow as an "intimal fatty change" in contrast to actual atherosclerosis.

If there remain today investigators who still separate these two processes, I am afraid that I must take issue with them emphatically. The so-called intima fatty change of youth is nothing else than the earliest beginning, or better still, a particular stage, of atheromatosis. It is the atheromatosis

Fig. 6. Atheromatosis in the ascending period of life (atheromatosis of puberty).

characteristic of youth which I shall term the atheromatosis of puberty.

What is the essential microscopic picture of the atheromatosis of puberty? I must first recall to your minds that the intima of the aorta possesses an outer elastic muscular longitudinal layer, and an inner elastic connective-tissue

layer which are separated from one another by what I have called an *elastic stria terminalis*. Outside the elastic muscular longitudinal layer lies the internal elastic lamella which divides the intima from the media. Where does the atheromatosis of puberty begin? A peculiar fatty change in the above-mentioned elastic stria terminalis in the deep layers of the intima is the first evidence of the disease process. This fatty change consists of a granular deposition of cholesterin esters in the cement substance of the elastic fibers which compose the stria terminalis. The entire process can be interpreted only as a sort of loosening and swelling of the cement substance with a simultaneous deposition of fat droplets.

The rest of the intima, especially the inner elastic connective-tissue layer, which lies over the stria terminalis, shows practically no changes, at most a slight loosening and swelling of the tissues. As the process continues the fatty deposits increase in the cement substance of the stria terminalis. At the same time there is a diffuse finely granular fatty deposition and precipitation of fat droplets between the elastic and connective-tissue fibrillae of the overlying intimal layer, and finally, there occurs an accumulation of fat droplets in the intimal cells themselves. In this manner a real accumulation of fat takes place in the interstitial, as well as in the cellular, tissue. Characteristic of the entire process, however, is the predominating interstitial fatty change. With the increasing deposition of fat, the entire process extends to the surface until it finally reaches the endothelium. Since, at the same time, there occurs a loosening of the surrounding tissues, which is caused, no doubt, by the presence of an increased amount of tissue fluids, and which is associated with a moderate multiplication of the intimal cells, the affected area tends to swell over the surface. The essential factors in this early picture of atheromatosis are, therefore, a swelling of the inner layers of the intima, with a diffuse minute granular deposition of fat beginning in the depths of the elastic stria terminalis, and extending further and further toward the surface. No further changes take place in the atheroma of the ascending period of the vascular system. At most, the process may retrogress and, as we know

with certainty of infantile atheromatosis, may entirely disappear. These retrogressive processes have not as yet been followed microscopically with certainty. In any case the structure of the intima does not undergo any more marked changes either microscopically or macroscopically.

How can this peculiar phenomenon be explained? Why is there this peculiar increase of fluid in the tissues and swelling of the intima? Why the deposition of fat? The chemical nature of the latter gives us the clue. As Adami and I have been able to demonstrate, it consists of cholesterin esters. Since this cannot arise from a transformation or decomposition of the elastin or collagen of the intima, it must be derived from an infiltrative process. The only source for such an infiltration or imbibition is, as Virchow had already correctly surmised, the blood plasma itself. This nourishes, as is generally known, the inner layers of the vessel wall through a kind of imbibition stream. What more likely than the fact that under special circumstances the imbibition is abnormally increased, as well as in a certain sense slowed down, and thus gives rise to those changes which we call atheromatosis? The condition necessary for an increased invasion of blood plasma is a loosening of the tissue elements. This is intimately associated with physicochemical changes which at present are not entirely understood. However, the fact that the process begins just at the origin of the intercostal arteries indicates that definite mechanical factors, especially forces of a dragging and pulling nature, permit an easier inflow of blood plasma. The fact that these deposits develop in a line parallel to the direction of the blood stream supports this conception. For an exact physical analysis of these forces, I must refer to Ranke.

There is no doubt that in everyone the aforementioned regions are under great physiological strain and therefore suffer a great degree of loosening and imbibition of plasma. This may occur even before puberty. However, as a rule, we observe the formation of these deposits at puberty, indeed, as the statistics show, in a definite and rather high percentage of cases. There is a second factor that must be present before these atheromatous spots may appear. This, it seems to me, is a sufficient concentration of lipoids, especially of choles-

terin esters in the plasma. From plasma of low cholesterin content no deposition of lipoids will occur, even though mechanical conditions are favorable. The greater the concentration of the cholesterin esters in the plasma, the more surely will the areas of the aorta subject to the greatest mechanical strain show this fatty deposition even macroscopically. I am convinced that systematic microscopic examinations would reveal puberty atheromatosis much more frequently. It is obvious that atheromatosis will be found especially in the ascending period of life, when the concentration of cholesterin esters in the plasma is particularly high. This occurs transiently during infancy. I know of no definite investigations of the cholesterin-ester concentration of the blood in the different decades of life. But the peculiar accumulation of lipoid in the gonads that occurs with the advent of puberty, and the changes in the adrenals, all indicate an alteration of the cholesterin metabolism. Thus we can understand that with puberty a new period of lipoid accumulation in the intima begins. This may, however, entirely disappear in malnutrition, especially when there is a deficiency of lipoids in the diet. This accounts for the decrease in atheromatosis in the later years of the war and in the post-war period in Germany.

ATHEROMATOSIS OF AGE

Before discussing how far this conception of the atheromatosis of puberty is supported by experience and experimentation, I should like to discuss the atheromatosis of the declining period of life. Here the picture is entirely transformed. Here there is a truly severe disease, known as atherosclerosis. You are all familiar with its macroscopic picture. Individual predisposition plays a large rôle. On the one hand, we find at the most advanced ages aortas that are entirely smooth with only the signs of senile ectasis and senile sclerosis; while, on the other hand, we observe even in the fourth and fifth decades the most advanced changes in the aorta. Here, too, we find the first signs of disease in certain areas, and particularly in those which are especially subject to mechanical strain. I again emphasize above all

the sites of origin of the intercostal arteries, the scar of the ductus arteriosus Botalli, and the division of the abdominal aorta into the two iliacs. The disease is characterized by the development of flat raised thickenings, sometimes round, sometimes elliptical, with sharply defined or indented edges. The color of these patches is variable. In contrast to the atheromatosis of puberty, in which the spots are always yellow, simply because the others are not visible in senile atheromatosis, we are struck by the polychromatic variety due to the coarser formation of the patches. Some are pale gray, some more cartilagenous, others of a more yellowish tint or even quite yellow and opaque. So they appear to us, so long as no further changes of a sclerotic nature set in. What is the microscopic appearance of these elevated areas of thickening? Fundamentally we find here the same imbibition process as in the ascending period of life. However, the process is developing not in a young and growing aorta, but in one that is ageing and worn out. In the general description of senile changes I have already indicated the alteration in the physical structure of the elastic tissue, and the marked increase in connective-tissue formation in the intima of the aorta. What is more likely than the assumption that, no matter what noxious influences act on the intima of the aorta, the process of swelling and growth will be more marked in the presence of the great excess of connective tissue in the aorta of the aged. Microscopic examination actually indicates that here, too, there are peculiar changes in the cement substance of the fibrillar and elastic elements. These fuse into a sort of hyalin substance, a process which is known as hyalin begeneration of the connective tissue. This process of swelling, in which the ground or intercellular substance becomes suffused or infiltrated with a sort of albuminous material, takes place especially in the deeper layers of the intima, and extends more and more to the surface. Because of the general tendency to overgrowth of the connective tissue of the intima in this descending period of the life of the vessel, the surrounding connective tissue reacts more intensely to the local lesion.

This results in a reactive process in which the areas of swelling are covered by newly formed connective tissue.

This, too, in time becomes affected by the swelling process. In this manner hyaline layer is added to hyaline layer, which leads to the formation of the patches so characteristic of early atherosclerosis. At first these are greyish white in color, but later assume a cartilaginous white appearance.

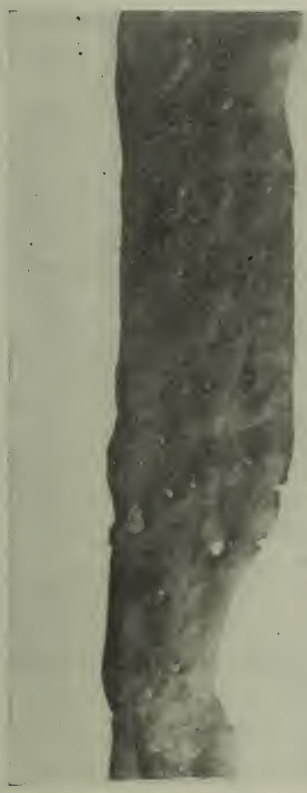

Fig. 7. Atheromatosis in the descending period of life.

Other patches, however, present another picture. The process of swelling is accompanied by a more or less widespread fatty change. This begins exactly as in the atheromatosis of puberty, in the elastic stria terminalis. It is of a finely granular nature and affects in particular the cement substance. Gradually the other layers of the intima, including an increasing number of connective-tissue cells, become involved

in the process, until finally there appears under the more or less swollen and hyalinized surface layer, an enormous fatty patch. This is conical in shape, with its broad base resting on the elastic stria terminalis and its apex extending upward to the intima. This marks the height of the atheromatous infiltration in the descending period of life of the vessel. These are the yellow shining opaque spots which are seen so commonly in all these transitional stages near the transparent hyaline-cartilaginous patches. Before we discuss the latter, we must ask ourselves how these patches originated. Localization, development and appearance indicate that here, too, mechanical influences are the main factors. Here, also, there is a process of wear and tear, a loosening of the fibrillar elastic structures, a physicochemical change of the cement or ground substances determining an increased inflow of the plasma, which physiologically nourishes the intima. It may be more correct to state that this is due to an increased swelling capacity of the altered structures. In youth, where the intima consists primarily of elastic tissue, the swelling is not apparent, while it is very striking in the descending period when the intima is rich in connective tissue. In the descending period, as in the young, this imbibition process is accompanied by a precipitation of lipoid substances in certain cases. Here also we must assume that it is the lipoid concentration of the plasma which determines the presence or absence of fatty changes. There is no need to emphasize the fact that not only the mere concentration of lipoid but the entire physicochemical structure of the plasma plays a fundamental part. We know from many investigations of recent years that the degree of cholesterin-ester deposition is dependent not only on the concentration of the substance itself but on accompanying factors, such as the fat, fatty acids, etc. We must, therefore, hold the mechanical wear and tear and the molecular changes in the intimal structures especially responsible for the origin of the intimal changes.

The particular kind of intimal fatty change, whether simple swelling, or swelling with fatty change, or fatty change primarily, we must, above all, attribute to the character of the invading plasma.

Thus we have formulated a conception of atheromatosis common to the ascending and descending periods of life. The same process involves two tissues: in one case the young, in the other the ageing, intima, which react in a totally different manner.

If our theory of the mechanical loosening of the intima and the imbibition of plasma that follows is correct, then the particular localization of the atheromatous patches in the intima of the aorta must be explainable. As already demonstrated, the entire process begins in the elastic stria terminalis. Here there must exist particular circumstances favorable to the processes of swelling and precipitation. Thus the elastic stria terminalis is the first densely woven membrane that the invading stream of plasma meets, and it serves, so to speak, as a filter. In it may be followed histologically the first process of loosening of the finer network of elastic fibers. I have already indicated that there is not an actual tearing of the fibers, but only an apparent one, in that the single fibrils are separated more and more from one another as a result of the increasing change in the cement substance. It is difficult to say just what this change of the cement substance is. Naturally there must be some sort of molecular change. I accept this as axiomatic, for without such change the separation of the elastic fibrils is unexplainable. In this molecular change of the cement substance, I see essentially what has been referred to as the process of wear and tear of the intima of the vessel. Although Hueck recently opposed the imbibition theory and considered the changes of the intima as purely degenerative, I believe this contradiction can be due only to a misunderstanding. I have repeatedly emphasized that in the places where the vessel wall is under greater tension, there must occur a more marked molecular wear and tear, a kind of destruction, as it were. It is accompanied and essentially influenced by the more marked changes that follow the imbibition of plasma, which only then gives the entire process the proper impression of swelling and fatty change. An independent degeneration, a so-called transformation or decomposition as conceived by Hueck, does not occur. It is essentially, indeed, almost exclusively, an infiltration or, as we may also term it, an imbibition. The experimental pro-

duction of the atheromatous changes which we shall discuss later allows of no other interpretation. If this molecular disturbance first appears in the elastic stria terminalis, and the inflow of nutritional plasma here enters the area of greatest absorption, it is readily comprehensible why the process of fatty change of the cement ground substance is first observed at this site. Only when this border layer becomes more or less infiltrated, so that a more marked damming of the stream of plasma occurs, the infiltration of lipoid substances appears in the overlying layers of the intima as well. Thus we can understand why the atheromatous patch grows from the depths out toward the surface and why its base must rest on the stria terminalis.

If we agree on the similarity of the atheromatous processes in the periods of puberty and senescence, and if we see in the changed tissue of the intima the only cause for the different manner of development in both periods, we must still consider another point. While in youth a reversibility of the process through a reabsorption of the lipoid substances is doubtless possible, such an involution of the atheromatous patch in the period of senescence is absolutely excluded. Resolution of the marked process of swelling and the fatty change, which is usually considerable, is all the less likely, since the organism in this period tends to develop precipitation processes. That is why in the senile period the atheromatous process not only reaches an extraordinary degree but undergoes further transformations that are entirely absent in youth. Most important among these is atheromatous softening. When the tissue cells and the intercellular substance become overloaded with lipoid substances, they finally become asphyxiated, so to speak, in the fat, and necrosis occurs. In the necrotic tissue there is progressive splitting-up of the lipoid elements in particular. The cholesterin ester decomposes, the cholesterin is freed and crystalizes out in the familiar crystals. As has been described by Klotz, the fatty acids form the usual soaps, the most important of which is the calcium soap, since this leads to incrustation and calcification of the atheromatous deposit and the tissue surrounding it. In this way there develops the peculiar impregnation of the atheromatous patches with their placques

of calcareous and bony hardness, which completes the picture of atherosclerosis. In other cases, however, the necrotic atheromatous masses break through the inner layers of the intima and form the atheromatous ulcers. The invading blood stream infiltrates the diseased intima, which accounts for the appearance of blood corpuscles in the loosened intima. This leads to pigmentation, which explains the pseudomelanotic spots in the atheromatous patches. Can we give any other reasons for this unitarian conception of atheromatosis as an imbibition and wear-and-tear disease? That mechanical factors play a very great part is well known. I have already mentioned the localization in those parts of the aortic system particularly exposed to stress. I refer to the marked atherosclerosis above the narrowed portion of an aorta with a narrowed isthmus, to the atheromatosis of the pulmonary arteries in heart failure, to the more marked disease of the respective coronary arteries in unilateral ventricular hypertrophy. To what extent these mechanical overstrains of the vascular system are in turn due to nervous influences is, at present, irrelevant. I recall the experiments of Klotz, who could produce intimal thickenings by purely mechanical means. However, I wish to emphasize that the nature of the mechanical stress is of importance. Thus, for example, hypertonia, whether primary or secondary to an arteriosclerosis of the kidneys never leads to an atheromatosis, but to a true hypertrophy of the entire aortic system with involvement of all the coats, while the real atheromatosis of the aorta is primarily a disease of the intima. Here, then, there must be other mechanical conditions in spite of similar rises in pressure. The problem of atheromatosis is not exhausted by a consideration of the more marked passive burdening of the vascular system. We know that the imbibition of plasma, especially in the process of fatty change, plays a decisive rôle. I have called attention to the increased cholesterin esters in the blood in the atheromatosis of infancy and puberty. Similar relationships may play a part in phthisis, diabetes, etc., not only in the ascending but in the descending period of life as well. The fatty change in the intima in young tuberculous individuals depends doubtless on disturbances of the lipoid metabolism. One might speak here of a cachectic

atheromatosis, in diabetes of dyscrasic atheromatosis. The character of the diet remains the most important factor.

There is no doubt in my mind that the lipoid concentration of the plasma is essentially influenced by the nature of the diet determined both by the richness and character of its lipoid content. All observations support this. Of these I desire to mention only those of Versé. I wish expressly to emphasize that the food, or better said, the lipoid content of the food, does not cause the atheromatosis, but essentially influences the character of the formation of the atheromatous patches by determining the presence or absence of fatty change. How far the lipoids advance or accelerate the loosening process in the intima must remain undecided. The lipoids do not exert an essential influence on the blood pressure. There is no doubt that the increasing fatty change of the atheromatous areas of softening affects the physical structures in the neighborhood and, finally, the underlying media, while a single area of swelling exercises less effect. It is not a matter of indifference, therefore, whether the atheromatosis occurs with or without fatty change. We observe that, as a rule, the worst cases of atheromatosis are distinguished by the advanced character of the fatty change. That the cholesterin content of the diet plays a rôle is readily demonstrated by artificial feeding of cholesterin and cholesterin esters in animals. I need recall only the well-known work of Ingnatovsky, Anitschkow, Lubarsch and Chalatow. We know today that the earlier observations of Saltykow, Steinbiss and others, who noted atheromatous changes in rabbits after injection of staphylococci and after meat feedings, must be attributed to the cholesterin in the food or to the liberation of cholesterin resulting from infectious injury to the body organs, especially the adrenals. More recent investigations undertaken by Maximow have shown that the picture of atheromatosis can also be reproduced in rabbits if one administers with the food, over long periods of time, very small doses of cholesterin in an easily absorbable form. One can demonstrate very prettily that the atheromatosis of rabbits again disappears with the withdrawal of food containing cholesterin. Thus, in this instance, it is in fact a reversible process.

The objection has been raised against these rabbit experiments that they do not produce real atheromatosis, since only the atheromatosis, but not the severe changes, are found. One must recall, however, that even in man real atherosclerosis is found only in the descending period of the life of the vessel, if we disregard the exceptional cases of presenile sclerosis. One cannot expect in rabbits, who do not pass through such definite age periods as man, any experimentally produced atherosclerosis. Of great significance are the investigations of Murata and Kataoka, who were able to demonstrate that the artificial so-called alimentary atheromatosis, which can be produced according to Kohl by lanolin feedings, appears much more rapidly in castrated than in non-castrated animals. Here, then, the general disturbance of the lipoid metabolism plays a definite part. Murata was further able to demonstrate that the castration-atheromatosis with lanolin feeding could be completely inhibited by the simultaneous administration of thyroid-gland substance. One sees, therefore, how great a part the metabolism plays in atheromatous arteriosclerotic changes.

If one glances over the entire province of atheromatosis of the aorta, it is evident that, to account for its origin and different forms, a large number of different conditions must be considered. First, age, which compels us to differentiate an *atheromatosis* of *infancy*, of *puberty*, and of *senescence*. Then the mechanical burden of the vascular system, which permits us to refer to simple *physiological atheromatosis* in those parts of the vascular system under particular stress, and to a *pathological atheromatosis* in the parts under unusual strain; for example, the pulmonary artery in heart failure. That the sympathetic and parasympathetic systems may play a large rôle, which, up to the present has not been demonstrated, cannot be denied. One would have to consider with the purely mechanical factors, the nervous factors as well, to distinguish a *sympathetic* and a *parasympathetic* form. Still, I believe this is primarily of importance in the peripheral system. Far more important for the aorta are the factors of the blood plasma. From this point of view we can speak of an *alimentary*, a *dyscrasic* and a *cachectic atheromatosis*. We must remember that because of the concur-

rence of several factors in its production, the picture of atheromatosis will arise more readily, the stronger one factor may be to supplement the other weaker factor. So, in the presence of a milder degree of wear and tear, a greater concentration of lipoid in the plasma will produce a marked fatty change, and, vice versa, a greater mechanical wear and tear will lead to fatty changes even if the lipoid content of the plasma is small. If we remember that the calcium content of the plasma plays a part in the further transformation of the lipoids, we begin to understand the complexity of the entire process.

I have intentionally limited myself to atherosclerosis of the aorta. The atherosclerosis of the arteries of the muscular type runs along quite other lines, for here the disease of the media, which in the aorta plays no prominent part, is very definite, indeed, dominates the picture. The process of wear and tear of the vessel wall is in evidence, of course, not only in the intima but also in the media, and particularly in the media of the vessels of the muscular type. Here, too, is found the loosening of the cement substance, the molecular splitting up, which is associated with the process of swelling. Here, too, arise fatty changes, above all, mucinous or mucoid softening, or, better still, swelling of the physiological mucoid substance, which is related to the cartilaginous matrix and exists in the media of the vessel. With these processes of fatty change and swelling are again associated the processes of calcification. That the muscularis of the media, in so far as it is dependent for its nutrition on the vasomotor nerves, can be injured by adrenal, thyreodin, etc., is well known. I will not discuss this relationship any further at this point.

SUMMARY

To summarize, then: in the atherosclerotic process of the vessels there is a peculiar process of wear and tear of a molecular nature, which we cannot at present understand, but which, through subsequent swelling and precipitation processes, especially of lipoid substances, and secondary transformation to calcium compounds, acquires a characteristic stamp. It involves a definite specific disease of the support-

ing substance, which occurs not only in the vessel wall, but in other parts of the body as well. Thus the calcium infarct of the kidney papillae, really a fat calcium infarct, is a typical atheromatosis of the kidney-supporting substance, which undoubtedly depends on a wear-and-tear and imbibition process from the continuous tumescence and detumescence of the underlying kidney papillae. To the atheromatous changes belong the so-called senile degeneration of cartilage and the arcus senilis of the eye. As we consider the atheromatosis of the vessels in the light of the larger category of the general processes of wear and tear of the supporting substances, it loses its special qualities, which have given rise to so many erroneous theories of infection, etc. If that process of wear and tear impresses us most strikingly in the vessel wall, it is due to the fact that our vascular system is the organ which is mechanically under greatest strain.

NOTE. The lantern slides used in this lecture may be ordered through The Bildarchiv, Freiburg i. Br.

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VII

OVULATION AND MENSTRUATION[1]

In discussing this problem I shall confine myself essentially to a description of the morphological processes. I must disregard the exceedingly difficult question of the chemical and hormonal disturbances and influences. However, it is my impression that during the last decade so much attention has been devoted to the experimental field of the questions of internal secretion, especially of the so-called glands of puberty of the ovary, that the purely morphological investigations, therefore, have been forced more and more into the background, It is, however, common knowledge that morphological and physiological investigation must go hand in hand, if one desires not to go astray. Again, morphological findings not uncommonly offer an opportunity to support an established clinical diagnosis and are, therefore, worth our knowing. If, in these morphological descriptions I may repeat many well-known facts, I beg your indulgence. I shall endeavor to give you a general survey of the process, but must limit myself, in any event, to the conditions in humans, for otherwise the subject would be too vast.

The question as to the time when ovulation occurs in the human female is more or less decided today, especially since the investigations of Robert Meyer. We can accept with certainty the fact that it does not, as was formerly believed, occur simultaneously with menstruation. We must place it rather in the interval period. Indeed, statements differ very greatly, as to the point in the interval period at which one may expect ovulation. According to my own material of corpora lutea of gravid and non-gravid women, of which the former was especially investigated by Marcotty, I find the fourteenth to the fifteenth day after the beginning

[1] Lane Lecture.

of menstruation, that is, the middle of the interval period, as the time when rupture of the follicle most often occurs. Robert Meyer and Triepel claim that the follicle ruptures earlier, sometimes even by the eighth day after menstruation has begun. The most recent statements of Tschirdewann, who studied the rich material of L. Fränkel, placed the rupture of the follicle between the eleventh and the twenty-first day, while Schroeder, to whom we in Germany are indebted for a very careful study of the entire problem of ovulation and menstruation, indicates the fourteenth to the sixteenth as the day of ovulation. We see then, that the majority of the German authors, at least, consider the middle of the interval period as the main period of ovulation. Before we discuss ovulation itself and the changes associated with it, from which are usually determined the age of the corpus luteum, and with it the end of ovulation, we must first concern ourselves with the question as to why the follicle ruptures at all. We know, of course, that the new-born child brings into the world in her ovary the entire mass of ova which are later to ripen. The estimations relative to the number of ova differ very widely. I mention only that, according to Hansemann, the count may amount to 40,000 or 80,000. In a ten-year old child he found only 20,000; at the beginning of puberty only 16,000 ova. From these 16,000 ova, according to Hensen, only about 200 ova in both ovaries ripen to a point capable of fertilization during the period of woman's fertility. All the rest retrogress either before or during the ripening period. It is a well-known fact that one always sees ripe follicles in the ovaries of a healthy woman at times other than pregnancy. Of these, only one follicle reaches its goal, that is, comes to ovulation and thrusts forth the ripe ovum. Is the ripening of the follicle a matter of accident, or is it governed by some law? If this were a matter of accident, then one would expect that ovulation of one ovum after another in one and the same ovary would be effected. If, on the contrary, it can be demonstrated that ovulation in the majority of women alternates so that each ovary, as a rule, reaches ovulation only every eight weeks, then, naturally, other conditions must exist. Up to the present there have been no complete statis-

tical investigations; I am acquainted with one work only (that of Paul Häggström, Upsala). I myself have had a larger number of cases investigated by Rabl. We estimated quite systematically the age of all the corpora lutea in both ovaries, according to definite morphological signs. We were able to establish the fact that alternating ovulation is actually the prevailing, if not the normal, state. If one considers this circumstance, the time necessary for the corpus luteum to disappear, as such, seems strikingly long. We often see in one and the same ovary, as well as in the other ovary of the same woman, three or four corpora lutea of different ages. Since ovulation ensues, alternately the formation of corpora lutea in one and the same ovary occurs at intervals of eight weeks. In four different corpora lutea, the oldest must therefore be at least four times eight or thirty-two weeks older than the youngest, that is, a period of almost three-quarters of a year. Against this theory of alternate ovulation in the ovaries may be raised the objection that women in whom an ovary has been removed, menstruate again at four-week intervals. Since menstruation and ovulation are intimately connected, one must accept an ovulation period of four weeks for the remaining ovary. From this it follows that the one ovary compensates for the other. Ovulation is not only, therefore, dependent on the number or size of the ripe follicles, but, in addition, on an influence of the entire body, which, after the removal of one ovary, releases the inhibitions formerly controlling the remaining one, so that the stimulus of ovulation is again efficacious after four weeks. We still know very little about these forces arising from the entire organism and overflowing into the ovary.

That the glands of internal secretion play a definite part is known. I need recall only the interrelationships of the thyroid, thymus, adrenals, hypophysis and the ovary. We also know that substances which are released by radiation of any part of the body in cellular metabolism, can effectually impair the sexual organs (radiation experiments of Poos).

The extirpation of the uterus also influences the ovary. The psychic and climacteric influences of ovarian activity

are sufficiently known to the clinician. If we grant the existence of these forces which influence the ripening of the follicle, and the fact that they reach their highest point in an eight-week cycle, first in one then in the other ovary, we are confronted with the next question: why does the follicle rupture? The earlier conception, that the hyperemia occurring with menstruation so raises the turgor within the follicle, that with the progressive thinning of the protecting cover, the ovarian shell, rupture of the follicle occurs spontaneously, is no longer tenable. We know that rupture of the follicle occurs in the interval period and, indeed, at a time when there can be no question of a hyperemia swelling of the genital apparatus. Even were we to grant that the ripening of the follicle is accompanied by a special hyperemia, which is, to a certain extent, true, we still could not understand why the follicles rupture only when they have reached a definite size, and why the ordinary follicular cysts, or other cysts of the size of a fist or a child's head, in which totally different pressure forces or forces of growth must be concerned, do not rupture. In explanation of this, one might cite the rapidity of the process in the follicles that rupture. However, the ripening of the follicle takes at least two weeks, if not longer; and this certainly is not an unusual instance of rapidity of growth.

During the past few years I have had Dr. Strassmann investigate the subject of follicular ripening and follicular rupture of human ovaries. His work has brought out the fact that rupture of the follicle is closely connected with its manner of growth and not with hyperemia. We find references to this growth even in the older literature. It is very striking that the position of the cumulus, which contains the real ovum, is very differently described by different observers. One group, especially Kölliker, Nagel, P. Strassmann, Bayer and Szymonowicz, state that it is directed toward the center of the ovary. Bum, Kollman and Sobotta consider that it is situated more toward the surface. Only Waldeyer and Schaffer suggest the possibility that the cumulus may be situated differently at different periods of the ripening of the follicle. Schaffer speaks directly of a rotation of the cumulus in the follicle, and the investigations

of Strassman have entirely corroborated this, and have enlightened us further concerning the beginning of the follicular rupture.

The primordial follicle presents a round form measuring 35–45 microns in diameter. The ovum lies in the center and is surrounded by a single layer of cuboidal epithelium, the membrana granulosa. The beginning of the ripening of the follicle is manifested by an enlargement of the ovum itself and by an increase of the granulosa cells. This, however, is not uniform, but occurs more markedly at both poles, so that the follicle is altered from the round form of the primordial follicle to the elliptical. Kölliker had already made these observations. With further growth the granulosa epithelium increases. The ovum lies usually in the center of the follicle. With the increasing growth of the poles, the elliptical form becomes more prominent. As soon as the impulse of the follicle to life and growth ceases, as is the case in early atresic follicles, the follicle again collapses and resumes its original spherical form. However, if it continues to grow, then the ovum gradually advances toward the central pole. In the peripheral pole of the granulosa, a slit-like opening appears, which is the beginning of the liquor-containing space of the follicle. Kölliker called attention to the fact that the site of the germinal elevation is on the side opposite the surface of the ovary. During this period of formation of the cavity of the follicle, there appears a differentiation of the surrounding connective tissue. A very distinct theca interna, rich in capillaries and cells, and a more fibrous theca externa is formed. The entire process of the formation of the space can be traced to a marked swelling and to a fluid imbibition by the intercellular substance of the follicle. An actual cellular destruction cannot be demonstrated. During the entire development up to this point, the ripening follicle is separated more and more from the surface, and has, so to speak, wandered into the depths, that is, the direction of growth has been primarily toward the center of the ovary. Now there commences a new period, which is characterized by a gradual ascension of the follicle and the progressive invasion of the cortex. This entire process is ushered in by a peculiar transformation of the theca interna.

While up to now the growth of the theca interna occurred concentrically, there now takes place an eccentric increase of the cells, in the sense that there is a striking thickening of the theca on the side of the follicle, facing the surface. As a result of this cellular growth of the theca interna, the follicle now develops toward the surface of the ovary. The growing follicle must extend toward the surface, since, surrounded from behind and both sides by firm connective tissue, it can

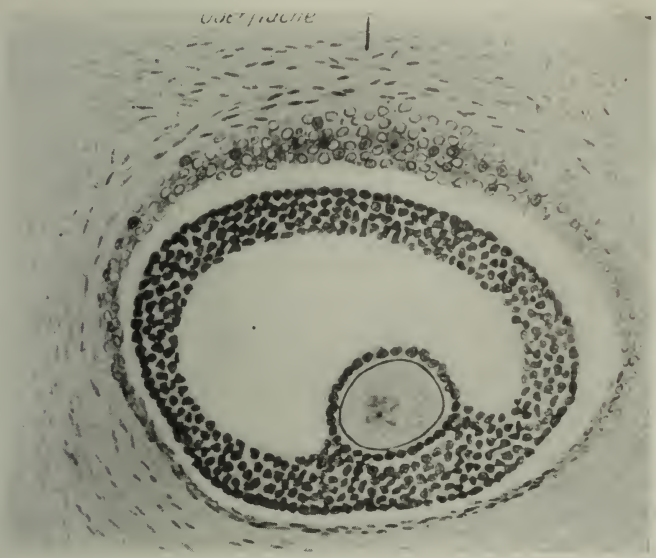


Fig. 8. Follicle, beginning of ripening period, cumulus directed toward center of ovary, excentrical differentiation of theca interna. (*After Strassmann.*)

advance most readily through the looser tissue near the surface. In the meantime, the follicle has reached a diameter of 0.4 mm. The germ-hill with the ovum still lies in the inner wall and with further growth of the follicle, there commences a gradual revolution of the entire contents. The displacement of the cumulus toward the side of and finally in the wall nearest the surface, can only be explained by a marked growth of the granulosa. In a follicle which has reached a diameter of 0.5 mm., the cumulus lies quite close to the surface, just beneath the loosened, highly cellular section of the theca interna. In this period of the wandering of the cumulus

inside the follicle, the interaction of the several follicles maturing simultaneously on one another, and of any existing remains of follicles which have already ruptured, exerts a deleterious influence. Now the degeneration of single follicles becomes evident. Some are destroyed, but others continue to grow. When the follicles, by further growth, reach a diameter of 2.5 to 3 mm., the degenerative processes appear in ever-increasing numbers, so that almost three-quarters of all the

FIG. 9. Ripe follicle, cumulus toward surface. (*After Strassmann.*)

follicles that had advanced to this stage are destroyed through necrosis of the ovum, or rather, of the granulosa cells. Only a few continue to grow. In the ripe follicle the distinct vacuole-formations in the germ-hill (*cumulus*) which loosen the ovum in preparation for the follicular rupture, are in evidence. We can recognize very distinctly the marked difference in the structure of the theca interna in the central and peripheral border of the follicle. With increasing maturity the covering cortical layer is drawn more and more into the growth of the theca interna, and thus a point of softening is produced through which the follicle with its contents can finally wander

out; but before this final breaking through, and before the out-pouring of the fluid contents together with the loosened germ-hill occurs, the latter has again wandered more to one side, as if the ovum wished to be guarded against the stormy movements at the point of rupture.

Thus we have followed the follicle in its ripening until its rupture. The ovum has left the follicle. There is not a trace of hemorrhage; now commences the transformation to the corpus luteum. The fate of this corpus luteum depends primarily on what becomes of the ovum which has just left it. If the ovum is not fertilized there develops a corpus luteum of menstruation; if it is fertilized, a corpus luteum of pregnancy. It would really be more correct to speak only of corpus menstruationis or corpus folliculare menstruationis or corpus folliculare graviditatis, respectively. For the transformed product of the ruptured follicle is certainly not a yellow body at first. The yellow body is a much later development and portrays, so to speak, a particular phase of development. In order to make it perfectly clear, we shall next follow the transformation of the follicle in an unfertilized woman who will continue to menstruate, that is, the so-called *corpus folliculare menstruationis*. It will later become evident why I name this structure the menstruation body. The former view regarding the changes in the follicle that followed rupture assumed that with the rupture there occurs marked hemorrhage into the follicle, so that the so-called corpus hemorrhagicum is formed, which, by the gradual transformation of this mass of blood into pigment, assumes the yellow color. This view is still held by many today. One cannot free oneself from the idea that the rupture of the follicle occurs under the influence of menstrual hyperemia. Of course, then, hemorrhage must also occur in the ruptured follicle! I have insisted for many years that this conception is wrong and that, as in the mouse, so in the human, no hemorrhage follows the follicular rupture. At any rate, these hemorrhages remain small and never, or only exceptionally, result in a structure which might be called corpus hemorrhagicum. What then becomes of the follicle if no hemorrhage occurs in it? It collapses. This explains in part the peculiar folding and the fluted appearance of the developing follicular body. As soon

as the ovum has left the follicle, a lively growth of the follicular epithelium begins, which leads to the formation of the so-called granulosa lutein cells. Simultaneously the cells of the theca interna, although their growth is less regular, proliferate, particularly in the region of the vessels growing into the granulosa-layer, and lead to the formation of the layer of the theca lutein cells. The granulosa lutein cell layer is vascularized in a short time, and along the inner surface a small border of delicate connective tissue becomes spread out, while the original follicular space is filled more and more with serum with a moderate quantity of red blood corpuscles. This accumulation of fluid is possible only because, in the meantime, the site of rupture of the follicle is closed by exudate and the approximation of its borders. In the interval until the next menstruation, that is, in about fourteen days, the follicle body reaches a point of greatest development—the stage of its blossom, as it has been called by other authors—and becomes the *corpus folliculare efflorescens*. The structure has now reached its greatest size. It has a light yellow coloring which is due to a moderate lipoid content of the lutein cells. But the real yellow color, which has given the body the name of corpus luteum, is still lacking. We shall see that this transformation of the corpus folliculare efflorescens into the corpus folliculare luteum passes through still another very important interval period, which is a determining factor in the entire fate of the follicle. *This is the hemorrhage into the follicle, which occurs with menstruation.*

Although, undoubtedly, at times small hemorrhages into the follicle occur during its "bloom period" (hemorrhages which may be independent of all external influences), nevertheless, only with menstruation occurs the very characteristic hemorrhage throughout the follicle and the transformation of the corpus folliculare efflorescens into the *corpus folliculare hemorrhagicum*. This corpus hemorrhagicum is therefore not the beginning of the corpus luteum formation, but rather the end of the follicle body, inasmuch as the menstrual hemorrhage brings about the definite retrogression of the corpus folliculare and its transformation into the true

corpus luteum. I have repeatedly emphasized the importance of this participation of the usual corpus folliculare in the process of menstruation. This diffuse hemorrhage is the most certain indication that a new menstruation has set in, or, as one may express it, that the ovum belonging to the follicle has died.

Where and how does the menstrual hemorrhage in the corpus folliculare occur? The bleeding comes from the rich capillary system of the layer of granulosa lutein cells. That smaller hemorrhages occur in the lutein cell layer as well, is correct. The main mass of blood, however, pours into the newly existing follicular space, which till then was filled with an essentially serous, often partly clotted, fluid. The fresh mass of blood displaces the old fluid, mixes with it and brings about the definite coagulation of the contents. We can see with the naked eye the granulosa layer overlying the layer of blood, frequently heaped up at one pole, which, no doubt, is explained by the settling of the blood during fixation. Since this marked diffuse hemorrhage, if we except certain operative traumas, develops only during menstruation, I have named the entire picture of the transformation of the follicle, the corpus menstruationis. With this, the second, and indeed the most important period of the corpus menstruationis, is closed.

Now commences the third phase, the retrogressive period, that makes itself known through a marked lipoid infiltration of the lutein cells. So arises the characteristic yellow coloring of the corpus luteum, the *corpus luteum menstruationis*, more correctly, the corpus luteum period of the corpus menstruationis, while the lipoid infiltration of the lutein cells becomes greater and scarring processes become manifest. First there is a marked connective-tissue formation in the follicular space—a kind of organization of the bloody effusion that takes its origin from the connective-tissue coat bordering the layer of lutein cells. It is self-evident that the blood corpuscles of the effusion become transformed into blood pigment. Thus, we find, beside the lipoid infiltration of the lutein cells, a more or less distinct deposition of iron-containing pigment in the connective-tissue core of the

corpus luteum. From the lipoid, or accompanying it, there develops the characteristic color substance of the luteum cells. These become gradually smaller and a hyaline intercellular substance appears that swells more and more, and thus very gradually leads into the fourth developmental period of the corpus folliculare menstruationis, to the real involution body, to the corpus candicans. One may also term this the *corpus folliculare involutum.* Thus we have learned to recognize four successive periods of the corpus folliculare menstruationis: The corpus folliculare menstruationis efflorescens, the corpus folliculare menstruationis hemorrhagicum, the corpus folliculare menstrationis luteum, the corpus folliculare menstruationis involutum or candicans.

This description of the transformation phase of the corpus folliculare would not, however, be complete without mention of the fact that the transformation process of the corpus luteum to the corpus candicans occurs very gradually and stretches over a period of several months, taking, on an average, one-half to three-quarters of a year. During this time new menstruations are occurring and these always exercise anew their diffuse hemorrhagic effect on the corpus luteum, as long as the latter has not become definitely changed into a scar poorly vascularized. It need not astonish us, therefore, to observe even in older corpora lutea a rather high hemosiderin content, or even a recent bloody effusion. All this must be considered, in order to reach a true estimation of the age of a corpus folliculare menstrationis luteum.

Entirely different, however, is the development of a corpus folliculare if the ovum belonging to it is fertilized and pregnancy is initiated. Then the *corpus folliculare graviditatis* is formed. The essential difference between it and the ordinary corpus folliculare is due to the fact that, as a result of pregnancy, menstruation is suppressed for many months. All the changes brought about by menstruation in the usual corpus folliculare, do not occur. For this reason I have contrasted the latter as corpus folliculare menstruationis or, briefer, corpus menstruationis, with the corpus folliculare graviditatis, or for short, corpus graviditatis. The investigations to date concerning the corpus graviditatis, especially

those of Miller and Marcotty, which have been essentially confirmed by Cohn, show that the corpus graviditatis has only two developmental periods, a period of growth and a period of retrogression, since the period of diffuse hemorrhage, with the following period of yellow coloring, is absent or barely indicated in pregnancy. Therefore, at the beginning of pregnancy there is no deep yellow colored corpus luteum such as is seen in normal continued menstruation, but a much paler yellow body, whose color intensity cannot be compared with that of the usual corpus luteum. The acme of development of the corpus graviditatis is characterized above all by the more marked growth of the entire lutein cellular tissue. One gains the impression that this ascending developmental period, because it is not interrupted by the menstrual hemorrhage, is very much more prolonged and so leads to the development of a much larger body. In this enlargement the follicular cavity is essentially concerned, since it can accumulate a much larger amount of fluid without becoming organized or transformed into scar tissue. The cystic cavities remain distinctly preserved until the middle of pregnancy. The lipoid infiltration and the pigmentary coloring of the lutein cells are as ill-defined in a corpus graviditatis, as in a corpus menstrationis before menstruation. The striking lipoid infiltration, setting in in the latter after menstruation, is entirely absent in the corpus graviditatis during pregnancy, and is even less evident after birth. On the other hand, there develops in the lutein cells of the corpus graviditatis a peculiar colloid, which has been described by Miller. There is a further difference, in that the connective tissue of the central body, growing slowly in the second half of pregnancy, contains either no hemosiderin whatever, or only traces of it, because of the absence of menstrual bleeding. The absence of this menstrual hemorrhage retards the entire menstrual retrogression and the corpus graviditatis remains during the whole duration of the pregnancy in the "blossoming stage." Only then the second phase commences, the actual scarring, the transformation into a corpus candicans, which corresponds to the fourth period of the corpus menstruationis. How rapidly

this involutes and how far it, too, may be interrupted by new menstruations has, unfortunately, been as yet insufficiently investigated. It seems to me that in the real corpus graviditatis no hemorrhage occurs even after the end of pregnancy in the puerperium, so that all the retrogressive disturbances induced through menstrual hemorrhage play no rôle. From this then follows the remarkable fact that a corpus graviditatis does not need much more time for its total metamorphosis than a corpus menstruationis.

As I have said before, the ordinary corpus menstruationis persists eight or nine months until it has undergone complete scarring. The corpus graviditatis does not take much longer to complete its metamorphosis, but the nature and duration of the successive stages in the two are entirely different.

We cannot complete these reflections on the corpus luteum without considering the question of its significance. As you know, since the experiments of Fränkel on the interruption of pregnancy after cauterization of the corpora lutea in animals, a protective property for the continued duration of pregnancy has been attributed to them. On the other hand, the lutein cells are essential elements in the so-called interstitial glands, and play an important part in the field of hormones. Ancel and Bouin, Steinach, Sand and others, believe that the lutein cells are the centers of a specific hormone production, on which depend the development of secondary sex characters. I cannot, at this time, go deeper into this doctrine, but I should like to point out that human pathology has not been able to establish any sex-determining effects, either for the interstitial cells of the testes or for the lutein cells of the ovaries. All the experiments of the French, which consist primarily in the ligation of the vas deferens, as well as the further experiments of Steinach and Lipschütz in the transplantation of gonads have always shown this one fact, that the effect of the respective gonads on the secondary sex characters continues as long as the specific gonad-cellular material, that is, spermatogonia or oogonia, persisted and could be resorbed. As soon as this specific cellular material with its potent components has been definitely destroyed and consumed by resorption into the body, the influence of the gonads on the secondary sexual

signs ceased. Steinach, in his transplantation of testicles and ovaries in castrated animals, had the same experience. If he transplanted a testicle into a castrated female, or an ovary into a castrated male, there were undoubtedly established in the castrated female, male characteristics, and in the castrated male, female characteristics. This influence lasted weeks and months. Microscopic examination of the gonads revealed that apparently only the so-called interstitial cells, or lutein cells remained, while the specific cells were lost. From this Steinach concludes that to the interstitial cells or lutein cells are to be attributed the main influences on the sex characters of an organism. Against this important experiment the following objection may be raised. The resorption of the dying spermatogonia and dying oogonia progresses slowly. At any rate the last remains of these cells are very difficult to recognize histologically, so that one can never say with certainty whether or not all the spermatogones or oogones have been destroyed. If one ligates both vasa deferentia in the animal, there first occurs a complete stagnation of the production of semen and an apparent death of the specific spermatagones. Therefore, Ancel and Bouin also believe that from such ligated testes pure interstitial cellular tissue can be obtained. Steinach speaks of a pure puberty gland. Actually, however, all the spermatogones are not lost. As Tiedje has shown, one need wait only long enough, that is, a few months, in order again to observe spermatogenesis reappearing, in spite of the continued presence of the ligature or of resection of the vasa deferentia. We see from this how difficult it is to decide entirely from the histological picture whether or not the specific sex cells are present. In any case, this holds true for the testes. The second objection which is raised against the experiments of Steinach is the following: If it is true that in the transplated gonads the specific cells are all destroyed and only the interstitial cells remain, then the transplanted gonads must influence the development of secondary sexual characters, as long as the interstitial glands are visible. Now the observations of Steinach himself show that the influence of the transplanted gonads is lost after a certain time, generally after a few months, so that one must again implant the heterosexual

gonad in order to obtain a further influence in the castrated animal. If, however, one examines the first transplanted gonad in this inert stage, one still finds interstitial cells or lutein cells. This is the best proof that they cannot be the main factor in the development of secondary sex character. I shall only add that I myself have had the opportunity of examining several cases of female hermaphroditism, in whom, in the atrophic testes, the interstitial cellular tissue was very well developed, resembling in structure the male interstitial cells, in spite of which the secondary sex characters showed a more feminine type. From this it follows that the interstitial cells cannot be the determining elements. What is true for the interstitial cells of the testes, is true in the same way for the lutein cells of the ovaries.

If we must deny the theory of the puberty gland or the corpus folliculare, there still remains the question whether the corpus folliculare in some manner prepares the uterus for the fertilized ovum and further influences the pregnancy. I should like to point out that this theory too is untenable. I have described in detail how intimately the life of the corpus folliculare is bound up with the fate of the ovum, not in the sense that the corpus folliculare determines the fate of the ovum, but, on the contrary, the ovum determining the fate of the corpus folliculare. The corpus folliculare, whether a corpus menstruationis or a corpus graviditatis, cannot accordingly play the important rôle ascribed to it today by so many authors. I miss real experimental proof in all the old and new theories concerning the corpus luteum. I myself am under the impression that the corpus luteum possesses more of a *local significance* for its respective ovary. What the nature of this local significance is, is truly difficult to say. Perhaps it concerns a particular regulative mechanism, which, through the goodly storage of lipoid and other substances, governs the chemical metabolic processes and the physical pressure-relationships in the ovary to the extent that through it the growth and ripening of the remaining follicles are influenced. One may conceive of the corpus folliculare as a sort of inhibiting body only through the involution of which the remaining follicular apparatus can return to full function. At any rate, I believe that the local effects of the corpus

luteum will first have to be explained before one concerns oneself too theoretically with its general effects.

As you know, in pregnancy all the existing remains of the corpus luteum menstruationis show more or less distinct signs of growth, while the ripening of the follicles is markedly slowed or entirely discontinued for the duration of pregnancy. Here, too, exists, therefore, a certain inhibition.

This concludes all that I wish to say concerning ovulation. I turn now to the process of menstruation. Since the fundamental investigation of Hitschmann and Adler, which were confirmed and furthered by the observations of Schickele, Schroeder, Robert Meyer and others, we know today that the mucous membrane of the uterus undergoes a regular cycle of morphological changes, which reach their acme with each menstruation. Which parts of the genital tract are involved during menstruation? Since we have previously heard that the ovary, at any rate, the corpus follicularis and the older corpora lutea themselves, are concerned in each menstrual cycle, one may assume that the entire remaining genital tract takes part in the process as well. This is indeed true to the extent that the menstrual congestion involves all the pelvic organs. If, however, one understands by menstruation the characteristic hemorrhagic process and the peculiar excretion, then one should be able to establish very easily that only a definite part of the genital tract, namely, the corpus uteri, is the seat of the menstrual process. As you know, we differentiate the uterus into three parts—the real body, with its many characteristic glands, the isthmus, with a somewhat narrower mucous membrane and fewer glands, which, however, resemble the glands of the body, and finally, the cervical portion with its special mucous glands. I consider this division of the uterus into three parts as very important, since normally only the mucous membrane of the body is involved in the process of menstruation as well as in the preparation of pregnancy, while the isthmus and especially the cervical canal, play a more passive part. One may best compare the isthmus with the tubes. These too are passive, as a rule, in menstruation as well as in pregnancy, or undergo only such changes as may be described as accompanying or resulting phenomena. However, we never find

the characteristic expression of the typical reaction of pregnancy, as we see it in the mucous membrane of the body. If, as a rule, the menstrual process is limited to the mucous membrane of the body of the uterus, we may then ask to what extent the menstrual destruction involves the uterine mucous membrane. Before we approach this problem more closely, we must briefly review the menstrual cycle of changes of the mucous membrane in the body. At the time when the follicle bursts and releases the ovum, the mucous membrane of the fundus is in a so-called rest period. The destruction produced by the previous menstrual period is again compensated for—the mucous membrane prepares itself anew for the reception of an ovum. This preparation shows itself in a more marked formation of mucin granules in the glandular epithelium, because of which the latter increase in size and extent. Gradually there occur changes in the intercellular tissue, which lead to a characteristic premenstrual swelling. This obtains its characteristic expression in the last eight days before the expected menstruation. The mucous membrane which, in the rest period, is about 2.0 to 3.0 mm. thick, now swells to from 3.5 to 4.6 mm. With this there appears a characteristic division of the membrane into three parts, which is especially recognizable by the glandular picture. While the basal portions of the glands are as good as unchanged, the middle portions show a very marked widening, with fine capillary prominences, and an epithelium well filled with secretion. Because of this the entire layer appears loosened in a cribriform or spongy manner and, for this reason, is also termed the spongy layer. Over this lies the so-called compact layer, which consists primarily of proliferated stroma cells, only here and there broken through by glandular ducts. The names spongiosa and compacta are nevertheless more used for the changes of the mucous membrane of pregnancy, where, through further decidual swelling of the stroma-elements and increased growth of the glands, the three divisions of growing mucous membrane are more clearly defined. There is, however, no doubt that the premenstrual swelling is nothing more than the first stage of the decidual swelling; so that the terms compacta, spongiosa and basalaris, can be applied as

well to the premenstrual swollen mucous membrane. I should like to observe at this point that Schroeder has used for the spongiosa compacta the new expression "functionalis," in order to indicate that it is these two layers which, according to his opinion, are more or less completely destroyed in menstruation, as well as at the beginning of the puerperium, and are renewed from the basalaris. With this I come to the important question: "What part of the premenstrual swollen mucous membrane is destroyed during the process of menstruation?" Just before menstruation begins, the mucous membrane, following the sudden increased hyperemia, widens to about 7.5 to 8.0 mm., that is, it becomes two to three times as thick as the resting mucous membrane. With the commencement of menstruation the thickness of the mucous membrane rapidly diminishes and measures on the average only 0.5 to 0.8 mm., according to Schroeder. There has, no doubt, occurred an enormous loss of substance. To what is this attributable?

Formerly, when our knowledge of the uterine mucosa depended on post-mortem material, it was assumed that a very thick layer of the mucous membrane was destroyed with menstruation. With the introduction of improved methods of preservation, and as a result of the examinations of uteri obtained by operation, the conviction grew that the loss of substance was really very small. The superficial epithelium was found well preserved and the findings in the dead body were ascribed to cadaverous changes: a very just conclusion. One must not forget, however, that the uterus is generally observed only several days after the expiration of menstruation, since operations are seldom done during menstruation itself. Thus, in the meantime, the various processes of regeneration may have set in to reproduce a normal mucous membrane. Only in the last decade, as a result of examinations of the uterus during menstruation, has material been obtained that is free from criticism. The several investigations, especially those of Schroeder, show that with menstruation a large portion of the mucous membrane is destroyed. By collecting the menstrual blood, one can establish that, as a rule, on the first day (seldom on the second, never later), small, macroscopically recognizable

shreds of sequestrated uterine mucous membrane come away (E. von der Leyen, Lindner, Sekiba). From a histological examination of these cast-off shreds we can reconstruct an approximate picture of the nature of the process of menstruation. While it was formerly believed that with menstruation only a diffuse hemorrhage into the superficial layers with partial destruction of the epithelial coat occurs, we know today that the marked hyperemia of the uterine mucous membrane is very soon followed at the onset of menstruation by a stasis, which leads to a more or less extensive hemorrhage into the mucous membrane, and to a practically complete necrosis of certain layers. The glandular epithelium is preserved for an astonishingly long time in this dying tissue. During the onset of the menstrual circulatory disturbance, there occurs a marked accumulation of lymphocytic and leucocytic elements; this can be confirmed very easily by means of the oxydase reaction. Menstruation then is accompanied by an extensive necrosis of the mucous membrane; the necrobiotic layer is cast off by continued hemorrhage. We are dealing in menstruation not with a superficial desquamation, but with a real sequestration.

The only question is how deep this sequestration process extends. According to Schroeder, who possesses the greatest experience in this field, it includes the entire compact and spongy layers, that which he terms "functional" layer. Our own investigations, which were done by Sekiba, lead to a somewhat different result, and we grant that the conditions vary in individual cases. In some, very large tissue fragments and in others, barely recognizable particles are cast off. Our histological investigations lead to the conclusion that this microscopic difference is traceable not so much to a different thickness of the necrobiotic layer as to a different degree of destruction of the same. If one correlates all the histological examinations, the result becomes more uniform, to the extent that essentially the compact and the bordering layers of the spongiosa become necrotic. We believe that the greater portion of the spongy layer remains and is not destroyed. We would, differing with Schroeder, indicate only the compact layer as the true functionalis and not include

the spongiosa. We agree with Schroeder that at least the entire compact, and, in a few women, perhaps, the larger part of the spongy layer as well, are sacrificed to the necrobiotic process of menstruation.

It is of special interest to follow the reconstruction of the mucous membrane after menstruation. This has often been

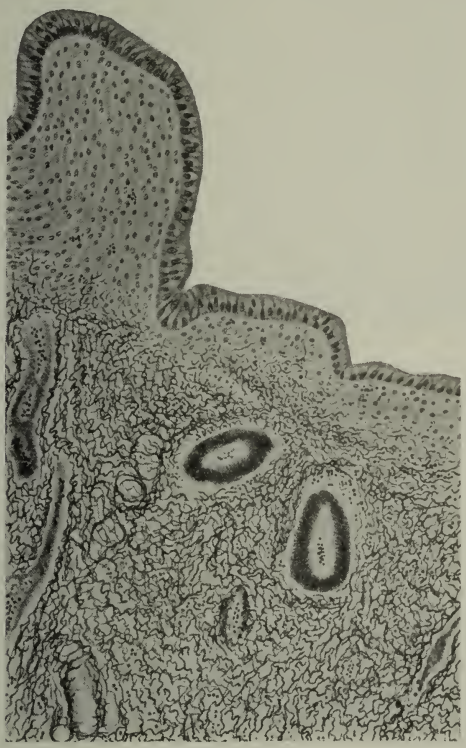
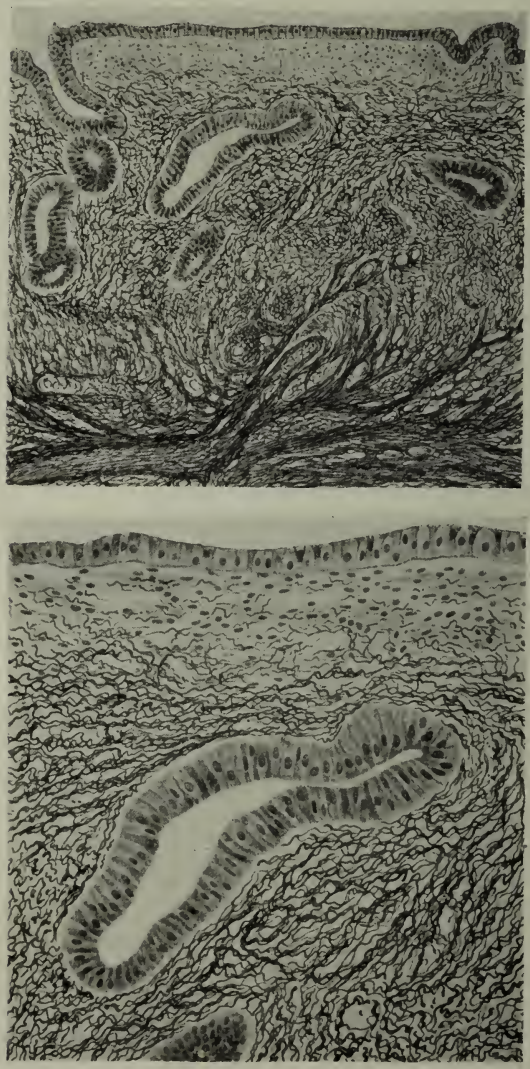


FIG. 10. Mucous membrane of uterus seven days after menstruation. Regenerative layer free of reticular fibers.

done. The work of the several authors are in agreement. On about the seventh day after menstruation the mucous membrane is again epithelialized and, after another eight days, has again grown to its original thickness. Then, at the time of the new follicular rupture, there begins the formation of the developmental type. Since the finer structures, especially the reticular fiber system, must be included in the

entire reconstruction of the mucous membrane, I had Dr. Sekiba undertake more definite investigations of this



FIGS. 11 and 12. Mucous membrane of uterus showing gradual invasion with new reticular fibers derived from the old mucous membrane.

point. The results were most interesting. On the seventh day after the beginning of menstruation, a freshly regener-

ated mucous membrane that has been stained to bring out the reticular fibers, (Fig. 10) shows the following picture: The old mucous membrane, recognizable through the entangled network of the coarse reticular fibers, is overlain by a tissue layer that is free from reticular fibers, but covered by a uniform epithelial layer. This layer, which is free from reticular fibers, and which I might call the regeneration layer, is a very characteristic sign of a recently menstruating uterine mucous membrane. This regeneration layer is only gradually invaded with new reticular fibers derived from the old mucous membrane (Figs. 11 and 12). The uterine mucous membrane, eight days after the onset of menstruation, shows very definitely the gradual invasion of the regeneration layer with reticular fibers; while the sub-epithelial layer is more or less free. In sections which are taken ten days after the beginning of menstruation, the reticular fiber network has already reached the epithelial coat. The entire regeneration layer is now infiltrated by fine reticular fibers. In spite of this, one can still recognize very clearly the difference between the old mucous membrane and the newly forming mucous membrane. While the old glandular layer is built up from a thick maze of rather coarse reticular fibers, the new glandular layer is built very loosely. This new glandular layer increases in thickness and becomes slowly transformed into the new compact and bordering spongy layer.

On about the tenth day after the onset of menstruation, the mucous membrane has reached the height of regeneration. The difference between the regeneration layer and the old mucous membrane layer is practically gone. The reticular fibers are thick and strong and almost the same in all parts of the section. However, the arrangement of the newly built reticulo-fiber system is not everywhere functionally fused with the old system. No sooner has this happened than the new preparation period commences. It begins with an increasing loosening of the reticular fiber system, extending from the surface slowly to the deeper layers. On this account there is again a separation between the upper and lower layers, as is distinctly evident in a specimen taken on the twentieth day after menstruation.

In the last week the marked widening and the tortuosity of the glands begin to appear. Now menstruation commences and by necrobiosis destroys the superficial layers of the compact and spongy layers. Only the lower two-thirds of the spongy layer and the basilaris remains intact. From this the functionally active mucous membrane tissue grows anew. We see, therefore, that we can very well distinguish with Schroeder a functionalis and a basalaris, even if our ideas of the border zone between the two parts differ. I consider it more accurate to differentiate the layer that is newly formed after menstruation until the middle of the interval as the *regeneration layer*, from the *functional layer* that develops only in the second half of the interval. The functional layer is evidence of the fact that a fresh follicular rupture with ejection of an ovum capable of fertilization has occurred, and that the mucous membrane is preparing itself for the reception of the ovum, in case of its fertilization. The regeneration layer indicates that an ovum has just been destroyed and through the menstruation process has been made ineffectual for the rest of the body. Both structures, the functional layer, as well as the regeneration layer, with their particular peculiar construction, are of great importance in clinical diagnosis. If we find, for example, a resting uterine mucous membrane, then we know that no new follicular rupture has occurred, or that, at least, it has taken place very recently; otherwise the characteristic premenstrual swelling and the development of a functional layer would have begun. Unless we examine the mucous membrane with special stains for the reticular fibers, we cannot tell whether or not a menstruation has recently occurred. If we find, on the other hand, a definite regeneration-layer with the reticular fibers still poorly developed, or a reticular fiber system arranged in a functionally asymmetric manner, we may conclude that destruction of the uterine mucous membrane has recently occurred. If this regeneration layer is arranged fairly symmetrically, there is no doubt (with sufficient consideration of the clinical history, to exclude other possibilities), that a menstruation process must have recently occurred. If we find, however, a resting uterine mucous membrane with a perfectly developed reticular fiber system, uniformly constructed through the

entire mucous membrane, without any trace of stratification, we can draw the conclusion that probably the uterine mucous membrane has not recently undergone a menstrual destructive process. In Figure 13, a preparation from a woman with a six months' amenorrhea shows this very clearly. One can recognize very distinctly the quite uniform construction of the mucous membrane and the absence of any regeneration

FIG. 13. Mucous membrane of uterus from a case of amenorrhea. There is no regenerative layer; the reticular fibers are well developed throughout the mucous membrane.

layer. We have been able to confirm this finding in all similar cases. It is self-evident that the regeneration layer can be observed only in the fertile period of woman from the onset of the menses to the menopause. Before this, and especially later, the mucous membrane possesses a uniform amount of reticular fibers and there is no stratification recognizable.

The accurate knowledge of the construction of the regeneration layer is necessary, not only in order to differentiate uteri which have menstruated recently from those which are found

in a period of amenorrhea, but also as a means of judging pathological processes.

In the mucous membrane of a myomatous uterus we find, as you well know, hypertrophy of the mucous membrane. This has, however, nothing to do with the premenstrual swelling, but depends on a more uniform edema and hyperplasia of the tissue elements. In such cases, because of the edema, the regeneration layer will appear even paler than otherwise, but will still show a regular regeneration of the reticular fibers. The picture is quite different, however, if infectious inflammatory processes attack the endometrium. Schroeder has especially pointed out that in gonorrheal infections the reconstruction of the functionalis may suffer considerable disturbance. We can also establish the fact that, especially in cases of gonorrheal infection, no true regeneration layer is formed. More often the formation of the reticular fibers in the upper sub-epithelial layer, which is infiltrated with plasma cells and leucocytes, does not occur. The entire regeneration layer does not reach the advanced stage it ought to reach. It is therefore self-evident that here, too, the process of menstruation must be disturbed. To what extent the inflamed healing of such infected and inflamed mucous membranes results in scar formations, is a separate question. It is striking, indeed, that in the usual processes of regeneration no pigment is formed in the mucous membrane of the uterus with the resorption of the hemorrhagic mass. In contrast to this, one finds not infrequently, in pathological conditions, cases in which, in place of the regeneration layer with its delicate reticular system, there is a coarse fibrous scar with a collection of pigment. I cannot say to what these scar formations are traceable.

We see, nevertheless, that the study of the uterine mucous membrane in the various phases of the menstrual cycle furnishes a lead in the diagnosis of certain disease conditions of the mucous membrane. It is of especial importance, it seems to me, to consider the picture of the mucous membrane in relation to the disturbances of function of the ovary. I am sure we are all convinced that the great majority of all menstrual disturbances are due, not to changes of the uterine mucous membrane, but to the alterations of the follicular

apparatus, or of the organism as a whole. We differentiate, as you well know, a hypo- and a hyper-menorrhea, depending on whether the hemorrhage is too small or excessive; an oligo- or a poly-menorrhea, if the hemorrhage recurs at intervals that are too long or too short; and a metrorrhagia, if the hemorrhage occurs quite irregularly and independently of the menstrual cycle.

How are these anomalies of uterine hemorrhage related to the functional disturbances of the ovary? It has been impossible up to the present to find definite morphological evidence of a causal relationship. Nevertheless it is generally believed that we must connect premature or delayed menstruation with a concomitant premature ripening of many follicles, a kind of small cystic degeneration of the ovary, or, on the contrary, with a delayed ripening of the follicle. There may certainly be some truth in this, for ovulation and menstruation are certainly related. Nevertheless, ovulation may occur without menstruation, but menstruation can hardly occur without ovulation. Even more difficult is the explanation of metrorrhagia, the so-called metropathia hemorrhagica. Here the prolonged persistence of a single ripening follicle, the failure of the follicle to rupture, and the absence of the formation of the corpora lutea may exercise a continuous irritation on the uterine mucous membrane, without the occurrence of true menstrual hemorrhage. Thus the picture of the glandular hyperplasia, as we frequently see it in the uterine mucous membrane prior to the beginning and at the onset of the menopause, is supposed to arise. In such mucous membranes, which furnish particularly rich material for curettage, one finds very frequently, as Schroeder correctly describes, extensive necrosis of the mucous membrane. I have found it repeatedly. One gleans the impression that the necrobiotic process which menstruation calls forth in the mucous membrane, is initiated but not carried through to the end. The line of demarcation which is the rule for normal menstruation does not develop. The mucous membrane bleeds to death, as it were, in this imperfect process of demarcation.

There occur, however, irregular hemorrhages or abnormally prolonged menstruations in young persons, in which the histological picture of the uterine mucous membrane

demonstrates the astonishing fact that no premenstrual swelling has taken place. The mucous membrane did not react, so to speak, to the ovarian activity. It is possible, however, that such a hemorrhage is due, not to the ovary, but to other influences. One is not dealing with a usual menstrual hemorrhage, nor with a premature, nor with an abnormally prolonged one, since the typical picture of the menstrual changes is lacking.

We are only at the beginning of new systematic investigations which will assure us a deeper insight into the relationship between menstruation and ovulation. For this there is needed a large amount of material, not only of the uterine mucous membrane, or of the ovary alone, but of both organs of the same individual. I am convinced, however, that here, too, the fundamentally important study of the function and the hormone actions of the ovary, as well as a knowledge of its predominating position in its interrelations with the rest of the genital apparatus will be established on a sound basis only through fundamental morphological studies. Yet the pathologist will never forget in what a large measure he is indebted to experimental biology, and especially to the clinic.

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VIII

THE ORTHOLOGY AND PATHOLOGY OF THE EXTRAHEPATIC BILE PASSAGES

Affliction with gall-stones is, apart from rare exceptions, a disease of the extrahepatic bile passages. Among these, the gall-bladder assumes an especial position, inasmuch as it may serve as the real source of almost all stones to be found in the other bile passages. But without an understanding of the normal function of the bile passages we cannot comprehend the disturbance of function which manifests itself in the formation of stones. Indeed, the Swedish surgeon, Berg, to whom we are indebted for very valuable investigations on the anatomy, physiology and pathology of the bile passages, goes so far as to replace Naunyn's current concept of infectious stone-forming catarrh. Since, according to Berg, the dysfunction is the main thing and the stone formation only an accessory, and indeed not always to be found, a new disease picture is created, namely that of *simulated gall-stone disease, pseudocholelithiasis.* Such a dysfunction presupposes a knowledge of normal function. It is, therefore, my object, as an introduction, to give a brief summary of our present conception of the bile passages in so far as it concerns the realm of operative surgery.

The most striking feature of the extrahepatic bile passages is the *special position of the gall-bladder,* which is ordinarily looked upon as only a superfluous accessory, and rudimentary organ, all the more so since a number of animals, including the horse and rat, are lacking in this organ. But it will be asked, with justice, what does the gall-bladder do when not in a rudimentary state? Embryology also shows that the gall-bladder has special features, being a peculiarly altered part of the anlage of the liver itself. The lack of mucous glands so characteristic of the bile passages and the presence of the remarkable Luschka's crypts which penetrate

the entire wall, are still recognizable traces of this special development. This pear-shaped organ, the gall-bladder, is connected by the cystic duct with the rest of the bile passages. It is rare to find in textbooks of anatomy a correct representation of these relations. According to the textbooks the gall-bladder is ordinarily continued by a funnel-shaped narrowing into the straight cystic duct. It was the researches of surgeons, especially those of Berg, that first called our attention to the necessity of more exact considerations. The changing structure of the wall in the individual portions of the gall-bladder should in itself lead us to a more accurate delineation (Fig. 14). The gall-bladder itself, according to Charpy, 8 to 10 cm. long, in which we recognize a fundus, a body and a neck, is characterized by a well-marked net-like arrangement of the musculature analogous to that of the urinary bladder. This is best developed in the fundus. By contrast, the elastic fibers are not well developed. The mucous membrane, which lies in delicate, closely interwoven folds, has practically no glands. Instead of them, we find the Luschka's crypts which penetrate deep into the muscularis. The epithelium shows very little or no reaction for mucus; on the other hand, it contains, almost consistently in adults and occasionally in children, granules of bile pigment. In the neck, muscle bundles, circularly arranged, are somewhat more prominent (Berg). This funnel-shaped part of the gall-bladder is incorrectly called in pathological, anatomical and surgical literature the neck of the gall-bladder. The true neck (*collum*) only starts where the first of the *Heisterian* folds is found. It ends where the narrow cystic duct starts. Ordinarily any one surface shows several folds (about two or three). It is readily demonstrated that these folds are formed by inward projections, particularly of

Fig. 14. Diagram of the extrahepatic bile passages.

the circular muscle fibers, while the longitudinal ones run further into the wall (Hendricksen, Berg). In the mucous membrane of the neck, the delicate system of folds of the true gall-bladder can still be recognized, but to a slighter degree. Approaching the entrance of the gall-bladder it disappears gradually. The glands which are already present in small numbers in the funnel-shaped portion are here very plain. With the beginning of the cystic duct the muscularis disappears rapidly and is limited to very slight longitudinal and oblique bundles in the wall and in the folds. The cystic duct, the length of which is ordinarily variable (according to Charpy, 3 or 4 cm.), has no closed muscularis (Hendricksen, Aschoff, Bacmeister, Rietz). On the other hand, its wall is all the richer in elastic and nervous elements (ganglion cells and nerve fibers). Its upper, readily movable part (*pars proximalis s. valvularis*) is especially narrow and made more difficult of passage by an irregularly crossing system of coarse folds which cause it to appear like a corkscrew. The lower, better attached part is to be designated as almost flat (*pars distalis s. glabra*). The structure of the latter is entirely similar to the hepatic and common ducts; it is the real excretory duct of the gall-bladder. All these distal *bile passages* (distal cystic duct, hepatic and common ducts) have practically no smooth muscle, being built from only connective tissue and elastic fibers, and are very rich in specific glands. When examined in the fresh state, the epithelium often shows a deposition of very fine lipoid droplets, occasionally also of bile-pigment granules. Hence, the relations are the reverse of those found in the gall-bladder, where there are almost always pigment granules and very much more rarely lipoid droplets in the cells. The epithelial cells of the bile passages also seem to be lacking in the peculiar border which is often so plain in the epithelium of the gall-bladder.

The length of the hepatic and common ducts in adults averages about 10 cm., but may vary between 8 and 12 cm. The common duct itself has three divisions, the suprapancreatic, pancreatic and duodenal. Where the cystic and hepatic ducts meet very deeply, i.e., in the pancreas itself, there naturally is no suprapancreatic portion. The duodenal

portion is transformed by more markedly developed longitudinal and independent circular musculature coming from the intestinal muscle into the well-known sphincter of Oddi, about which we have precise knowledge through the investigations of Hendricksen, Mann, Westphal and Helly. It is important that we differentiate on the basis of pharmacologic experiments between a *sphincter in the narrower sense* and an antrum (Westphal). But the thorough study of this duplex organ is reserved for the future.

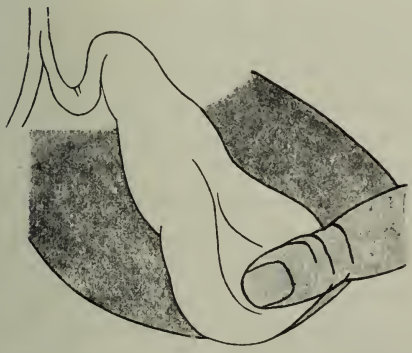
In the relationship of the above-mentioned systems to one another and to the liver, there are many variations, especially in the attachment of the bladder to the liver, in the development of the neck, in the angular relation of the latter with respect to the funnel-shaped part, in the development of the valves, in the length and direction of the cystic duct, as well as the point of union of the latter with the hepatic duct; all these present numerous variations, to which especially the surgeons (Courvoisier, Körte, Kehr, and finally Berg, Schmieden and Rohde) have called attention.

The difficult problem is to decide what is to be regarded as normal. Systematic descriptions of the variations in position of the gall-bladder and bile passages at the various periods of life are not known to me. According to my own researches carried out with Drs. Luetkens and Tschmarke, it must be accepted that the transitional section from the funnel-shaped portion to the neck, which forms the upper portion of the gall-bladder, swells like the neck of a horse when filling, as was already noted by Charpy and Berg (Fig. 15). During this, the neck is separated from the funnel by a groove on the hepatic and lateral surfaces. It bends forward, downward, and laterally (right or left) into the funnel portion and joins the cystic duct in an S-shaped bend. The latter runs in a steep or more gradual curve through the arch of the so-called liver-hilus angle (Berg) to the common duct. The angle at which it opens into the common duct varies markedly, according to the height of the junction. In the much more frequent deep opening (two-thirds of all cases) it runs almost parallel to the hepatic duct (Ruge, Pallin). It is understood that all this topography must vary according to the position of the body, the filling of the

bladder and all the other abdominal organs. There are variable transitions to pathological relations so that it is difficult to draw the exact border. Thus, the axis of the

Without pressure.

Light pressure on the fundus.



Pressure in a more nearly normal condition.

FIG. 15. Gall-bladder turned cranially.

bladder often shows slight or more marked bends, which are usually marked by very evident grooves on the intestinal or intestino-lateral surface of the infundibulum of the body of the fundus (*Incisura infundibuli*, etc.). When the fundus is pinched there arises the picture of the Phrygic cap. On a

cross section of the gall-bladder one sees that these folds correspond to infoldings of the entire wall and not only to bending in of the circular musculature as in the case of the true folds. Furthermore, the delineation of the individual portions of the extrahepatic system of bile passages just given is very schematic, whereas the development and arrangement of the valves, on which depends the separation of the neck and the cystic duct, is ordinarily very variable. Thus, the circumference, width and length of the neck as well as of the proximal and distal portions of the cystic duct vary greatly. The latter may be totally absent, the proximal portion forming the entire cystic duct. Sometimes the neck appears as a large independent structure, on other occasions as a scarcely widened portion at the beginning of the cystic duct. Only by means of very extensive material carefully studied in casts and hardened specimens, will we be able to get a broad view of these physiological variations. What has as yet been done on this subject, as well as on our own material, is still insufficient. Valuable help in this connection is promised us by roentgen examination *in situ*, which has already been successfully tried by Burckhardt and Mueller.

Despite the great variability, we must adhere to the division given above as far as possible. It alone affords us the possibility of *functional analysis. What does the gall-bladder do?* The fact that in rare cases the gall-bladder is congenitally lacking and that many people for years after operative removal of the gall-bladder enjoy healthy life, does not prove that the gall-bladder is a rudimentary organ. If this were so, one would also have to designate the spleen, half the stomach, the large intestine, and even the arm and leg as rudimentary organs. The gall-bladder has been further looked upon as a reservoir for the bile furnished by the liver which is made available according to need. But the gall-bladder holds on the average only 50 c.c. The total quantity of bile furnished daily by the liver amounts, however, to 800–1200 c.c. Therefore, the gall-bladder would have to empty itself repeatedly during the day, which is practically impossible because of the anatomic-physiologic structure (flat fixation in the bed of the liver). Empty gall-bladders are very rare at operations or in

the cadaver. This disposes also of the assumption that the gall-bladder has the function of secreting a special substance which is essential for digestion. The most it could supply would be some mucus which alters the colloid condition of the bile fluid and prepares it for certain tasks. That the gall-bladder, as a specially differentiated portion of the liver anlage, also possesses the ability to secrete the constituents of the bile, perhaps cholesterin, will be later considered. It is nearer to the truth to look on the gall-bladder as the regulator of pressure in the bile-passage system. Although the sphincter of Oddi plays an important part here, yet there is hardly a doubt that the gall-bladder can relieve the load on the bile-passage system by diminishing its tonus. By doing this, it can hold several times more bile than it usually does (C. H. Mayo). But this is not its main function. The well-known experiments of Hammarsten on the chemical composition of the hepatic and gall-bladder bile have shown a considerable concentrating power of the wall of the gall-bladder; this resorbing function has also been experimentally demonstrated by researches of Peyton Rous and McMaster, of Haemmerli and Herzfeld. These authors have measured by the bile pigment the concentrating work of the gall-bladder of the dog and obtained similar figures to those obtained by Hammarsten by studies of the total dry substance in humans. They show that the gall-bladder concentrates hepatic bile to $\frac{1}{8}$–$\frac{1}{10}$. Even if the gall-bladder, by the establishment of a gall-bladder fistula, is only used as a passage for the hepatic bile, the latter is thickened to $\frac{1}{2}$–$\frac{1}{3}$. From this it is to be seen with what caution gall-bladder fistula bile is to be used for investigations on the hepatic bile. Only by this great concentrating work is it possible for the gall-bladder to take up the quantities of bile produced daily by the liver, in so far as they do not flow into the intestine. This concentration takes place, so to speak, more quickly than the filling, so that a completely empty dog's gall-bladder still appears collapsed after twenty-four hours—it already contains bile that has been concentrated 8 to 10 times. On the other hand, it may be assumed that the gall-bladder never empties itself completely but only partially. The gall-bladder is, therefore, to be looked upon as a regulatory mechanism shunted into a system of

rigid tubes which even in an already well-filled condition can collect by concentration all the bile secreted between two periods of digestion (an amount which could never find place in the bile passages) and thereby prevent any injurious rise in pressure within the bile passages. For this it is also presupposed that all connecting passages are open and readily permeable.

Where and how does this resorption occur? According to Rous and McMaster, it occurs somewhat through the lymphatics which are well developed in the gall-bladder (Sappy, Sudler), but to a greater extent through the blood-vessels of the mucous membrane. According to Harer, Hargis and Van Meter, potassium sulphocyanide which has been injected into the gall-bladder can be almost immediately demonstrated in the lymph vessels. The granular crystalline deposition of bile pigment in the epithelium of the gall-bladder is probably to be attributed to these resorption processes. The apex of the folds is partly affected. Occasionally there are also found droplets of lipoid. Both are predominantly supranuclear but do also occur infranuclearly. Still rarer is the deposition of lipoids (in this case always doubly refractile) in the histocytic elements which line the tissue spaces of the system of folds. Even macroscopically, one sees the entire system of little folds as a sulphur-yellow spotting. It appears to be of importance, though it should be verified on a larger material, that this "resorption fatty change," if I may call it so, occurs only in the true gall-bladder; the neck of the gall-bladder, therefore, has a special position. It forms a sort of intermediary between the true bladder and the cystic duct.

Now what is resorbed by the wall of the gall-bladder? As comparison of hepatic and gall-bladder bile shows, mainly water and inorganic salts. The resorption of bile pigment is of little importance, as is shown by the investigations of Rous and McMaster, although it is morphologically demonstrable in the epithelium. The resorption of proteins and fats is equally slight under normal conditions. According to Rous and McMaster, the transformation of the cholates increases in the gall-bladder. Haemmerli and Herzfeld found a similar condition as with the bile pigments.

The opposite activity is shown by the bile-ducts, according to the investigations of Rous and McMaster. In the dog the gall-bladder is not attached as in man to the main excretory duct, but to the left branch of the latter. If one ligates the duct to which the gall-bladder is attached the entire duct system becomes filled with thick green bile as the concentration of the gall-bladder bile and the hepatic bile gradually equalize (green bile in the communicating system). If the right branch, to which no gall-bladder is attached, be ligated, after transitory filling with dark bile, there gradually occurs a filling with light, and finally water-clear bile (white bile in the non-communicating system. This means that in the completely closed-off system which does not communicate with the gall-bladder, the pressure regulator is lacking. The secretion of the bile soon stops because of the rise in pressure, the bile pigment present in the ducts is destroyed, and the obstructed ducts are gradually filled with the colorless secretion of the cells of the bile-ducts and other glands. The bile ducts, therefore, have at least in the dog a predominantly secretory, i.e., a diluting, function. This is in direct opposition to the gall-bladder. When a system communicating with the gall-bladder is ligated, both sections start to work, but for a time at least the concentration function of the gall-bladder predominates. Hence the filling of the bile passages with dark, tenacious bile. The similarly constructed distal portion of the cystic duct apparently behaves like the bile-ducts. But what is the task of the *proximal* part of the cystic duct? It is characterized by its narrowness and its especially involved system of folds. Since it is practically lacking in a muscular coat of its own, the first thought is of purely passive mechanical tasks. At all events, a pumping and sucking action which is attributed to this part by some authors is very improbable, indeed practically excluded. One would rather think of a valve-like action by a very inadequate muscular activity. Naturally the in- and outflow may be hindered or obstructed by the somewhat more active tension of the valvular musculature. Also, the less erect folds and sufficient elastic tension of the walls prevent the simple flowing of the bile from the conduction system into the concentration system, and vice versa.

A definite rise in pressure will always be needed in one of the two systems to cause a flow from one to the other. The diminution of pressure in one system can by itself cause no effect, even in the sense of a suction. At all events, we were never able, by suction on the bile-ducts in cadavers, no matter how strong, to draw even thin bile from the gall-bladder. According to observations on cadavers, which are naturally to be applied only with caution, the pressure for forcing the contents of the bile-ducts into the gall-bladder is much less than that which is necessary to empty the gall-bladder. How far this is dependent on the arrangement of the valves and how far on the greater viscosity of the bladder bile, is difficult to decide in the individual case.

Since there are numerous ganglion-cells and nerve fibers in the walls of the cystic duct, the question naturally arises in how far, during the passive dilation of the cystic duct, reflex stimuli are exerted on other portions of the extrahepatic bile-duct system or on the liver itself. For example, there has to be considered relaxation of the gall-bladder on the one hand, and of the sphincter of Oddi on the other. At all events, this system is well worth systematic investigation. A true muscle-closure action has also been thought of. Especially do the noteworthy experiments of Westphal on stimulating the vagus, point to such sphincter-like activity of the region of the neck and of the cystic duct. Westphal believes that he has seen circumscribed contraction of this region following strong stimulation of the vagus. In the latter time Dr. Luetkens could find a special muscle system in form of a node, which may serve to occlude the cysticus. Westphal further maintains that on bringing stones into the gall-bladder and the neck of the gall-bladder, he has never observed cramp-like contractions of this region. On the other hand, introduction of the stones into the common duct caused evident spasms when they entered the region of the sphincter. For the present, therefore, we are lacking in proof of sphincter-like action, which according to the entire histological structure should be most likely found at the junction of the neck and of the cystic duct. Berg, also, who formerly thought of a sphincteric action, at least of the neck, gave up this view. Though some authors attribute to the neck even a suction

and pumping action at the same time, I find no support for this in the arrangement of the musculature.

Finally, Berg has attributed to the region of the neck and the cystic duct an especial rôle. He says that by independent exudation of mucoid fluid it regulates the pressure relations between the conducting system and the condensing system, by which this fluid will flow now into the bladder and again into the bile passages. Berg thinks independent activity within the neck and cystic duct region is important because from pathological exaggeration of this function there arises the peculiar picture of mucostasis, which will be described later. Berg believes that in the ampulla of the common duct and also in the hepatic duct, marked, similar, independent

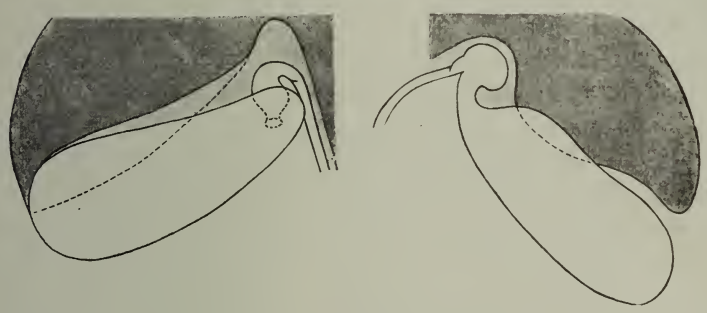


Fig. 16. So-called mucostasis.

secretion of mucus can occur which, especially during the emptying activity of the gastrointestinal canal, increases the pressure by closing the bile-ducts so that secretion of the liver stops. Can one bring proofs of these views of Berg from the findings in the normal gall-bladder? In support it can only be said that in the above-mentioned place glands occur, in the neck and proximal cystic duct, to be sure, less than in the hepatic and common ducts. Aside from this, however, sufficient proof is lacking. In a careful investigation of the bile passages in the cadaver one finds no closing by masses of mucus at the points mentioned. The much-discussed plug of mucus of the papilla of Vater is nothing more than a product of post-mortem epithelial desquamation. The same thing is found in the bile-ducts themselves. But this question should be more exactly investigated in sufficiently freshly

preserved material. Whether the bile-ducts were blocked or not is best seen in the cadaver by the positive or negative post-mortem bilious coloration of their walls (Fig. 16). If the extrahepatic bile-ducts be thus examined there are noted quite constant changes. The region of Oddi's sphincter is, as a rule, pale, almost uncolored, a sign that it was closed after death also. The bile passages including the cystic duct, the latter exactly to the beginning of the neck, are light yellow, that is to say, of the same color as the hepatic bile, while the neck as well as the rest of the gall-bladder is dark, the color of bladder bile. From this it seems to me to follow with a certain probability that the border between the conduction and the condensation system is at the junction of the cystic duct but not in the neck, and still less at the junction of the neck and the infundibulum. I am doubtful if one may, therefore, rate the neck and cystic duct as functionally similar, as is done by Berg.

There is no reason for going into the nervous regulatory system of the extrahepatic bile passages and the recent abundant literature on this topic. I call attention, aside from the American researches (Auster and Crohn, Lyon, Jacobson and Gydesen, Chester), especially to the work of Westphal. It appears to me to contain all that is essential. Slight stimulation of the vagus causes contraction of the gall-bladder with relaxation of the entire sphincter of Oddi. The consequence is increased flow of bile, especially bladder bile. Strong stimulation of the vagus causes still more marked contractions of the gall-bladder and similarly partial or total spasm of the sphincter. The consequence is a more difficult flowing-out of bile, even bladder bile which may, as a matter of fact, be forced back. Stimulation of the sympathetic, on the contrary, leads to the diminution in tonus of the gall-bladder and the bile-ducts. The sphincter, however participates only in its antrum part in this diminution of tone, while the sphincter proper is contracted. There occurs, therefore, an inhibition of bile flow, naturally also of bladder-bile flow. It is said that in the sphincter region there exists an opposition similar to that of the stomach in the region of the pylorus. The physiological emptying of the gall-bladder is therefore caused by its contractions coincident with dilatation

and peristaltic movement of the sphincter region as in slight stimulation of the vagus. According to the clinical observations with the duodenal sound or on the experimentally exposed papilla, there is no doubt but that the sphincter of Oddi can also be influenced independently of the gall-bladder, so that only hepatic bile but no gall-bladder bile flows into the duodenum (W. Meyer, P. Hecht, and J. Mantz).

This exhausts essentially what there is to say about the function of the extrahepatic bile passages. The question of the utility of the gall-bladder is a pressing one in view of the frequent necessity of extirpation. In considering this question, one must, of course, differentiate between the healthy functioning and the diseased, functionless gall-bladder. To remove the latter is no unnatural step. Nature itself has, so to speak, "extirpated" this gall-bladder from its functional connections. The consequences of a chronic cholecystitis and those of the extirpation of a relatively healthy gall-bladder must be, to a certain extent, the same. Their effects will be primarily voiced in a functional disturbance of the bile-duct system, apart from the altered chemical working of gastrointestinal digestion. Experimental investigations (Rost, Klee and Klüpfel, Judd and Mann) and clinical experience (Berg, Homans) have shown that as a result of loss of the pressure-regulating organ there may occur a dilatation of the bile passages. But in this, not only mechanical but nervous causes play a part. According to the investigations of Jacobson and Gydesen, Judd and Mann, the pressure in the bile-ducts of animals (dogs, cats) whose gall-bladders have been extirpated is much less than in the healthy animal. This is attributed to an independent relaxation of the walls of the bile passages and to an increased irritability of the sphincter. The fact that in animals whose gall-bladders have been extirpated, the flow of bile is first continuous immediately after the operation, and later periodic as in the healthy animal, shows that the adaptive process in the region of the closing muscle sometimes occurs with more difficulty and sometimes more easily. This also holds for man, in whom, after extirpation of the gall-bladder or any severe gall-stone disease, there occurs sometimes widening of the bile passages and sometimes none. How

large a part the nature of the operation (extirpation of a larger or smaller part of the cystic duct containing ganglion cells) plays in this, must be shown by further investigations. There is also a complete lack of histological investigations on such compensatory dilatation of the bile-ducts.

On the basis of these unfortunately very incomplete histological and physiological facts concerning the extra-hepatic system of bile passages, we may now turn to the question: What is the origin of the bile stasis which has hitherto been looked upon as a most important condition for the formation of all gall-stones? Berg has justifiably criti-

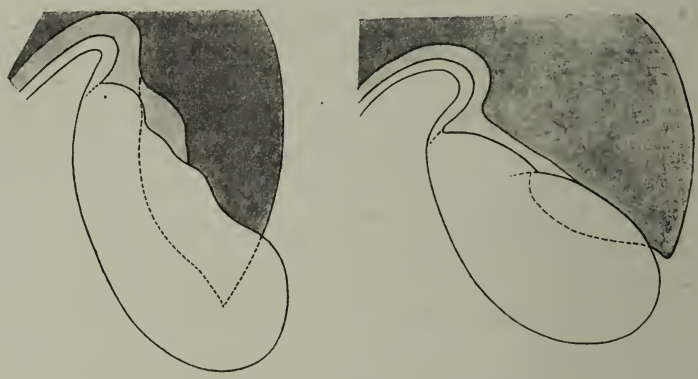


Fig. 17. So-called cholestasis.

cized the current explanations of the production of this stasis, pressure by corsets, lacing, lifting of the liver in pregnancy, or sedentary habits, because these statements do not permit the recognition of the finer mechanism of stasis, the true seat of the obstruction. He attributes to the influences just mentioned only the rôle of accessory factors and believes the main cause of the stasis to lie in certain, mostly congenital, anatomical and functional anomalies of the bile passages. Berg believes that we must separate from the physiological, certain definite pathological types. These are sometimes characterized by greater protrusion of the funnel into the liver-hilus angle with simultaneous lateral displacement or bending of the neck or more marked stricture of the neck of the funnel without lateral

displacement (Type I, Fig. 15), or by a more horizontal position of the gall-bladder with deeper imbedding in the liver tissue, displacement of the neck and the cystic duct, and compression of the latter by the cystic artery (Type III). Others are characterized by an abnormally long mesentery, drawing in of the neck into the funnel-shaped portion of the bladder (Type II, Fig. 17) with a straighter exit of the cystic duct from the neck, dilatation of the cystic duct up to the common duct, opening at an obtuse angle into the common duct, a form that may be united with rudimentary conditions, as lack of the valves (Type V, Fig. 18).

Fig. 18. Rudimentary bladder.

Rohde is in essential agreement with the views of Berg. The contracted gall-bladder is said, occasionally even under ordinary conditions, to be able to press the cystic duct against the hilus of the liver. The cystic duct often leaves the gall-bladder laterally instead of straight, the latter manner being looked on by Rohde as normal. In agreement with Schmieden, he was repeatedly able to demonstrate in the cadaver compression of the cystic duct during sudden strong pressure on the gall-bladder. As still more important, he considers a diverticulum-like protrusion of the upper pole of the gall-bladder, which would correspond to Berg's Type I. It is also mentioned that the cystic duct may leave the neck at an acute angle, then running parallel and adherent to the latter. Rohde also emphasizes the spur-like development of the valves which may impede the flowing out of the bile or, in case of increased pressure in the bladder, cause a stenosis at the point in question. Similarly he notes a bayonet-like bending of the cystic duct and the strangulation of the latter by the tension of the cystic artery. A very long and especially spiral-shaped cystic duct running parallel to the hepatic duct is said to more markedly block the passage to the gall-bladder. The common duct does not play any great rôle in

causing stasis, though bending of it by crossing of the arteries is said by MacConnel to be possible. Finally, traumatic hemorrhages and adhesions are also mentioned as a basis of stasis. Rohde lays special weight on the various impressions which are made on the soft, yielding gall-bladder, on its funnel by the duodenum, on the body by the transverse colon, and on the fundus by the anterior abdominal wall. To these influences on the bile passages are to be added indirect ones: breathing and the position of the diaphragm in general, a low position of the latter in senile emphysema, the posterior sinking of the liver in the erect posture, narrowing of the lower aperture of the thorax by lacing, relaxation of the abdominal musculature, obstipation and ptosis. Rohde and certainly Schmieden also believe that they can prove from their observations that in consequence of the anomalies just described in the course of the neck and the cystic duct, sudden stenosis of the cystic duct may be brought about. There then develops the picture of the acute attack just as it is otherwise characteristic of true gall-stone disease. We would, therefore, have to distinguish between the picture of *chronic* and *acute* stasis. Though the attacks so convincingly described by Schmieden and Rohde in gall-bladders which neither contain stones nor are infected are not to be doubted, yet the explanation is difficult. Since the acute stasis of the so-called "attack" as a rule develops on the basis of a chronic stasis, we must first consider the latter.

The very manifoldness of the pathological forms described causes us to doubt if we are really dealing in every case of these anomalies with the final cause of such a chronic stasis. I believe that a very great amount of comparative anatomical material must be investigated before we can judge the significance of one or another anomaly. Thus the often-mentioned stenosis of the lumen of the neck or of the cystic duct by the position of the valve is only to be determined by injection experiments. Then the experiments on the gall-bladder of the cadaver are not unobjectionable, because the duct system is lacking in tonus. I have not, as yet, in contradistinction to Schmieden and Rohde, found a single case where by sudden strong squeezing of the gall-bladder its emptying was made more difficult by a compression of the

cystic duct, but this may be an accident. However, one must consider that such sudden contractions of the gall-bladder would occur only with difficulty during life. Everything speaks for slow contractions. Also the mutual impression of the organs as shown to us in the formol-fixed cadaver is no permanent condition. Rather, the relations vary momentarily with the filling of the organs and the filling of the gall-bladder itself. We can speak only of transitory influences but we do not know if they are effective enough. It is something different when the gall-bladder, as a result of external causes, is continuously overstretched or already filled with stones. How difficult it is to harmonize the observations on the gall-bladders of cadavers is shown by the fact that Berg never saw a filling of the neck following moderate pressure on the gall-bladder, because Heister's valve is said to prevent this filling, but we saw in almost all cases immediate filling of the neck following the simple act of bringing the liver forward with a vertical position of the gall-bladder. The true resistance is noted in this position only at the bending point of the cystic duct. The latter was only filled up to a certain pressure at the right position of the bladder. One gets from these observations the impression that the closing valve between the condensation and the conduction system is at the beginning of the cystic duct and not at the neck of the bladder and that the purely mechanical relations of the angle formation play an important rôle in this process. But there is to be noted that this may be unfavorably influenced, as maintained by Berg, Schmieden and Rohde, by conditions of position.

The evaluation of these relations becomes more difficult when one notes that Berg looks upon all these anomalies as essentially of secondary nature, due to a primary dysfunction of the neck and cystic duct on the one hand, or ampulla of the larger bile passage on the other hand, while other authors look on the abnormal course of the cystic duct, the bends and compression of the neck by adhesions, as the *primum movens*. I might recall the disease pictures formulated by Foerster presenting phenomena of a duodenal ulcer or a gall-stone disease. According to our findings in the cadaver, we pathologists must assume that even widespread adhesions

of the body of the gall-bladder and its neck which lead to suitable displacements of the organ, approximation of the gall-bladder and the pyloric region, etc., may run their course without complaints and without clinical phenomena of stasis in the gall-bladder. It is certain that such adhesions frequently occur. While I cannot give more exact statistics, as I remember they are often united with dilatation of the entire gall-bladder. The abnormal mesocyst formations must not be confused with these adhesions; the former stretch sail-like or string-like between the gall-bladder on the one hand, and the duodenum, pyloric canal and large intestine on the other hand. The question whether congenital anomalies or adhesions are present must often be left undecided. At all events, it seems that such mesocyst formations are much more frequent than true adhesions. The cause of the adhesions remains very uncertain, at least in many cases. There is no duodenal or gastric ulcer, no cholelithiasis or healed cholecystitis, no old appendicitis, no demonstrable parasite, no perisplenitis, no perihepatitis, no disease of the female adnexa. Systematic investigations of the lymph-nodes around the cystic duct at the hilus of the liver and at the head of the pancreas are necessary to exclude the old tuberculosis which not infrequently localizes there.

Even though we can only in certain cases attribute to these adhesions lasting effects on the bile passages, it is comprehensible that Berg also does not place much emphasis on the other mechanical obstructive causes and does not look upon them as of primary moment but rather sees this in a dysfunction of definite portions of the system. Berg has gone more thoroughly into the question of this dysfunction in several publications, thereby presenting the problem to the entire European surgical world. But I must confess that no clear stand has been taken on the question, either by the German or the English surgeons so far as I am aware. I can only briefly go into this theory of Berg's. He differentiates two entirely different forms of disease of the extrahepatic bile passages. One is the so-called *mucostasis*. It is said to be characterized by abnormal mucus formation in the gall-bladder, particularly in the neck on the one hand and in the ampulla of the large bile passage

on the other hand. By bending of the neck or abnormal development of the folds (Type 1 of his anomalies) the high pressure due to mucostasis can be confined to the gall-bladder and there causes the picture of *hydrops*. But he believes that this increased mucus formation depends upon a congenital dysfunction, especially of the cervical part of the gall-bladder, and that no infection is responsible for it. But it cannot be understood how such an increased mucus formation occurs in the neck of the gall-bladder, which normally is very poor in mucus glands. Moreover, I have observed clear signs of the inflammation in the specimens sent me by Berg. I believe, therefore, that Berg has fallen victim to an erroneous interpretation of the findings. It also cannot be understood why the hydrops should develop from an overproduction of mucus. In a discussion on the formation of gall-stones I will return to this problem more thoroughly. I will here show that apart from rather special cases, hydrops of the gall-bladder is always infectious-inflammatory and always develops from an empyema, only occurring isolated when there is a closure of the cystic duct.

As far as hydrops of the bile passages, the origin of the white bile of Kausch, is concerned, Berg believes this hydrops to be due to an overproduction of mucus in the ampulla of the common duct. Here, also, infection or primary stenosis is said to play no rôle. But here the relations are entirely different than in the gall-bladder. We may once again recall the experiments of Rous and McMaster on the different results of ligation of the bile passages which do communicate with the gall-bladder and those which do not. What have we then to expect in man, presupposing that the findings can be applied to man? In all cases in which the obstruction is in the hepatic duct the actual filling with white bile is comprehensible. The pressure-regulating organ, the gall-bladder, is lacking. The pressure rises quite rapidly; so high that secretion of bile into the bile passages no longer occurs, but the secretion of the walls of the bile passages continues. In such cases we must find thickened, colored bile in the otherwise unaltered gall-bladder which is blocked off from the rest of the bile passages and only communicates with the common duct. This applies for the case of Bertog. It is

entirely different where the papilla of Vater or the common duct below the opening of the cystic duct is blocked. Because of the presence of the pressure-regulating gall-bladder, the pressure in the bile passage system will rise only slowly, the secretion of bile into the bile passages continues and the gall-bladder and bile passages become filled with ordinary bile which is thicker than it usually is in the bile passages but thinner than it ordinarily is in the gall-bladder. This also is often seen in a cancerous stenosis of the common duct. It is entirely another question if the collected content of the bile passages through admixture of the secretion of the glands of the ducts does not become lighter and hydropic as the resorbing power of the gall-bladder gradually diminishes. But if the gall-bladder is lacking (by an earlier operation), or the cystic duct is at the same time closed by metastasis, or the gall-bladder no longer functions properly as the result of earlier inflammatory fibrous degeneration of the wall, the pressure rises quickly and the consequence is hydrops of the entire bile passages, including the gall-bladder as far as it is still accessible. Whether this conception is correct will only be decided in future cases by exact, including histologic, investigation of the wall of the gall-bladder, which hitherto has not always been exhaustively carried out. At all events, it must be admitted, as Kausch first maintained, that such a hydrops of the bile passages without infectious irritation of these passages is possible. I maintain this all the more because I formerly did not regard such a noninfectious origin of white bile in the bile passages as plausible, having applied my experience with the gall-bladder to the bile passages.

Just as unproved as the entire mucostasis is Berg's cholestasis, in which there is an especially weak sphincter and bile passages whose walls are yielding; resorption predominates. The ordinary pressure in the bile passages suffices to cause a widening of these passages, especially of the common duct and the cystic duct, as well as of the bladder (Type II of his anomalies). In contradistinction to the hydropic gall-bladder, a concentrated hepatic bile collects in the bladder.

With this mucostasis and cholestasis, gall-stone formation is said by Berg to be most intimately connected. Indeed he attributes cholesterin and cholesterin-calcium stones to

mucostasis, pigment-calcium stones essentially to cholestasis. Berg does not believe that stasis alone causes stone formation. Still less does he believe that the infection of the bile passages is necessary for stone formation. According to this, one of the most important theories of stone formation, with which Naunyn's name will forever be connected, loses its basis. I must look upon this theory of Berg's as disproved by the facts. As was mentioned before, I was able to find inflammatory changes in his own specimens. Anyone who has carried out systematic investigations on the gall-bladder knows how difficult it often is to demonstrate previous inflammatory processes. The same holds here as in the case of the appendix. All Berg's statements lose their force with the demonstration of the inflammatory changes. I also had an opportunity of seeing Berg's stones. I was able to determine that he did not make any sharp differentiation between cholesterin stones and calcium-cholesterin stones. But anyone who does not learn to differentiate exactly between the individual forms of human gall-stones will never be able to pass clear judgment on the genesis of the individual stones. Since Berg has worked up his material with great diligence and is highly regarded as a surgeon throughout Europe, I believe myself all the more in duty bound to report on his work.

Despite this disagreement with the theory of Berg on dysfunctional gall-stone formation, we must be thankful to him for having thoroughly criticized the current representations of the stasis gall-bladder and stasis as the sole cause of certain stone formations. In our future investigations on the development of the stasis bladder, we will not content ourselves with indefinite manners of speaking, like pressure through lacing, and also not with coarse anatomical anomalies, but we will also consider the functional disturbances of the individual sections of the bile passages, above all their abnormal nervous and muscular irritability. For it may well be thought that part of the so-called false gall-stone attacks do not arise on the basis of a chronic stasis but quite independently of this, as the result of nervous predisposition. Only when the spastic attacks are repeated, will the picture of the stasis gall-bladder be able to develop, if at all. At all events, we will have to separate

the Westphal hypertonic or stasis bladder from the hypotonic or ectatic gall-bladder. Pathological anatomy can, it is true, draw the picture of these two in the finished condition, but can say very little about the final causes of their development. This becomes all the more difficult when it is shown that the dyskinetic factors, with which name Westphal designates the especial irritability of the neuromuscular apparatus of the bile passages, or their particular weakness, play a very essential rôle in the origin of the disturbances for which until now we have only sought mechanical explanations or for which we have held infections and swelling caused by the latter as responsible. I need not again describe the picture of the hypertonic stasis bladder. I should only like to maintain that the spot-like lipoid resorption, described by me, which gives the folds such a characteristic yellow spotting, does not unconditionally belong to this picture. So that we can only view as characteristic for the hypertonic stasis bladder the more powerfully developed musculature, the greater development of Luschka's crypts, and the somewhat greater prominence of the cellular elements of the mucosa.

For the atonic stasis bladder we must, on the other hand, mention as remarkable the thinning of the muscular layer, flattening of the folds and the disappearance of Luschka's crypts. The accidental condition of contraction in which we see the gall-bladder primarily determines the picture. The gall-bladder in the contracted state appears totally different from one which is relaxed. Likewise, I should like to warn against diagnosing a stasis gall-bladder as responsible for clinical symptoms if one sees macroscopically no signs of infection. Among the gall-bladders which were clinically diagnosed as stasis bladder and sent to me, are some in which the microscope revealed a fresh phlegmonous cholecystitis but were macroscopically not recognizably altered. On the other hand, I must admit that in a large number of such clinically well-characterized stasis bladders as were sent me by Schmieden, Rohde, Enderlen and Lexer, no trace of infection could be demonstrated. In a whole series of cases the picture was entirely that of a normal gall-bladder, not that of a chronic stasis gall-bladder. In the extir-

pated organ the pathological anatomists quite occasionally find remains of adhesions but no other abnormalities. These cases, therefore, have been due to special mechanical movements hidden by the extirpation, or in the case of the totally normal gall-bladders, to dyskinetic factors in the sense of Westphal. Whether these are always in the neck, cystic duct region or perhaps in the region of the sphincter of Oddi, appears to me to be worth special clinical control. For a cramp of the sphincter could also cause the picture of stasis bladder by increasing the pressure in the entire system, as was seen by Westphal in animals after strong stimulation of the vagus.[1] I have never as yet been able to find any evidence of dysfunctional moments in the sense of Berg. But for the final settlement of all these questions there is needed a thorough microscopic investigation of the region of the cystic duct itself, which usually is unfortunately the victim of operative technique.

The older and newer lessons on the peculiar structure of the extrahepatic bile-passage system, the varying distribution of the musculature, the great significance of the sphincter of Oddi, the sphincter-like thickening of the smooth muscle at the beginning of the cystic duct, the inclusion of a nervous apparatus in the wall of the cystic duct apparently serving as a regulatory center—all these things throw new light on the clinical pathology of the gall-bladder, with and without stone formation. We see that not only the coarser involvement of the gall-bladder region by clothing, corsets, posture, pregnancy, etc., plays a rôle in stasis and infection but that disturbances in the regulatory mechanism of the sphincter and cystic duct region are equally important. The old dispute as to whether the symptom complex of the so-called gall-stone attack is always caused only by a stone or whether through infection of the gall-bladder alone, is now further complicated by the fact that the same symptom of painful cramp can occur without either, i.e., in a purely reflex manner. These noninfectious and nonlithogenous attacks of pain may play a special rôle in the so-called recurrence of gall-stone disease after removal of the gall-bladder.

[1] von Bergmann, G. Neuere Gesichtspunkte bei den Gallenblasenkrankheiten. *Jahresk. f. ärztl. Fortbild.*, March, 1922.

It requires further investigations to show of what significance for this question is the nature of the operation, whether or not removal of the ganglion apparatus of the cystic duct plays a part. Unfortunately, in the ordinary operative technique, precisely the upper part of the cystic duct, which is of most importance for the pathological anatonomist, is destroyed by the ligation and is useless for further investigations. Since we must now recognize that the occurrence of such dyskinetic attacks of cramp in the gall-bladder region are more frequent than was formerly thought, three forms of the so-called gall-bladder complex must be differentiated more sharply than previously:

1. Those of lithogenous origin in which the entire cramp is due to the impaction of a stone in the neck of the gall-bladder; the cramp may, however, also involve the region of the sphincter of Oddi.

2. A complex of infectious origin which not uncommonly occurs in combination with a lithogenous origin, and

3. Those of dyskinetic origin which can occur alone but usually occur combined with the other two.

It must be a task of the future to separate these three symptom-complexes of the gall-bladder disease more sharply than previously and to determine their frequency. I am already convinced that the dyskinetic form is frequently found where we formerly thought we found only the infectious. Thus Naunyn has recently again maintained that infectious cholangitis is extraordinarily frequent and that this *infection of the bile passages*, especially of the intrahepatic bile passages, causes the picture of colicky pain. Newer bacteriological investigations in the Giessen Clinic under Poppert seem to indicate that, in reality, a descending or ascending infection of the bile passages is strikingly frequent. I do not believe that in these investigations all sources of error have been considered but nevertheless the fact remains that such infections occur with relative frequency. I believe, however, that they affect the gall-bladder or extrahepatic passages. I have had a large number of unchosen livers examined for possible inflammatory reactions, with the help of the oxydase stain. Aiello was able to determine that apart from typhoid fever and tuberculosis, in the ordinary infec-

tious diseases the intrahepatic bile passages are entirely intact, while in the gall-bladder the causes of ordinary infectious diseases (staphylococci, streptococci, pneumococci) can be more or less frequently demonstrated bacteriologically. But the gall-bladder, despite the positive bacteriological finding, showed no trace of inflammatory reaction. It follows from this that excretion of bacteria through the liver and perhaps also through the wall of the gall-bladder as a rule runs its course without a special reaction. In order that a hematogenous cholecystitis of bacterial nature may originate, something else must be added; either an especial virulence of the germ, a stasis within the bile passages or the presence of foreign bodies, especially of stones within the bladder itself. In the production of stasis the neuromuscular reflex apparatus of the bile passages plays an important rôle, and since the latter is influenced by the diet, bodily activity, the psyche and the rhythm of life, particularly in women, we can understand to a certain extent why in certain cases the infection "takes" and not in others. If we add to this that a not inconsiderable portion of gall-stones do not arise on the basis of infection but through the metabolic disturbance, as e.g., pure cholesterin stones, we have here a new cause for the successful "taking" of hematogenous or enterogenous infection, in which again the presence of the stone may act unfavorably on the neuromuscular reflex apparatus.

Through all this the theory of infection loses much of its previously prominent position as the main source of all gall-stone disease, particularly stone formation. To it are added, with more or less justice, the metabolic and dyskinetic theories. We see that here also, in the case of the symptom-complex of gall-bladder disease, the old principle holds—not to search for a *cause* but for the various *conditions* of the disease.

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IX

THE ORIGIN OF GALL-STONES

A recent article by the venerable clinician, Naunyn, formerly of Strassburg, who, despite his years, is still so active in research, entitled "Die Enstehung und der Aufbau der Gallensteine," impels me to summarize the present state of our knowledge on this question. Modern investigation of the formation of gall-stones originated in the fundamental work of Naunyn, "Die Klinik der Cholelithiasis." In this, Naunyn maintained the thesis that the only established general cause for the origin of gall-stones is bile stasis. But he maintains, at the same time, that this in itself cannot cause the formation of gall-stones because it is readily shown that the numerous gall-stones, which are often found by hundreds or thousands in a gall-bladder, must, in view of the complete similarity of their structure, all have originated at the same time. But such a coincident origin appears to him to be irreconcilable with the usually very long duration of the stasis, which is increased by the presence of the stones. So there must be added a second cause, having only a transitory action. As such, Naunyn views ascending infection of the bile passages, particularly that of the gall-bladder, with B. coli communis. This infection produces the so-called "stone-forming catarrh of the vesical mucous membrane." Under the influence of this catarrhal inflammation there occurs an abundant production of cholesterin by the epithelium of the gall-bladder. This forms the real source of the cholesterin stones and of the cholesterin of the mixed stones. Also, the calcium is looked upon by Naunyn as a secretory product of the inflamed mucous membrane of the gall-bladder. In his opinion the cholesterin and calcium are not as a rule dissolved in the hepatic bile, but are first formed, under certain conditions, as a direct secretion or decomposition product of the epithelium of the bile passages. But

bilirubin-calcium masses can originate as precipitates from bile. Thus arise, partly from heaps of disintegrated cells, partly from precipitates, the beginnings of gall-stones. These grow by the absorption of stone-forming substances and often develop a hard shell, while in the semifluid center crystals are formed, the solvent remaining in a central cavity. Even more important than these changes in the nucleus is the gradual transformation of the entire stone, including the nucleus, by subsequent infiltration of cholesterin, which changes the position of the cholesterin involved in the original construction of the stone—the so-called cholesterinization of the stone. Naunyn does not admit any demonstrable influence of diet or constitution on the formation of gall-stones or their nature.

This theory of Naunyn's, which constitutes a further elaboration of the theory of Meckel von Hemsbach, seemed all the more satisfactory because it maintained the intimate connection of gall-stone formation with infectious processes. Even today, we still look on these ascending and hematogenous infections of the gall-bladder as the most important source of gall-stones. In this direction, Naunyn's theory has not been shattered; but it has had to undergo amplification and change in certain details, and especially with respect to the origin of the formative constituents of gall-stones. The increasing knowledge of cholesterin metabolism for which we are indebted to French (Chauffard, Guy LaRoche and Grigaut), English (Dorée, Gardner, Ellis), Dutch (Hijmanns van den Bergh, Klinkert) and German investigators forces us to a consideration of these facts for the domain of gall-stone formation.

The first attempt in this direction was by myself, later working with Bacmeister, in a series of experimental, morphological, and histological investigations summed up in our monograph "Die Cholelithiasis." In this book we detailed why we, contrary to the previous assumption of a common inflammatory cause of all gall-stones, differentiated two fundamentally different forms; the noninflammatory or metabolic and the inflammatory.

To the first belong two forms: all the so-called pure or radially built cholesterin stones and a sort of the so-called

pigment-calcium stones. The cholesterin stones being more important are characterized by the following features:

1. They consist almost entirely of cholesterin and contain only slight traces of protein and calcium, so that one may correctly designate them as pure cholesterin stones.

2. They show a coarsely crystalline structure. On section it looks as though they were composed of a heap of inter-

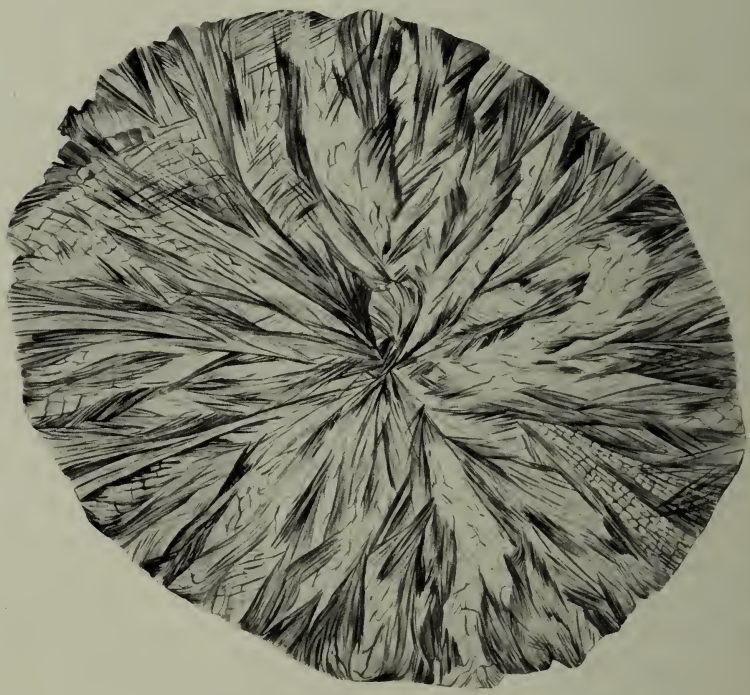

Fig. 19. Pure cholesterin stone.

twined tree trunks (coarse cholesterin columns). They lack the lamellation characteristic of most other gall-stones.

3. They occur only *singly*, because of which they were already designated by Meckel von Hemsbach as cholesterin solitaires.

4. The gall-bladders in which they are found usually show no signs of inflammation.

5. These are the gall-stones which are occasionally found in individuals who have never in their lives shown signs of gall-stone disease.

6. They occur at *all* times of life, even in children. In women it is probable that they arise after pregnancy.

If one variety of stone is differentiated by so many characteristics from all other stones, it must have an especial origin. The otherwise current explanation of infectious catarrh fails here. To be sure, Naunyn has again expressed an opinion on this question in his above-mentioned article "Die Gallensteine, ihre Enstehung und ihr Bau." He believes that an infection of the bile may have existed without leaving histological signs in the gall-bladder. If these infections should cause nothing other than a decomposition of the bile, Naunyn's assumption would be allowable. But in that event this decomposition must have as its sole consequence the precipitation of cholesterin. But we know of no such action of microorganisms. Naunyn himself has maintained that the bacteria first stimulate the epithelial cells to stronger secretion. But such a stimulation of the mucous membrane could doubtless be proved by some histological changes. I must emphasize again that such changes are not to be found in pure cases.

Now, there is still a dispute as to the origin of cholesterin. Naunyn continues to believe that cholesterin is furnished by the disintegration of the gall-bladder epithelium or by its extruding myelin-like masses, but now admits the possibility of the precipitation of cholesterin dissolved in bile, as we have maintained. In our opinion it is not the epithelium of the bile passages and the gall-bladder that furnishes the cholesterin, but principally the liver cells, which secrete the cholesterin present in the blood without disintegrating in the process. The best proof of the excretory activity of the liver is the dependence of the cholesterin content of rabbit's bile on the cholesterin level of the blood. Normally, rabbit's bile contains practically no cholesterin. But if the cholesterin content of the blood is increased by artificial cholesterin feeding or by extirpation of the adrenals (Hueck, Weltmann and Blach, Landau, Rothschild, Versé) cholesterin is excreted by the liver into the bile. Participation of the epithelium of the gall-bladder cannot be demonstrated, at least morphologically. Also the marked cholesterin excretion in the bile of bitches which have recently borne young

but are prevented from suckling (Bacmeister), as well as the varying cholesterin content of the bile in pathological conditions in which no catarrhal changes of the bile passages can be recognized (Pearce, Nathan), speak for a certain dependency of the cholesterin content of the bile on that of the blood.

To be sure, this dependence of the cholesterin content of the bile on that of the blood does not say at which point the increased cholesterin excretion occurs. Just as Naunyn holds the epithelium of the bile passages, and especially that of the gall-bladder, responsible for the normal excretion of cholesterin, one might with equal justice blame them for a pathologically increased excretion of cholesterin. It is therefore necessary to test as accurately as possible the cholesterin excretion by the epithelium of the gall-bladder. Dr. Torinoumi has done this under my direction. He has undertaken these investigations on the ligated gall-bladders of dogs. By aspirating the contents and then re-injecting half into the gall-bladder, he was able to calculate from the other half the percentage of cholesterin in the bile. The ligated gall-bladder was then replaced, and after some weeks was finally removed at a second laparotomy and the contents again chemically analyzed for their cholesterin content. If Naunyn were really correct in his assertion that the epithelium of the gall-bladder secretes cholesterin, and indeed in sufficient quantities to form pure cholesterin stones, one would expect a readily demonstrable increase in the cholesterin content of the remaining bile. Now, the investigations of Dr. Torinoumi gave very variable findings. In a portion of the cases the cholesterin content was slightly increased, in another portion clearly diminished. The more exact histological investigation of the gall-bladder showed that in those cases in which the cholesterin content was increased, there was also an inflammatory irritation of the wall of the gall-bladder. This was lacking in those cases in which the cholesterin content had decreased. From this it was evident that the increase in cholesterin content must be attributed, not to a physiological secretion of cholesterin by the gall-bladder epithelium, but to the inflammatory exudate, slight though it might be. This inflammatory exudate was caused by the injection of Normosal,

the purpose of which was to refill the half emptied gall-bladder. After the injurious effect of normal saline solution on the wall of the gall-bladder was determined, it was no longer used. The gall-bladders no longer showed inflammation and the cholesterin content was, as expected, not increased but lowered. From this the conclusion must be drawn that in a normal dog's gall-bladder there is no secretion, but rather a resorption of cholesterin, which is not very great. Recent investigations of Rous and McMaster have very plainly shown the great resorbing powers of the mucous membrane of the gall-bladder, which had already been indicated by Hammersten's chemical investigations of gall-bladder bile.

But we must not fail to mention here that there are considerable differences between the epithelium of the gall-bladder and that of the bile ducts. The experimental studies of the Russian investigator Zinserling, as well as those of the Japanese, Torinoumi, have shown that when cholesterin esters are abundantly ingested they are stored in the epithelium of the bile passages, which might be interpreted as evidence of cholesterin excretion by the epithelium of the bile passages. (But we now know from numerous investigations that storage and excretion are by no means the same and that a cell may very well store fat and yet not excrete it.) Older investigations by Chalatow[1] have shown that this peculiar lipoid infiltration of the epthelium of the bile passages, or lipoid secretion, is dependent not only on the ingestion of lipoids, but also on their nature. Thus the deposition of cholesterin compounds was especially abundant when the cholesterin, dissolved in sun-flower oil, was given to the rabbit. Indeed Chalatow was able, by especially abundant and protracted stuffing with cholesterin dissolved in sun-flower oil, to produce a lipoid infiltration of the epithelium of the gall-bladder. Since the rabbit excretes practically no cholesterin in the bile, this abnormal behavior of the gall-bladder epithelium is to a certain extent comprehensible. Chalatow believes that when the liver cells are overloaded, the epithelial cells of the bile passages and finally those of the gall-bladder also compensate for them in the excretion of cholesterin. I do not know to what extent one may deduce a

[1] *Virchow's Archiv.*, 1912, Bd. CCVII.

cholesterin excretion from the purely morphological findings. At all events, in the rabbit it occurs only under pathological, entirely abnormal conditions. The relations in the rabbit are entirely different from those in the dog, and these even more different than in man. At any rate, the experiments of Torinoumi show that under certain conditions, in the dog, there occurs a resorption and not a secretion of lipoid by the gall-bladder. And the same must be assumed for omnivorous man.

But even if a marked local cholesterin excretion by the epithelium of the gall-bladder in man be conceded, according to all observations made on man and also according to the experimental results in rabbits, this still remains dependent in the last analysis on the cholesterin content of the blood. Thus Dewey was able, by feeding cholesterin to the rabbit, to bring about so marked an excretion of cholesterin by the liver and bile passages that small cholesterin stones were formed.

We therefore maintain that pure cholesterin stones are to be attributed to a disturbance in metabolism consisting in a transitorily increased excretion. Worthy of attention is the repeatedly established fact that pure cholesterin stones not rarely originate following pregnancy, as a result of the markedly increased cholesterin metabolism demonstrated by the Viennese and Parisian Schools (Neumann and Herrman, Chauffard, LaRoche, Grigaut). I believe that the rapid loss of fat, be it in the course of treatment for obesity, following infections or otherwise, may lead to the formation of pure cholesterin stones.

Of great interest are the investigations which Okuneff has carried out on the morphology of the lipoid substances in hunger. He was not only able to confirm the statements of Landau, that in hunger the cholesterin esters of the adrenal cortex are increased, but was further able to show that these cholesterin esters are more abundantly stored in the reticulo-endothelial system and occur in increased quantity in the epithelial cells of the bile passages. From this one may infer, with due caution, that there is an increased cholesterin excretion via the hepatic bile. The quicker the emaciation or removal of fat occurs, the more marked must be the

excretion in the bile of the cholesterin which has become superfluous for the emaciating body. And all the more readily can the concentration of cholesterin in the bile, even in colloidal solution, be increased until precipitation occurs. Hence the nutrition and general condition of the organism is of the greatest importance for the cholesterin excretion and the possible precipitation of cholesterin in the gall-bladder.

The connection of the bodily constitution with such stone formation is also indicated from another direction. It is to be emphasized that also disturbances in the formation of the other bile constituents, for example, diminution in the bile acids, may be of importance for the precipitation of cholesterin. Investigations of the gall-stone-dissolving properties of desoxycholic acid (Wieland) are at present going on in this laboratory and have already yielded positive results.

Thus in the Freiburg Laboratory, Dr. Rosin carried out experiments on the power of desoxycholic acid to dissolve gall-stones. Attempts to dissolve gall-stones within the gall-bladder of the living man are very old. The starting point was the results of experiments carried out either *in vivo* in dogs or *in vitro* with bovine bile. It cannot be too strongly emphasized that the results of such experiments cannot be immediately applied to humans. To begin with, it is very different if human gall-stones are brought into animal or into human bile. The thorough investigations of Wieland on the cholesterin and bile acid content of the various varieties of animal and human bile have shown how extraordinarily variable these relations are in the individual species. It is, therefore, not astonishing that human gall-stones which are rich in cholesterin dissolve in the cholesterin-poor bovine bile. But it would be a great error if one were to conclude from this that such a solution also occurs in human bile. Dr. Aoyama has carried out comparative investigations in my laboratory by bringing human gall-stones first into bovine bile and later into human bile. The results were that these gall-stones lost distinctly in weight while in the cow's bile, and increased in weight during their stay in the human bile. It seems reasonable to assume that this increase resulted from renewed infiltration of the store by the cholesterin present in human bile.

Unfortunately, no decision of this question could be attained morphologically. The same holds for dog's bile. This also possesses a certain solvent power for human gall-stones, especially if the stone is brought into the gall-bladder of a living dog. The body heat of the dog is naturally not the decisive factor, for if the same stones are brought into human bile at the same temperature, they do not lose, but gain, weight. Dog's bile is also relatively rich in cholesterin, so the deciding factor in the process of solution by cow's bile cannot be the poverty in cholesterin. Other relations must also play a part, which is perhaps more important than the cholesterin content. These seem to be the content of the bile acids. But here again there are important differences. The investigations of Dr. Rosin showed that sodium desoxycholate has a strong power of solution, which is three or four times as great as the dissolving power of the cholates—taurocholate and glycocholate. Therefore the solvent power of human bile for cholesterin depends not only upon the total content of bile acids but also on the proportions in which they are mixed. The more desoxycholate present in the bile, the greater the solvent power, and vice versa. Since the formation of bile acids is again dependent on the diet and the excretory power of the liver, it may well be that variable mixtures occur in which too little cholesterin or too little solvent bile acids are present. This assumption would be all the more justified the more it could be shown that the bile acids are built by the liver cells at the cost of the cholesterin. The chemical relations of the bile acids to cholesterin have been determined by the investigations of Windaus. Hence we are dealing here with a special variety of disturbance of cholesterin metabolism. The assumption of such disturbance as the cause of the pure radial cholesterin stones explains to us all the properties of the latter, the lack of the infectious gall-bladder catarrh, the coarsely crystalline structure, the lack of lamellation and above all, the single occurrence. Sedimentation and crystallization occur in the non-infected bile which is free of all foreign admixtures; they occur on a *single* center because other points of crystallization are not present. If a renewed attack of hyper- or dyscholesterinosis leads to new precipitation in the bile,

a new stone will be added to the old stone without changing its structure. Despite diligent questioning and searching in all possible gall-stone collections, both at home and abroad, I have never been able to find a case in which there was more than *one* coarsely crystalline cholesterin stone.

Naunyn formerly attributed pure cholesterin stones to a secondary cholesterinization of ordinary gall-stones. He now concedes the primary occurrence of pure cholesterin stones but doubts the participation of cholesterin in normal bile, depending on the fact that human gall-stones dissolve when brought into the gall-bladder of a dog. Naunyn, therefore, still doubts the origin of gall-stones by precipitation in a hypercholesterinated bile. As a matter of fact, in the hypercholesterinated rabbit no formation of pure cholesterin stones has been observed, apart from the experiments of Dewey, which cannot be judged with certainty. But human and rabbit bile are entirely different. We still know so little of the dependence of the solubility of cholesterin on that of the other constituents of the bile and its physiochemical structure, that conclusions drawn from the bile of the herbivorous animal cannot be applied to the bile of an omnivorous animal. Naunyn believes that he can make probable the inflammatory genesis of pure cholesterin stones by the demonstration of minute, brown-colored nuclei within them. He attributes these nuclei to minute concrements of bilirubin-calcium which originated primarily in the bile passages as a consequence of a cholangitis and then were washed into the gall-bladder. When later we come to speak of the ordinary cholesterin-pigment-calcium stones, I will return to this theory, which was first stated by Meckel von Hemsbach and recently very strongly defended by Rovsing, although Rovsing attributes these bile cylinder forms of pigment-calcium more to metabolic disturbances. Here we are only dealing with the occasionally observed brown coloration of the center of the pure cholesterin stones. In contradistinction to Naunyn and Rovsing, I must maintain that these brown centers are not actually concrement-forming nuclei but only a mixture of bile pigment deposits on the crystallization center of the radial cholesterin stone. This bringing along of definite

bile constituents to the side of the primary, and therefore most active, crystallization process is readily comprehensible. Here the bile pigments are only superficially laid on the coarse columns of cholesterin masses. It is not a question of substances colored through as in the case of bilirubin-calcium, which, as we will later hear, plays so great a rôle in the formation of the cholesterin-pigment-calcium stones. There is, therefore, a great difference between the structure of the nucleus of the pure cholesterin stone and the structure of the nucleus of the cholesterin-pigment-calcium stone. In the pure cholesterin stone the nucleus is built up exactly as the other parts of the stone, i.e., there is no nucleus in the true sense of the word, but the central portions are occasionally colored dark by the absorption of pigments; the structure is the same throughout the entire stone. It is quite different in the case of the cholesterin-pigment-calcium stones, where one can differentiate a real nucleus and cortex by their varying structure and where the nucleus consists of true bilirubin-calcium besides cholesterin, and not of tinted cholesterin only.

I believe that by these statements I have sufficiently controverted the assertions of Naunyn and Rovsing, that the pure cholesterin stones are nothing else than a precipitation about a nucleus which has come from the bile passages. It would be incomprehensible why in all these cases of coarse, crystalline, pure cholesterin stone, there is always only a single stone in the gall-bladder, when one must assume that numerous small precipitations exist in the smallest bile ducts and therefore would wander in large numbers into the gall-bladder, if these precipitations result from inflammation (Naunyn) or a metabolic disturbance (Rovsing). For the authors assume that ordinary gall-stones, which mostly occur in a multiplicity, even hundreds or thousands, are to be attributed to the transport of such intrahepatic precipitation. We will later take up the question whether this theory, with which I immediately disagree in the case of pure cholesterin stones, can be upheld for other gall-stones.

Moreover, comparative investigations by Torinoumi on the contents of the gall-bladder and the bile passages show that free nuclear structures with typical gland formations,

characteristic for cholesterin-pigment-calcium stones, do not occur in the bile passages. From this the conclusion must be drawn that the true formation of the nucleus takes place in the gall-bladder. From what variety of precipitate the nuclei are formed requires further investigation. The previous descriptions are not exhaustive enough. Naunyn's more recent objections, therefore, do not at all suffice to weaken the theory that a certain variety of gall-stones, namely, the pure radial cholesterin stones, are not due to inflammatory catarrh of the bile passages but are a consequence of the disturbed cholesterin metabolism. Thereby, metabolism as the source of gall-stones is again brought within the field of the physician who is practicing prophylaxis and therapy. In which direction our tasks here will lie can only be learned from more exact investigation of lipoid metabolism and bile secretion in general. Yet the importance of the newly-won learning would appear slight if these cholesterin stones formed a rare exception and had practically no significance for the patient. But this is not the case. On the basis of a very large, thoroughly studied collection of gall-stones, I have estimated that the pure cholesterin stones resulting from metabolic disturbances form one-third of all varieties of gall-stones. To be sure, they do not always present themselves to us immediately as such, but in the form of so-called *combination-stones*.

With this we come to the subject of *true gall-stone disease*. As was already mentioned, the pure cholesterin stone usually gives no symptoms. But with this stone, as with all gall-stones, there is the danger of impaction in the neck of the gall-bladder or the cystic duct. This causes the afebrile, or at most slightly febrile, noninflammatory gall-stone attack. It may be repeated several times, until under the influence of the mechanical and reflex bile stasis there arises an ascending or accidental hematogenous infection. Today we are much better oriented, by the investigations of Hendriksen, Mann and Westphal, on the great significance of the sphincter of Oddi. Through the investigations of Auster and Crohn, Lyon, Jacobson, Gydesen and Chester, Willy Meyer, and especially Westphal, Judd and Mann, we know further how readily this sphincter can be influenced in a reflex man-

ner from the gall-bladder, the bile passages or the intestine. Irritation of the neck of the gall-bladder by the impaction of cholesterin stone or by any increase in pressure within the gall-bladder can readily lead to disturbances in the sphincter region, to reflex disturbances of bile secretion and to ascending infections of the bile and gall-bladder. On the other hand, it is not excluded that a hematogenous deposition of microorganisms in the gall-bladder contents can cause an irritation of the wall of the gall-bladder, and increase in pressure an impaction of the stone in the neck of the gall-bladder. The inflammatory reaction can develop to a dangerous degree in the stagnant bile, no matter how the infection of the gall-bladder may have arisen. The gall-stone disease which, until this event, has run its course without fever and which only occasionally has given rise to local spasms in the neck of the gall-bladder or the gall-bladder, or to reflex spasms in the region of the sphincter, may now be changed into *inflammatory gall-stone disease.* Either the pure cholesterin stone remains impacted in the neck of the gall-bladder and the pus collecting behind it leads to an empyema, from which in the course of years develops the well-known hydrops of the gall-bladder (Kümmell), which is characterized by its particular variety of closing stone, namely, the radial cholesterin stone; or the radial cholesterin stone returns into the now inflamed gall-bladder. This is naturally only possible when the pressure in the gall-bladder decreases by resorption of the inflammatory exudate. To what extent loosening of the stone makes possible discharge of the inflammatory content of the gall-bladder is difficult to say. At all events, the motility of the gall-bladder is diminished for a long time. As far as the content of the gall-bladder is concerned, we may indeed assume that it is no longer bile. Either the bile formerly present is for the larger part forced out by the pressure of the inflammatory exudate or, in so far as it is retained by the closing stone, is decomposed by the inflammation. Thus the fresh bile that now flows in, encounters a peculiar magma with which it mixes and forms a new colloidal system, in which the colloidal precipitation products (proteins), or morphological agglutination products (microorganisms, leucocytes, epithelial cells) furnish sufficient conditions for new

precipitation phenomena in the incoming bile. There occurs a precipitation of bilirubin-cholesterin in the form of granular semi-crystalline masses which develop under the influence of the protein-rich environment to rosettes of a thick crystalline structure. So long as the primary cholesterin stone present in this colloidal mixture suffices to take on the masses which crystallize out, the precipitation will only occur on it. It becomes surrounded by a slowly growing cortex; thus originates the so-called combination-stone. Under the influence of the inflammatory exudate of the mucous membrane which is rich in calcium, and of infectious decomposition of the bile, there occur precipitations of pigment-calcium masses rich in cholesterin, which form layers of a shell of cholesterin and pigment-calcium around the nucleus of the radial cholesterin stone. Thus originates the so-called combination-stone from a nucleus of pure cholesterin not of inflammatory origin, and the inflammatory shell of cholesterin-pigment-calcium. It was formerly believed that these nuclei were to be attributed to secondary cholesterinization. Now Naunyn also admits that the classical combination-stone arises in the manner just described. To be sure, he separates from these stones with a true cholesterin nucleus those with a false nucleus in which these nuclei are said to have originated by a later, more marked accumulation of cholesterin in the center. How far this occurs will be later discussed. At all events, one can readily recognize the true combination stones from the false by the fact that in a gall-bladder with many, indeed hundreds and thousands, of stones, there is always only *one* true combination-stone, while false so-called secondary nuclei may be contained in many or all of the stones. The reason for this is that the true combination-stone presupposes a radial cholesterin stone which is only formed singly. This cholesterin stone is usually the largest stone in the gall-bladder. For besides the shell around the radial cholesterin stone there may arise from the precipitating cholesterin-pigment-calcium masses, more or less numerous independent concrements, which are lacking in a radial cholesterin stone for a nucleus. These are the well-known facetted cholesterin-pigment-calcium stones which strike one especially by the lamellation on their cut surface,

and therefore may be opposed as lamellated stones to the purely radially built stones. The lamellations of these stones are entirely similar to the layers of the shell of the combination-stones and have therefore originated at the same time as this shell.

Before discussing these stones, which constitute the most frequent variety of gall-stones, I should like to summarize the significance of the pure solitary cholesterin stone. It is the sign of a metabolic disturbance and to that extent a characteristic symptom. On the other hand it is a harmless stone formation, inasmuch as it leads to no mechanically caused (by pressure, etc.) inflammatory change of the gall-bladder. It can rather be shown that the wall of the gall-bladder in such cases is unaltered as long as no infection is added. Though I have therefore designated pure cholesterin stones as "harmless in themselves," still I cannot understand the incorrect conception of my surgical colleagues when they maintain that I have explained these stones as totally harmless. I have repeatedly pointed out that these stones, through occasional impaction or other reflex influence of the sphincter system of the extrahepatic bile passages, favor infection of the latter and especially of the gall-bladder, and may become dangerous for the bearer. The stone does not act immediately on the wall of the gall-bladder and is to that extent harmless; but indirectly it can have effect by favoring infection and is to that extent dangerous. Whether, besides the pure cholesterin stones, there are other stone formations which originate on the basis of the metabolic disturbance, it is difficult to say. Apparently the *pure pigment stones* belong in this class. These pure pigment stones always occur in multiplicity and are ordinarily found in the gall-bladder, more rarely in the hepatic duct or the smaller bile ducts. They are usually mulberry-shaped, rarely spherical, oval or facetted. They are of the size of a grain of rice to at most the size of a pea, of hard, brittle consistency so that they are difficult to cut with the microtome knife. In drying, they sometimes disintegrate into coarse, black sand. The cut surfaces are mostly very black, have a metallic sheen and rupture like coal in a crystalline form. Their surface is sometimes very brightly colored, this being caused by a very thin layer of cholesterin-pig-

ment-calcium which is demonstrable as a precipitate formation in the depressions between the nodules.

According to Boysen, the stone is built up of small individual concrements which lend it the nodular appearance. The hard, fragile consistency of the stone makes it impossible to prepare sufficiently thin sections of it. As far as can be demonstrated it is a more or less homogeneously built stone without any particular formation of layers, without distinguishable nucleus and cortex. In this respect it is entirely like the cholesterin stone.

The origin of the pure pigment stones is still not clear. The statements of Naunyn, Boysen and Rovsing, that these stones are formed in the finer intrahepatic bile passages have found no general assent. I, personally, would believe that it is a question of a dyscrasic stone formation, without being able to say on what this dyscrasia depends. Under my direction, Dr. Torinoumi found these pigment stones four times in forty-eight autopsies, twice in 89 operated cases. Chemically, these stones consist almost entirely of bilirubin-calcium. Cholesterin is present only in traces. If, aside from the pure cholesterin stones and the pure bilirubin-calcium stones, there exist still other metabolic stone formations, as I should like to call them, it is as yet unknown. Perhaps the laminated pure cholesterin stone also belongs here. Since this variety of stone is very rare and in genesis unexplained, I will disregard it.

It is self-understood that all that has been said about the significance of the radial cholesterin stone as a blocking stone and as the cause of secondary infection, also holds for the pure pigment-calcium stone. This can also be made into a so-called combination-stone by secondary layering with cholesterin-pigment-calcium, so that we have to differentiate two varieties of combination-stone. In one variety the nucleus is formed by a radial cholesterin stone, in the other by a pigment-calcium stone. It may be emphasized here that a reversal of the relations, i.e., the formation of a nucleus from laminated cholesterin-pigment-calcium masses and the building of a shell of radial cholesterin or pure pigment-calcium has never yet been observed. This development must, therefore, occur according to a sort of law, i.e., the

pure cholesterin stone or bilirubin-calcium stone must precede the lamellated precipitation structures.

As was mentioned before, one finds, as a rule, besides the combination-stone, a greater or lesser number of laminated cholesterin-pigment-calcium stones. These are the stones which we designate, in contradistinction to the metabolic, as the *infectious stones*. Since it is self-understood that an infection of the bile passages and the gall-bladder, i.e., a cholecystitis, may also occur without a blocking stone (radial cholesterin stone), infectious stone formation must also occur without such preceding metabolic stone formations. Then, naturally, the combination-stone is lacking, the gall-bladder being filled only with infectious stones.

We now must concern ourselves more exactly with how these infectious stone formations arise. According to all we know, they are most intimately connected with an inflammation of the gall-bladder. The form, size, number and appearance of these stones vary extraordinarily. Two groups can be distinguished: first, the *facetted cholesterin-pigment-calcium stones* which ordinarily occur in large numbers, and second, the *cylindrical cholesterin-pigment-calcium stones*. Let us start by considering the first. The greater their number, the smaller they usually are. Also the shape seems to depend to a certain extent on the number. The typical tetrad-shape is usually best developed where there is a medium number of stones. The stones are as a rule more or less movably suspended in the bile. The color of the surface varies; likewise the color of the layers which are to be seen on the section of such a stone. This section reveals immediately a characteristic structure. In the middle there is a nucleus which is built up of plain, quite coarse rosettes, and round this nucleus a cortex made up of numerous finer and coarser systems of lamellae. In contradistinction to the combination-stone described above, there is here no sharp border between nucleus and cortex, but only a gradual transition, i.e., nucleus and cortex consist of the same material. Exceedingly characteristic of the nucleus is a more or less broad, stellate, branching cleft, projections of which occasionally reach to the cortex. The central masses are

strikingly soft. The nearer we come to the cortex, the harder the stone becomes.

As a rule all the stones in a gall-bladder, even though they vary greatly in size, appear on section to be of the same structure, with a similar nucleus, and a similarly layered cortex. The nucleus is ordinarily darker, being yellow or brownish to a brown-black, the cortex a light yellow, brown, white,

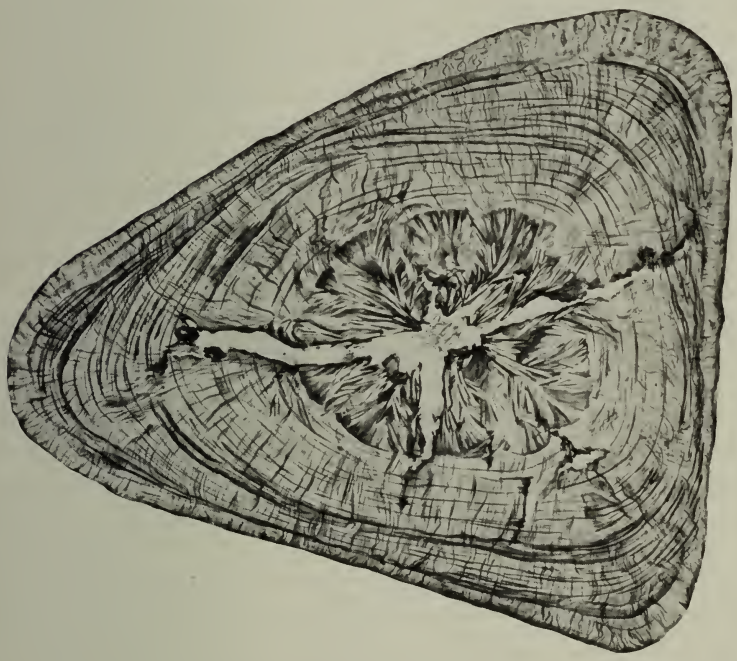

FIG. 20. Cholesterin-pigment-calcium stone with typical central fissure formation.

etc., with delicate lamellation. The successive coloring is the same in all stones of the same gall-bladder. Very rarely it occurs that besides this generation of stones characterized by their similarity, a second also is found, members of which are similarly akin to one another. Still more rarely, a third. From this we may draw the important conclusion that as a rule all stones of a gall-bladder have originated at one time, and that they grow equally with every new inflammatory attack, but that very rarely new stones arise.

How are these stones formed and why do no new stones arise? These two questions are intimately connected. If one wants to answer them the microscopic structure of the stones must be studied. It is seen that these lamellated cholesterin-pigment-calcium stones are of entirely different structure from the pure cholesterin-pigment-calcium stones. While the latter consist of a pure material, the former are made up of a mixture of cholesterin and pigment-calcium. The center is usually especially rich in pigment-calcium, the cortex richer in cholesterin. The central rosettes as well as the layers of the cortex are seen in the microscopic section to be composed mostly of thin and relatively short columns of cholesterin crystals. Nowhere does one find the coarse columns of the cholesterin stones. There are also no complicated intertwinings, but a well-marked radial and concentric arrangement which is evident to the periphery. The impression is that in the center the crystalline masses are more loosely imbedded in a softer mass; the closer to the periphery the denser the crystalline masses are to one another. Within the central rosettes the admixture of cholesterin-calcium is very clearly seen. In the cortex it is seen only in layers. If one removes the crystalline masses by chloroform or ether, there remains a protein framework which shows the same radial and concentric lamellation as the stone. This protein framework is practically entirely missing in the pure radial cholesterin stones. From this the most important conclusion as to the origin of the cholesterin-pigment-calcium stones may be dawn: *The cholesterin-pigment-calcium stones originate only in a medium rich in protein, the coarsely columned pure cholesterin stones only in a medium poor in protein.* There is a difference in the arrangement of the crystals of cholesterin—in the one instance in fine columns, in the other in coarse columns. There is also a different arrangement of the crystallized masses—in one case radial-concentric, in the other case confusedly thrown with one another. Both these differences must depend on the different make-up of the colloidal medium within which the crystallization takes place. What is the change in the contents of the gall-bladder which occurs during inflammation? In every inflammation an exudate rich in calcium and protein is poured into the gall-

bladder, thereby saturating or entirely replacing the original contents with this protein mixture. It seems entirely impossible for gall-stones having the character of the cholesterin-pigment-calcium stones to originate in a gall-bladder containing more or less pus. For this the admixture of bile is unconditionally necessary. It is very probable that this admixture only occurs when the inflammatory process regresses, and by resorptive concentration of the contents of the gall-bladder the entry of bile becomes again possible. It is immaterial how the admixture of the bile with the calcium and protein-rich exudate takes place. At all events, the necessary conditions for crystallization from the bile are furnished by the changes in the colloidal solubility relations, by the more marked admixture of calcium, by the presence of numerous centers of crystallization in the form of leucocytes, disintegrated masses of epithelial cells, etc. In the development of every cholesterin-pigment-calcium stone one must differentiate three periods:

1. The period of crystallizing out, i.e., the peculiar formation of rosettes.

2. The period of agglutination, i.e., the accumulation of the rosettes in the so-called nucleus.

3. The period of apposition, i.e., the formation of the cortex.

All three periods are essentially influenced by the colloidal state and the concentration of the bile. It is to be assumed that the more tenacious the bile mixture in the inflamed gall-bladder and the more abundantly it contains crystallization centers, the greater will be the number of rosettes formed. The first formation of these rosettes has unfortunately never been observed. It is, however, to be assumed that there is first a sort of decomposition with the formation of a semi-fluid mass which, through processes of contraction and condensation, undergoes a peculiar crystallization in a radial form. But before or during this process, there begins the process of agglutination. Whether the nucleus is made up of many small rosettes or a few large ones depends entirely on the time relations of the rosette formation on the one hand and the agglutination process on the other; but the number of final stone nuclei is also dependent on this. The

further growth within the bile itself determines again the number, size and shape of the stone nuclei. In this connection it must be stated that the apposition period, as we will term the formation of the cortex, usually occurs in an already changed environment. The first mixture of bile so rich in protein has been more or less purified, so to speak, by the processes of crystallization and agglutination. The newly arriving bile assumes more and more the composition of the normal bile. Crystallization now occurs more slowly and, corresponding to the altered surface, in a continuously thicker form. Thus the cortex is of increasing hardness but is not, however, the result of increased calcium content, as I formerly believed. The fact that the precipitates in the crystallization and agglutination periods are usually richer in calcium than the precipitates of the apposition period, strongly favors the view that this increased calcium content of the center or of the central region must be caused by something special, namely, by the admixture of the exudate.

If one looks on the lamellated cholesterin-pigment-calcium stone as a product formed according to the laws of crystallization, agglutination and apposition processes in a well-defined colloidal medium, a medium which is first furnished by the inflammatory process, then the differences between nucleus and cortex formation are thoroughly comprehensible. The greater protein content of the center enables us to understand the softer consistency of the rosettes. We also understand, thereby, the greater absorption of bilirubin calcium during these precipitation and crystallization processes. And still another finding becomes comprehensible: the colloidal system of the gall-stone nucleus, precisely like all other colloidal systems, must go through its ageing process. But since the cortex is harder than the center, the contraction cannot occur from the periphery toward the center but must on the contrary take place, as in a dying tree-trunk, from the center toward the periphery. Thus originate within the stone the clefts already observed and carefully described by Naunyn, which I at first thought were due to drying in the air, but which, as Naunyn correctly maintains, are intravital phenomena. It is readily understandable that the water of swelling which exudes from the colloidal

substance of the nucleus and collects in the clefts may contain all sorts of dissolved substances, among them cholesterin. This may again precipitate out, never in the form of crystalline columns as they characteristically occur in the original stone formation, but in the form of fine needles.

As far as the shape of the stone is concerned, it is obvious from what has been said that the facettes can never originate through pressure. This is shown by a glance at any section of such a stone. On this it can be plainly seen that the laminae, with very rare exceptions, are never broken through as would necessarily be the case if they had been rubbed. But one does see at the so-called angles of the cube a more marked development of the layers, a proof of a greater growth at the projecting portions. When the stones are together in a gall-bladder the greater growth of the angles is obvious, since they are washed here by the fluid more than at the surfaces.

Thus all the findings in these cholesterin-pigment-calcium stones are comprehensible, even though we cannot as yet explain their individual phases in their minute details according to the physical and chemical laws of their formation.

A word about the second variety of infectious stone formations, i.e., the barrel-shaped. Even when they occur in twos or threes they are plainly differentiated from facetted stones by the possession of two varieties of surfaces, a facetted surface where they are in contact with one another and a non-facetted finely nodular surface where they are in contact with the mucous membrane. For the essential difference between these stones and the facetted stones is that the latter are freely movable and the former are to a greater or less extent immobile in the gall-bladder. If one prepares microscopic sections of such barrel-shaped stones, one sees immediately the characteristic difference between them and the facetted stones. In the facetted stones the nucleus consists of a few large half or quarter rosettes, in the barrel-shaped stones of a conglomeration of numerous small rosettes. While in the case of the facetted stones there occurs an equal lamellation around the nucleus, in the barrel-shaped stones this is well marked only at either pole. It is totally lacking or not well marked in the places where the

stone lies on the mucous membrane. From this it follows that here, in contradistinction to the other instance, the bile is not the sole source of the gall-stone-forming material, but that the inflamed mucous membrane is the source; not, however, the intact mucous membrane, but the ulcerated, in which the chronic pus formation is readily noted. From these masses of pus there comes the protein, in part the calcium, and also the cholesterin which, together with the cholesterin of the bile, furnishes the material for the building of the cortex. According to the laws developed above, the crystallization and agglutination processes do not come to a stop, because new material is continuously furnished. And thus the nucleus of the stone grows irregularly without receiving a real shell. The different composition of the nucleus does not permit the formation of any real cavity in the center. In short, we see under these special conditions an entirely different variety of stone development.

Now we must still answer the second question: why as a rule no new stones are formed. It must be assumed that the presence of an already finished stone acts, when periods of inflammation again occur, as so strong a precipitating center that while the new cortical layers may indeed have a somewhat altered structure, yet no independent crystallization and agglutination processes occur. At all events, that will only exceptionally be the case, and then there arises a second or even a third generation of stones.

This finishes the description of the two main groups of gall-stone formations—the metabolic and the infectious. We still have to point out that there is a third variety of stone formation which originates essentially through stasis. This *static* stone formation is differentiated from the two others above all by its location. While the latter, disregarding the rare exceptions, only arise in the gall-bladder, the static stone formations, on the contrary, arise only in the bile passages, and only in the gall-bladder when this has, through exceptionally unfavorable circumstances, lost its protecting valve, the narrowly wound cystic duct. The static stones form the second variety of bilirubin-calcium stones which are often designated also as the *earthy* stones. They are more or less soft, fragile, equally colored, plainly laminated, red-

brown to brown-black structures; sometimes egg-shaped, sometimes rounded, sometimes sausage-shaped or angular. They develop only when there is stasis of the bile in the passages. These stones are most often found around foreign bodies and the most important of these foreign bodies are gall-bladder stones which have wandered from the gall-bladder. There thus arises a new variety of combination-stone. While we previously counted only those which consisted of a nucleus of pure cholesterin or pure pigment-calcium and the shell of cholesterin-pigment-calcium, we now learn of a third variety in which the various varieties of gall-bladder stones receive a new shell. This new shell consists of a soft earthy bilirubin-calcium rich in cholesterin. According to the variety of the gall-bladder stone which has wandered, the new combination-stone may be of varying structure. While the shell always consists of earthy bilirubin-calcium, the nucleus may be any of the stones described above, cholesterin-pigment-calcium, or a pure cholesterin stone, or a combination-stone. When the nucleus is a combination-stone of the gall-bladder, a new combination, a combination-stone of the *second* order results.

This ends the enumeration of the various stones. You see that three different processes play a part in the formation of human gall-stones: metabolic disturbances, infection and bile stasis; and that according to the predominance of any one of these conditions in the extrahepatic system of bile passages, entirely different stones are formed. One cannot, therefore, speak of a *single cause* of gall-stone formation, at least not in man. Hence, I do not consider it justifiable on the basis of experiments of one definite kind to draw conclusions as to human gall-stones which occur in so great a variety.

If, therefore, Dewey has produced real gall-stones by feeding animals cholesterin, and if, on the other hand, Gilbert and Fournier, Mignot, Ehret and Stolz produced gall-stones by infection of the gall-bladder in dogs, and finally if Rous, McMaster and Drury attained gall-stone formations by artificially leading bile through glass and rubber tubes, these only prove that gall-stone formations may occur under the most different conditions. But if one wants to find experi-

mentally precisely those conditions under which *human* gall-stones arise, then one must produce in animals, stones which coincide with human gall-stones. Unfortunately, there are very few reliable structural investigations on the gall-stone formation attained in previous experiments on animals. The only ones who hitherto have undertaken investigations are Rous and his coworkers. They found in the dogs whose bile passages had been intubated for a long time, a formation of precipitate of calcium and calcium carbonate as well as organic flocculi on the walls of the glass and rubber cannulas. Since they also found similar, in part plainly concentrically laminated bodies in the bile of men who suffered from cholelithiasis, they believe they have thereby found the final and true cause of gall-stone formation. They believe that wherever the formation of precipitates of organic substances is possible for some time, a precipitation of bilirubin-calcium or calcium-carbonate can occur. They are, therefore, of the opinion that infection of the bile passages does not so much prepare for gall-stone formation by furnishing an exudate rich in protein and calcium as by a sort of paralysis of the wall which no longer contracts when in an inflamed condition and can no longer remove the precipitated structures. Though I highly value and recognize the researches of Rous and his coworkers on the function of the gall-bladder in the formation of bile, I cannot agree with this opinion of theirs. I also have had the contents of human gall-bladders and bile passages in many cases histologically examined by Dr. Torinoumi. In 84 cases gall-bladders and bile passages, and 15 cases only the gall-bladders, were examined. The result of the examinations was that in 56 cases precipitates were found in the gall-bladder. On the other hand, in only 39 cases were they found in the bile passages. In this, the following varieties of sediments were concerned:

1. Granular, crystalline, mostly brightly colored precipitates, which besides bile pigment, perhaps also contain cholesterin.

2. Evenly, bile-colored, wax-like, drop-like to cake-like precipitates.

3. Pale, uncolored even or cloudy, protein-like precipitates, with which may be united the formation of hyaline-like,

doubly refractile drops with transitions to cholesterin needles or tables.

4. Completed cholesterin crystals.

5. Myelin figures.

6. Peculiar spherolithic and otherwise shaped precipitates of calcium which were exceedingly rare and apparently identical with those described by Rous.

No more than Rous were we able to determine the relations of any of these varieties of precipitates to true stone formation. I can, therefore, recognize only *sedimentations* but no *true stone formations* in the protein and calcium precipitates found by Rous in the dog. But this is a very great difference. Accepted that the precipitations produced by Rous are really stones, the completely different structure of the various varieties of human gall-stones unconditionally speaks for different conditions.[1]

A final word as to therapy. I must here neglect surgical therapy. It appears to me when the indication is present, and that as a rule is so only when there is an infectious complication, to consist solely in cholecystectomy. But if one wants to proceed by non-surgical methods, there are three lines:

1. The avoidance of gall-stone formation, the metabolic as well as the infectious varieties. Unfortunately, we have very little influence on either. However, we know today that intentional disturbance of cholesterin metabolism, as for instance the diminished elimination of cholesterin by the breast in a non-nursing woman, or rapid obesity cures, can lead to the formation of cholesterin stones. We could try to treat women who are not able to nurse, with desoxycholates for preventing the formation of cholesterin stones. We know that, on the other hand, disturbances of gastrointestinal activity, psychic affects, etc., can lead to reflex disturbance of sphincteral activity and therefore to infection. These must also be taken into account to prevent stone formation.

2. Inasmuch as we cannot prevent the formation of stones, we must by suitable food and drink secure the best possible

[1] One of them may be the changing of H. ion concentration, as Rous has shown in his last paper.

irrigation of the bile passages where the gall-bladder contains stones, in order that new infections shall not occur following cramp of the sphincter.

3. Since we cannot prevent the formation of gall-stones and also not always avoid their consequences, we may ask ourselves if it is not possible to dissolve the stones. Unfortunately, the conditions for this are exceedingly unfavorable. As was shown by the experiments of Dr. Rosin, in desoxycholate solutions the weight of the stone can be diminished. But this gradual solution of the stone is associated with a great danger. The thoroughly described cleft formations in the center of the cholesterin-pigment-calcium stones which result from a contraction process, will, if the cortex be gradually loosened, finally split the stone. So that the result of medicinal treatment with such solvents will not cause a disappearance of the stones, but only supply a new stone nucleus. It is difficult to say whether or not it is easier to remove the small fragments. The situation is, however, all the more dangerous in case of a new infection; for then all these stone fragments, as experience shows, will grow to new stones. Therefore, because of our better knowledge of the morphological structure of gall-stones, we must warn concerning such solution therapy. The main task of the internist will remain to protect the bile-passage apparatus as far as possible from new traumata and infections. Wherever this is not successful, surgical therapy holds the field.

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X

THE SITE OF FORMATION OF BILE PIGMENT[1]

The celebrated experiments of Minkowski and Naunyn, carried out on geese whose livers had been removed, in which despite the severest degree of arsenhydrogen poisoning no jaundice occurred, appeared to have offered a final solution to the question of the formation of the bile pigment. Considering these experiments, the conclusion had to be drawn that the liver is the sole site of formation of the bile pigment. From this result the principles were deduced: "without the liver no formation of bile pigment;" "without the liver no jaundice." Thus, only hepatogenic but not hematogenic icterus was recognized. The validity of this principle of Minkowski and Naunyn has recently been much impaired by two observations. Firstly, Whipple and Hooper were able to show by apparently irrefutable experiments that if the liver, and indeed all the abdominal viscera, is excluded from the circulation, bile pigment is still found in the blood plasma. On the other hand, investigations by McNee directed to the same end as those of Minkowski and Naunyn, led to the suspicion that in the physiological formation of bile pigment, not so much the liver cells as rather the reticulo-endothelial elements enclosed in the liver tissue, the stellate cells of Kupffer, might be involved.

Later Keyes reported observations similar to those of McNee. He arrived at the same conclusions as had McNee. Both came to the conclusion that the stellate cells of Kupffer, even normally, but to a much greater degree in arsenhydrogen poisoning jaundice, participate in the phagocytosis of the red blood cells and the elaboration of their products to iron and iron-free pigment.

In any event, the experiments of Minkowski and Naunyn were not unequivocal, for when the liver was removed, not

[1] Lane Lecture.

only were the parenchymatous cells eliminated, but also the reticulo-endothelial elements, the so-called "splenic tissue" enclosed in the liver. Now, since birds have a strikingly small spleen and very little bone marrow, but a very large liver, it is clear that there is very little splenic tissue outside of the liver.

Consequently, the question of the formation of bile pigment and of jaundice had to be formulated in an entirely different manner. One must not say: Is there only a *hepatogenous* formation of bile pigment, and only a *hepatogenous* jaundice? But the question must rather be put: Is there only a *hepato-cellular* production of bile pigment and a *hepato-cellular* jaundice? Lepehne first sought to answer this question by functionally paralyzing the reticulo-endothelial apparatus, included in which are the Kupffer cells of the liver, by loading them with collargol. He believed to have observed, following this collargol storage, a distinct diminution in the formation of the bile pigment. These experiments have met with all sorts of contradictions and objections. It was thought, on the basis of contradictory experimental results, that the conclusions of Lepehne, as well as the opinions voiced by McNee might be regarded as fully controverted. I would like at present to assume a new attitude with respect to this problem.

At the time of the experimental studies of McNee and Lepehne I pointed out that when considering the question of bile pigment formation, not only the liver cells, but also the reticulo-endothelial apparatus, must be given close attention. I believed that through this study a new way to the solution of the difficult problem would be presented. Our conception of the predominant involvement of these cells in the decomposition of the hemoglobin complex and the formation of bilirubin was based above all on *histological findings*. The conclusions drawn from the latter were supported to a certain degree by the experiments of Lepehne on the storage of collargol. But even if it should be found that Lepehne's experiments dealt only with accidental findings—in the sense that precisely here a paralysis of the reticulo-endothelial apparatus was attained by the loading with collargol, while in other cases the so-called blockade does

not affect, or on the contrary accelerates, the formation of bile pigment, i.e., acts as a stimulus—then all these results, contradictory though they are, would not annihilate the histological findings. I should like to remind you once again that the problem of the more intimate involvement of the reticulo-endothelial cells in the formation of bile pigment in various animals was expressly left an open question. Although in birds a direct, and in rats certainly an indirect, participation of the reticulo-endothelial cells in the transformation of hemoglobin was shown to be probable, such a demonstration could not be furnished in the case of the rabbit. In the latter instance humoral forces must be involved (Lepehne). At all events, it was emphasized from the start that the relations in the individual species of animals are different. The basis for this opinion was in part purely morphological, inasmuch as the development and arrangement of the reticulo-endothelial system, even in closely related species, is uncommonly variable, a fact to which sufficient attention in the evaluation of the findings has not yet been paid. Finally, we did not neglect to point out that the question of the involvement of the liver cells themselves in the formation of bile pigment remains an open one. Here there were only three possibilities: Either (1) the liver cells serve solely as an excretory organ for the finished pigment, or (2) by some transformation they make the essentially finished pigment suitable for excretion, or finally (3) they produce the pigment from the as yet not further elaborated hemoglobin. In evaluating the three possibilities mentioned, we decided, expressly because of the histological findings, *against the last and for the first* assumption, in doing which we left open the possibility of a physical or chemical transformation by the liver cells of an essentially fully prepared bile pigment. Thus McNee writes: "For the present it must be left unanswered if the biliverdin of the bile comes directly from the iron-free part of the pigment or only after it has undergone some preliminary preparation." I have pointed out the possibility of the modification by the liver cells of a hemoglobin already like bilirubin which has been transformed by other cells or body fluids. To be sure, the morphological and clinical findings in toxic hemolytic icterus speak

more for the formation of the bile pigment without the participation of the liver cells.

Rosenthal and Fischer, in particular, have objected to this interpretation of the morphological pictures. They believe that we are here concerned essentially with the results of the blood icterus. The stellate cells of Kupffer take up all foreign or superfluous substances from the blood, and among them, of course, bile pigment and iron. Thus, the findings observed in poisoned pigeons are to be interpreted as pictures of resorption. If this criticism is justified it would also turn against the experiments of Minkowski and Naunyn, for these two authors did not doubt in the least that from the hemoglobin freed as a result of the arsenhydrogen poisoning, bile pigment as well as iron was split off within the Kupffer cells. This transformation is described unequivocally on page 21 of their article. They also show that this is a question of actual bile-pigment formation. They remark at the close of their discussion: "The biliverdin must have originated in the cells containing the blood corpuscles and of course from the decomposed blood pigment. The taking up from the blood of particles formed outside of the cells and brought by the bile is excluded, because such green particles are not found free in the blood." How much more correctly than Rosenthal and Fischer these two authors have interpreted the findings, we will see later on. In any event, I can only take the same view as Minkowski and Naunyn. They write expressly: "Following the occurrence of biliverdin in the cells which contain blood corpuscles, it is certain that these furnish, in the blood pigment which they contain, material for the production of bile pigment in the liver." With this also I am in absolute agreement. But Minkowski and Naunyn believe that bile pigment is also formed in the liver cells. To be sure they write on this point: "The results of our experiments are unfortunately not unequivocal as to this point. In the liver cells *we were never able to find intact hemoglobin*." So that while they therefore regard as certain and proved the formation of bile pigment from hemoglobin within the Kupffer cells, they declare the formation of bile pigment within the liver cells to be only probable. The sole basis which they can furnish for the statement that the Kupffer cells are not the sole producers

of bile pigment is that in their opinion the number of stellate cells in the liver containing blood corpuscles, i.e., the bile- and iron-containing cells, is too small to be able to produce the quantity of bile formed. They believe all the more that the activity of these cells is insufficient since they were not able to demonstrate the formation of bile pigment in the cells of the spleen or the bone marrow which contain erythrocytes.

Hence we see how extraordinarily difficult it was for Minkowski and Naunyn to form a decision. If we could succeed in eliminating the doubts that Minkowski and Naunyn had of the exclusive significance of the Kupffer cells for the formation of bile pigment, we would put aside all compulsion to place the sole seat of bile-pigment formation in the liver, for which Minkowski and Naunyn were not able to bring the slightest further proof from their own experiments. We believe that we have destroyed these objections by our earlier investigations. McNee was not only able to demonstrate bile-containing cells in the spleen and bone marrow, but at the same time he made the further important observation that the bile- and iron-containing Kupffer cells of the liver are removed exceedingly rapidly and in great numbers from the liver, to be disintegrated within the pulmonary vessels. That is to say, there occurs a continuous desquamation of the cells as well as an uninterrupted liberation of bile pigment into the blood. It is self-understood that from the number of cells remaining in the liver one can draw no conclusion whatsoever as to their participation in bile-pigment formation, unless their further fate in the pulmonary vessels also be considered. Despite all this, the objection still remains tenable that the pictures which were interpreted by Minkowski and Naunyn, as well as by McNee and myself, as representing the taking up and elaboration of hemoglobin by the Kupffer cells in reality were only phenomena of resorption by these cells of bile pigment present in excessive quantities in the blood and originally coming from the liver cells. We will discuss this point later on.

Another objection concerns Lepehne's experiments with the storing of collargol. I should mention in advance that subsequent investigators did not confine themselves to a

cautious judgment of the results of Lepehne's experiments. Lepehne arrived at the conclusion that in certain animals a hemolytic jaundice without involvement of the liver cells was made very probable by his experiments. This had to be attributed to an anhepatocellular formation of bile pigment and indeed by the Kupffer cells. He believed that he had demonstrated in the case of the pigeon, that by means of collargol storage a sort of paralysis of the reticulo-endothelial apparatus, and with it a slowing or diminution of bile-pigment formation, could be obtained. He did not at all consider a complete or certain suppression of formation of bile pigment. Still less did he maintain this for rats, and not at all for the rabbit. If, then, one wants to corroborate Lepehne's statements, it is necessary to confine oneself to the species of animals and the manner of inducing storage which he used. As yet, only Rosenthal and Melchior have performed such control experiments. To the present, no subsequent investigators have carried out in sufficient number the same experiments with collargol storage and arsenhydrogen poisoning in pigeons. The other objections brought forth against these experiments will be considered as soon as it is possible in Germany to obtain the necessary animals. For the present, Rosenthal and Melchior believe, on the basis of their storage and poisoning experiments on dogs and cats, that they can exclude the involvement of the reticulo-endothelial apparatus in the formation of bile pigment. Bieling and Isaac also, on the basis of their experiments on jaundice due to hemolysins in mice and guinea pigs, disbelieve the theory of bile-pigment formation within the reticulo-endothelial cells. They believe that their experiments support the old theory of Minkowski and Naunyn, according to which not only the formation of bile pigment but also its excretion, is a function of the *liver cells*. They conclude from their "storage" experiments on mice, that the rôle of the reticulo-endothelial cells after production of an intravital hemolysis, is no longer to be considered. The further elaboration of the blood pigment into bile pigment is not their task. By this statement these authors also place themselves in perhaps unconscious opposition to Minkowski and Naunyn, who, as well as McNee and myself, expressly maintain the

formation of bile pigment from hemoglobin within the reticulo-endothelial cells.

But are the experiments of Rosenthal and Fischer and Bieling and Isaac really against the theory of the participation of the reticulo-endothelial cells in the formation of the bile pigment? I believe not. On another occasion, I called attention to the fact that the participation of these cells in the disintegration of hemoglobin may occur in various ways. In the one instance the hemoglobin may be directly taken up by these cells and then further transformed, as in the pigeon. In another instance the cells may furnish some ferment to the blood which itself makes possible the further elaboration of the hemoglobin in the blood. From the beginning we have maintained that it is necessary to assume humoral forces for certain animals, e.g., the rabbit. All this I say entirely apart from the fact that the manner in which hemoglobin is taken up, whether within the intact erythrocytes or in the dissolved state, may vary from one species of animal to another. Confronted by such a complicated problem, one can readily perceive that so relatively rough a method of influencing the cells as storage experiments may quite as readily lead to paralysis as to stimulation of the cells, and that the different functions of the same cell may be side by side stimulated and paralyzed. Hence, it is comprehensible that through storage the phagocytic property for corpuscular elements may be paralyzed, while on the other hand the excretion of active ferments may be increased. At all events, it is not surprising that, precisely as in the case of substances with a ferment-like action, e.g., the hemolysins, an increase in the blood has been demonstrated after storage experiments. I call attention to the most recent researches of Pfeiffer and Staudenach. Moreover Dr. Kodama, in my laboratory, was able to determine that in dogs after collargol storage and simultaneous toluylendiamine poisoning, bile-pigment formation occurs somewhat earlier in the blood than in dogs which have not stored collargol; but this requires further control. On the contrary, hemolysis of pigeon blood by phenylhydrazine could not be influenced at all by the storage. The hemolysis occurred in the same manner in animals which had stored collargol and those which had not. This is readily understood,

since only a purely humoral process is in question; on the other hand, it was very beautifully shown that the phagocytosis of the injured erythrocytes by the reticulo-endothelial cells which were loaded with collargol no longer occurred. That just these phagocytic properties are readily influenced and coincidentally the cell is blocked against other corpuscular elements, is also shown by the experiments of Nissen.

Therefore, I cannot admit that through the negative result of blocking experiments any decision can be arrived at in the question of the participation of the reticulo-endothelial cells in the formation of bile pigment. Against the majority of the experiments, I must also object that they have been carried out with much too massive doses of poison. When these are used, variations in the time of appearance of the bile pigment in the blood cannot be sufficiently controlled and one can only note acceleration or slowing of the entire process, for a complete suppression occurs only for very short periods of time. This is shown plainly by the work of Lepehne.

The third objection comes from the clinicians. Minkowski, Kraus and Bergmann believe in the primary importance of the liver cells. To be sure, they always maintain that an extrahepatic formation of bile pigment is possible in a manner akin to the formation of hematoidin in cerebral hemorrhages. That hematoidin is identical with bilirubin, or contains a body identical with bilirubin, has now been definitely established by the investigations of Fischer and Reindel. But the clinicians deny the formation of the bile pigment of the blood except by the liver cells and therefore the origin of jaundice without participation of the liver cells. In this connection, emphasis should be laid on the word *jaundice*. When Minkowski maintains that bile-pigment formation, but not *actual jaundice*, can occur without the agency of the liver cells, he naturally means by this that the physiological formation of bile pigment is carried out by the liver cells, but only a disease of the liver cells can increase this physiological formation of bile pigment to pathological jaundice. I am of the opinion that the question of jaundice must for the present remain an open one; it must first be decided where bile pigment originates under physiological conditions. Only

then may the problem of icterus be attacked. Minkowski and Naunyn themselves felt this, for in their celebrated research on arsenhydrogen jaundice in intact geese and in those whose livers had been removed, they continually speak of the formation of bile pigment, and indeed of the physiological formation. All other experiments are for the purpose of deciding *if bile pigment is formed within or without the liver cells.* Therefore, we will also confine ourselves to this problem.

The solution of this problem has been made easier by the fact that we are today in a position, with the help of the method of Hijmanns van den Bergh, to recognize the earliest stages of accumulation of bile pigment in the blood, at least above a certain threshold. This method has also led to differentiation of functional and mechanical bilirubin. An irrefutable explanation of the difference between the bilirubin said to have been formed in the blood and that which has been resorbed from the bile passages or from the injured liver cells, has not as yet been offered. The simplest assumption is that in the excretion of the bilirubin by the liver cells, some splitting off from a body with which it has been combined takes place. But it is quite as plausible that the blood bilirubin can be saturated or combined only up to a certain quantity and the excess is found as unbound bilirubin. I know that there are various other possibilities of explanation. For what follows it does not matter which explanation one holds. If it is desired to proceed further from a morphological viewpoint in the problem of bile-pigment formation, only two possibilities remain: First, one might compare the appearance of bilirubin in the blood in various poisonings with the changes in the liver and try to determine if the first appearance of the bilirubin is preceded by a change in the liver cells or a change of the Kupffer cells. As is well known, adherents of the theory of hepatocellular bile-pigment formation refer the varieties of icterus occurring in poisoning by toluylenediamine, etc., to a special injury of the liver cells, the so-called parapedesis. If the liver cells are really so injured by the icterogenous poison, as Minkowski and with him Rosenthal, Retzlaff and others maintain, that they give up the bile pigment formed by them no longer to the bile capillaries

but to the blood stream, then one should find by a careful investigation of the liver cells some morphological basis for so great a dysfunction, be it in the nucleus or the protoplasm. If the liver cells remain intact until the appearance of the bile pigment and only the Kupffer cells are changed in any characteristic way whatsoever, one must look on this as an indication of their participation in the formation of the bile pigment.

On the other hand, it is possible in the mammal, by excluding the liver, to test the findings of Minkowski and Naunyn in birds. Here also we have at our disposal a new method, that of Mann and Magath. The first of these two problems has been studied by Dr. Kodama, the second by Dr. Makino, in the Freiburg laboratory, and I should like to report briefly on their results. All the experiments on dogs poisoned with toluylenediamine which were carried out by Dr. Kodama show unequivocally that often where the serum had a well-marked content of bile pigment, so long as this gave the indirect reaction the liver cells remained entirely unaltered; the Kupffer cells on the contrary showed, before the occurrence of bile pigment in the serum, marked swelling and infiltration with a yellowish pigment. We do not attempt to decide if an intermediary decomposition product of hemoglobin or bilirubin itself is the pigment. Only the following fact is established: in the most exact investigation of the earliest stages of hemolytic bile-pigment formation, the Kupffer cells are already in lively activity, while the liver cells show no changes. Coarser obstruction of the bile capillaries is totally absent. As has already been noted by other authors, these are not to be considered as a source of purely hemolytic jaundice. When they occur, they are only coincidental and not the cause of the increase of bile pigment in the blood.

That the occurrence of indirectly reacting bile pigment is not to be attributed to a dysfunction of the liver cells is proved by the fact that when the icterus lasts longer the bile capillaries are filled with bile, which is only possible if the liver cells secrete in their natural direction—to be sure in increased quantity and altered consistency. That is to say, there is a hyperfunction rather than a simple dysfunc-

tion. I entirely agree with Lepehne's view that the *indirect bilirubin* which is found at first in toluylenediamine jaundice comes from the action of the reticulo-endothelial system. The appearance of *promptly reacting bilirubin* is to be attributed, with great probability, as is shown by the ligation experiment on the common duct to be mentioned later, to the formation of bile thrombi; more cautiously expressed, it occurs simultaneously with the formation of the bile thrombi. The formation of these bile thrombi is again in connection with the excretion of a particularly tenacious bilirubin. If when the reticulo-endothelial system is paralyzed this substance cannot be produced, then it can also not be secreted by the liver cells and there are no bile thrombi and stasis icterus. In my opinion, too little weight is laid on the more recent researches on the proteins accompanying bilirubin. I believe that Stadelmann and Eppinger are correct in their view of the increased viscosity of the bile formed as a result of toxemia. At all events, this aspect of bile secretion is worthy of renewed investigation. The decomposition of hemoglobin takes place quite differently in the various animals and under the influence of the various poisons.

Further experiments tried consisted of the ligation of the common duct. As is well known, there first occurs in the blood serum a delayed bile-pigment reaction and only later does the prompt reaction appear (literature given by Lepehne and Retzlaff). In the dog the delayed reaction is already evident after five hours, the prompt reaction after three hours more. Investigation of the liver revealed the remarkable fact that the prompt reaction occurs only when some sign of bile-capillary blocking is present, and indeed obvious bile cylinders. The explanation is probably to be sought in the fact that there is a sinking in the secretory power of the liver, for an anhepatocellular pigment is formed which accumulates in the blood and which certainly gives the delayed reaction. The latter accumulates so greatly in the blood that after a certain time it becomes demonstrable. Naturally a considerable time is required for the formation of the bile cylinders in the bile capillaries and the stasis of the bile in the bile capillaries, until a pressure has been attained which leads to a resorption of the already secreted and promptly reacting pigment.

Thus the direct reaction which is to be attributed to resorption from the bile passages lags behind a delayed reaction which depends on increased production in the blood. We may at least indicate another possibility for the appearance of the prompt reaction: So much bile pigment accumulates in the blood that not enough binding substance is at its disposal. As soon as the direct reaction has attained a more marked degree, it hides the delayed reaction more or less. Therefore, one should not conclude from the prompt reaction of the blood serum that the bile pigment in the blood is to be attributed solely to resorption or, as it is ambiguously put, to stasis of the bile pigment in the blood. The pigment may come from two sources at the same time: (1) a retention in the blood of the bile pigment formed with or without the help of certain cells and which gives the delayed reaction, (2) a resorption of promptly reacting bile pigment from the bile passages. The first can only be demonstrated at the beginning of the process but is still acting later on when it has long been masked, so to speak, by the other reaction. In this case one should always watch for the diphasic reaction of Lepehne. I am convinced that such a masking of the delayed reaction by the prompt one occurs more frequently in man than has hitherto been thought (van den Bergh, Lepehne, Retzlaff).

Another observation was made by Dr. Kodama in these ligation experiments. Immediately after the ligation the Kupffer cells began to store iron. After twenty-four hours all the cells contained more or less obvious iron granules. On the other hand, the liver cells remained free of iron. The appearance is as though the Kupffer cells further elaborate and store iron coming from the decomposed hemoglobin, because it is no longer sufficiently excreted by the liver cells. On the other hand, it is seen in the poisoning experiments (toluylenediamine), after twenty-four hours, that the liver cells are richly filled with iron granules; the Kupffer cells, on the contrary, but very sparingly. This negates the argument advanced by Minkowski and Naunyn, that because of the marked deposition of iron granules in the liver cells, while there is only a slight iron deposition in the Kupffer cells, a direct utilization of the hemoglobin by the liver cells is to be assumed. That the liver cells following poisoning store

such a large amount of iron is dependent not upon their participation in bile-pigment formation but is rather because they excrete the excess of iron and, in the process, store some of it. If one suppresses the iron excretion, as in the common duct ligation, they do not show any iron content; but the Kupffer cells behave entirely differently. Their activity cannot be suppressed by ligation of the common duct. That they participate in decomposing hemoglobin is first shown plainly by the iron reaction. Such an interpretation of the findings is certainly as much justified in the case of the Kupffer cells as that of Minkowski and Naunyn in the case of the liver cells. But if the iron storage in the Kupffer cells is not to be recognized as a sign of intracellular hemoglobin decomposition but only regarded as a resorption process from the blood—a conception which must certainly be considered—then all the conclusions drawn by Minkowski and Naunyn in the case of the liver cells are also fallacious, for everything that holds for the Kupffer cells must also obtain for the liver cells. I emphasize once again that these pictures are only to be found in the *dog*. In the *pigeon* the conditions are entirely different. If one ties off the common duct of the pigeon, no cylinders are formed in the bile capillaries and no biliverdin appears in the blood; apparently, in contradistinction to the dog, no resorption occurs. It appears, indeed, as if despite the ligation the secretion of bile by the liver cells keeps on, although more slowly, for the liver cells quite obviously store iron, the Kupffer cells much less. With this there exists quite evident icterus and bilirubin content of the serum.

Perhaps I may here add a few brief words on the phagocytosis of bile cylinders in the Kupffer cells. This occurs in the Kupffer cells only in the presence of well-marked bile-thrombus formation in the bile capillaries or otherwise well-marked blood icterus. In the first case, the Kupffer cells take up entire fragments of bile cylinders, as was shown by T. Ogata. In the other instance, the Kupffer cells are loaded with finely granular bile pigment. The changes which are, however, seen in the Kupffer cells in the early stages of toluylenediamine poisoning and those which McNee observed in arsenhydrogen poisoning of pigeons, are to be

identified with neither the one nor the other process. They represent something quite separate and therefore cannot be looked upon as simple phagocytosis or resorption of fully prepared bile pigment by Kupffer cells, as Rosenthal and Fischer have attempted to establish.

In arsen-hydrogen jaundice of pigeons, in contradistinction to the relations in obstructive jaundice, one sees very early a marked iron storage by the Kupffer cells, while the liver cells as yet show no iron granules at all. Since in both cases there is very evident jaundice, one would expect the same picture if it were only a question of storage of the individual constituents taken from the blood; but just the *reverse* pictures are found. Just as in arsenhydrogen-poisoning jaundice, one can readily observe how the iron is split off *in loco* from the red blood corpuscles which have been taken up; this is all the more important as the erythrocytes disappear. As another difference, we may mention that in this case bile pigment becomes visible in the Kupffer cells, but not in obstructive jaundice. Hence, the pictures of the Kupffer cells seen in arsenhydrogen poisoning of pigeons cannot be referred to resorption of already elaborated substances from the blood.

Although these studies rendered probable the occurrence of bile-pigment formation in the blood apart from that of injured liver cells or other bile-thrombus formation, it might be further objected that precisely as in the morphologically apparently normal liver cells, in these pathological cases (early stages of toluylenediamine poisoning, ligation of the common duct) the bile instead of being secreted into the bile capillaries was shunted into the blood by so-called parapedesis. Although no morphologist has as yet been able to conceive of such a secretory process in a direction directly opposed to the normal one, this question must nevertheless be considered. This was possible by excluding the liver itself. Dr. Makino attempted this by ligation of the vessels following an Eck fistula, as well as by extirpation of the entire liver after a reversed Eck fistula. Though he was not able to keep his dogs alive as long as apparently the introducers of these methods and Bickel were, nevertheless the time was long enough to be able to follow the appearance of

sufficiently large quantities of bile pigment. This was particularly easy when, after exclusion or extirpation of the liver, the complete removal of which was in every case verified at the autopsy, hemoglobin was injected intravenously. But in order to have as few sources of error as possible the animals were also observed without injections of hemoglobin; in this case, also, after about three and a half hours there appeared an evident pigment content of the blood. Hence, Makino was able to confirm the statements of Bickel. It was conceivable that during the extirpation of the liver some bile was forced into the circulation. To this may be objected that in the careful exclusion of the liver by ligation the bile pigment appears in the blood in almost the same time after the operation. Therefore, it cannot be only the consequence of mechanical pressing of bile into the circulation. Yet, a final objection is conceivable—Retzlaff believes he has demonstrated that even physiologically a resorption of bile from the intestine takes place. By this he explains the physiological bilirubinemia. He points out that from twenty to sixty minutes after the introduction of magnesium sulphate into the duodenum there regularly occurs an increased blood bilirubin, but only that bilirubin which gives a delayed reaction, not that reacting promptly, is increased. It is quite conceivable that there is here only a transitory expulsion of fully prepared bilirubin from the spleen or some other point. If it were really a question of resorption of bile from the intestine, a lasting increase of the bilirubin content of the blood during digestion would be expected. But the observations of Meyer and Kupffer are in opposition to this view. Two to five hours after eating they find a well-marked decrease in bilirubin content. They explain this, probably correctly, by an increased secretion of the bilirubin physiologically formed by the liver. This conception of theirs furnishes a good explanation of hunger bilirubinemia. If no digestion occurs, the pressure in the bile passages rises slowly. The secretion of the liver takes place more slowly. The bilirubin which is physiologically formed outside of the liver cells increases in the blood. Just why in the condition of hunger where little bile enters the duodenum, especially much bile should be resorbed from

the intestine, as is required by the theory of Retzlaff, is not readily understood. Schiff's finding of jaundice with a delayed bilirubin reaction in the blood of sufferers from congenital stenosis of the bile ducts, also speaks against the assumption that all bile with delayed reaction occurring in the blood must be resorbed from the intestine. Retzlaff supports himself by two experiments on the dog, in which he saw bile pigment appear in the thoracic duct and the blood of the portal vein after the introduction of ox bile into the intestine of the dog. Dr. Makino performed these same experiments with repeatedly negative results. We have as yet been unable to explain this contradiction. It is striking that the bile pigment found by Retzlaff in the lymph of the thoracic duct gave only a delayed reaction. The prompt reaction must, therefore, have been changed into the delayed during the resorption of the bilirubin from the intestine. This is in so far remarkable as the resorption of bilirubin from the bile passages allows only promptly reacting bilirubin to pass. It must, then, be assumed that the slowly reacting bilirubin found in the blood after the ligation of the common duct, also comes from the bile passages. But this interpretation is not reliable, for the slowly reacting bile pigment also occurs in exactly the same way in the blood of animals whose liver has been removed. So that it may properly be assumed that only promptly reacting bilirubin is absorbed from the bile passages. But Retzlaff maintains, with a certain amount of justice, that in resorption through the intestinal wall other possibilities are offered than in resorption through the bile passages. Dr. Makino's experimental investigations show that if any change occurs during the introduction of promptly reacting bilirubin into the circulation, it cannot be demonstrated. But to exclude the possibility of this resorption from the intestine, the portal vein of a healthy animal was ligated and the thoracic duct opened. Then a hemoglobin solution was injected intravenously. In the same time as in the other dogs the slowly reacting bile pigment formed, regardless of whether these dogs were normal, or had had their liver excluded, or entirely extirpated. The recent findings of Rous on increased bile excretion through the liver after injection of bile into the intestine are not decisive

because the appearance of bile pigment in the blood of the portal vein or the peripheral blood was not controlled.

These experiments demonstrate, probably irrefutably, that in the blood of the *dog* bile pigment is formed independently of the liver and without participation of the bile pigment of the intestine, and indeed in so considerable a quantity as to explain the quantity of pigment daily excreted in the bile. Unfortunately the animals do not live long enough to determine this exactly. This should be experimentally determined, working as Grunenberg did in the artificial perfusion of the surviving liver with blood of various bilirubin contents.

The problem of the site of formation of the bile pigment may be attacked in another way. If the liver cells are the most important or indeed the sole source of bilirubin, then bile pigment must be formed in the blood at entirely different rates after hemoglobin injections, according to whether the liver is normally perfused by the portal vein, whether it is excluded by the help of the Eck fistula, or whether it is overloaded by the reversed Eck fistula. Whipple and Hooper were able to show that after injection of laked blood, dogs with the Eck fistula showed bilirubin in the urine quite as quickly as normally. Dr. Makino took up the experiments for the bile pigment of the blood under all three conditions mentioned above. It was found that bilirubin formation occurred at almost the same time. This also points to the fact that the essential site of formation of the bile pigment in the *dog* lies without the liver.

The experiments of Retzlaff who, despite phenylhydrazine poisoning, saw no true icterus occur in animals whose liver had been excluded, are to be explained by the brief time of the experiment. In those of his dogs with intact liver and spleen, the bilirubin appeared at the earliest after forty-eight hours, and ordinarily appeared only several days after the poisoning. Although much larger doses were also given and indeed intramuscularly, still in considering the delayed resorption it must be remembered that the dogs were weakened by an exhausting operation. The time until death amounted to sixteen, seventeen and twenty hours. In the last case there occurred a weak reaction which, however, the

author explains by inadequate ligation of the portal vein.

Very recently, Rich has published experiments which cast grave doubt on the conclusions drawn by Whipple and Hooper from their experiments, quite apart from the fact that the reliability of their method of demonstrating bilirubin has been strongly called into question by Retzlaff. Rich excluded all the abdominal viscera, including the liver, by ligation and resection, and then found no bile-pigment formation in the blood. He also believes that even physiologically the liver has so many vascular anastomoses with the neighboring tissues that India ink intravenously injected reached the liver after its apparent exclusion according to the method of Whipple and Hooper. But according to the experiments of Dr. Makino the quantity of pigment going into the liver in this manner is relatively small. However, these vascular anastomoses might suffice to explain the bile-pigment formation in the experiments of Whipple and Hooper. We should emphasize that in our opinion the endothelial cells of the pulmonary vessels do not participate in the formation of bile pigment. Therefore, the experiments of Rich are not to be applied against the theory of the participation of the reticulo-endothelial system in the formation of bile pigment, because in his experiment the entire reticulo-endothelial apparatus of the abdominal cavity is excluded from the circulation. There was, therefore, not enough of the active agent, be it cellular or fermentative, to permit the appearance of bile pigment during the time in question. In his experiments, the dogs lived an average of half an hour. Only one dog remained alive for one hour and ten minutes, and the last dog, two hours and thirty minutes. Only in the last animal is a formation of bilirubin to be expected according to the investigations of Dr. Makino, and indeed only if the entire abdominal viscera with the exception of the liver are in a position to form bile pigment. Hence, the experiments of Rich are not decisive in this question.

Since we are thus forced to the assumption that an anhepatocellular formation of bile pigment is even physiologically present in the dog, it appears remarkable that we never find bile pigment in the blood of healthy dogs. The explanation

must be that the bile pigment threshold of the blood above which it is excreted through the liver, is so low that the method of Hijmanns van den Bergh does not show any reaction. Only when this level is surpassed does the reaction occur.

The problem of icterus is most intimately connected with that of the formation of bile pigment. The first traces of icterus are not to be tested for in the urine but in the blood (Hijmanns van den Bergh). Why in individual cases the accumulation of pigment in the blood becomes so great that a coloration of the tissues occurs, how far this is supported by the liver, how the two different varieties of bilirubin differ in their ability to stain the tissue, why in certain forms of jaundice bilirubin crystals occur in the tissues but never in others—these are all questions which must be answered in the future. But I should like to maintain now that the principle "without the liver cells no jaundice" will prove to be as untenable as the principle "without the liver cells no formation of bile pigment." In the present article I am only dealing with the latter question. All my explanations would, to be sure, lose their value if it should be demonstrated that other bodies aside from bilirubin give the reaction of Hijmanns van den Bergh in the blood serum. This is, however, very improbable because the appearance of the reaction in normal animals after the injection of hemoglobin plainly points to the formation of bile pigment. However, in animals in which the liver had been excluded or extirpated, the reaction appeared in a time interval quite similar to that of normal animals. This speaks very much for the fact that we are dealing with one and the same substance, that is to say, bile pigment.

To *summarize* all that is as yet known about the formation of bile pigment, in so far as the experiments on dogs are concerned, I may say the following:

In agreement with Whipple and Hooper, an anhepatic formation of bile pigment can be demonstrated. In animals deprived of their liver by the method of Mann and Magath there occurred regularly and within a definite time after intravenous injection of hemoglobin, a formation of bile pigment in the blood plasma. Also, without injection of hemoglobin, bile pigment is formed if the animal survives

the operation long enough. This formation of bile pigment in the blood could not be attributed to a resorption from the intestine, for it occurred after hemoglobin injection in the same time interval in animals in which the hepatic circulation was intact as in such in which all resorption from the intestine was excluded by tying off the portal vein and opening the thoracic duct. This bile pigment formed anhepatically in the blood occurs in such large quantities that the natural daily quantity of bile pigment excreted with the bile would be assured if the animal lived long enough.

Morphological investigations which show the first changes in toxic icterus to involve the reticulo-endothelial elements while the liver cells are still entirely unaltered, confirm the opinion that the reticulo-endothelial apparatus, i.e., the splenic tissue without and within the liver, and not the liver cells, plays an important rôle in the formation of bile pigment. Only in the further course of the toxic formation of bile pigment do changes in the liver cells occur, appearing in the form of bile cylinders. They are to be looked upon as pure stasis cylinders resulting from the tenacity of the bile. The change in the delayed bilirubin reaction of van den Bergh into the prompt reaction seems to be connected with their appearance.

If to these studies on the dog be added the observation on the goose, in which one can directly follow the decomposition of the injured red cells which have been taken up by the Kupffer cells into microchemically demonstrable iron and bile pigment, and indeed at a time when the liver cells show practically no changes, the totality of these observations permits the conclusion that not only an *anhepatic* but also an *anhepatocellular* formation of bile pigment occurs in the mammal as well as in the bird. In contradistinction to this, not the slightest proof has as yet been brought for an hepatocellular formation of bile pigment.

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XI

THROMBOSIS

In discussing the subject of thrombosis, permit me to emphasize that we are dealing exclusively with the problem of spontaneous thrombosis. This, as you know, because it leads to fatal emboli of the pulmonary artery, represents a most serious complication in surgical and gynecological operations as well as in a wide range of medical conditions. I shall therefore omit the question of traumatic thrombosis (thrombosis consequent upon ligation of vessels); the so-called capillary thrombosis, which evokes an entirely different clinical picture and which is of special interest in blood transfusion; toxic thromboses (due to salvarsan and mercury poisoning); the endogenous toxic thromboses in eclampsia; and confine myself to the field of so-called static thromboses of the large veins.

The more we try to obviate the dangerous complication of embolism, the more urgent is our obligation to find out the cause of thrombosis. Now, there is no doubt at all, to use a mathematical figure of speech, that thrombosis is the function of a number of variables. There is not a *single* cause, but quite a number of different conditions which are closely related to the occurrence of thrombosis. Among these may be mentioned here, first, changes in the blood-plasma (diminished or increased coagulability); secondly, changes in the blood elements (increased or diminished powers of agglutination); thirdly, changes in the blood flow (slowing and formation of eddies); and lastly, changes in the vessel wall itself (endothelial damage). An inquiry into the mechanism of thrombosis shows that sometimes one factor, sometimes another, plays the principal rôle.

The view that increased coagulability of the blood is an essential point for the production of thrombosis, has been

strongly upheld, especially by clinical observers. The existence of this increased coagulability, and the likelihood that it is a promoting factor, or, better, an accompanying phenomenon of thrombosis, cannot be denied. But all histological research since the early work of Zahn, Eberth and Schimmelbusch, Welch and others, speaks for the view that in human beings the occurrence of fibrin coagulation is not the first stage of thrombosis, but that important changes in the morphological blood constituents precede it. These last-named changes must be explained before the mechanism of thrombosis can be understood.

It is concerning the morphological structure of a thrombus, in continuation and amplification of my earlier review,[1] that I wish to write.

MORPHOLOGICAL STRUCTURE OF THROMBI

Since we have known from the work of Zahn, on the one hand, and of Eberth and Schimmelbusch on the other, that the blood-platelets and leucocytes really have to do with the building of a thrombus, the idea readily suggested itself that the whiter color of one part of a thrombus was to be referred to an accumulation of these elements, which would thus appear to constitute the first material laid down in the process. We have become accustomed to speak of white, mixed and red thrombi, but the relationship of these different appearances to one another, in spite of the early work of Zahn and others, has not been wholly and correctly appreciated in the literature of the subject. We must remember with Welch —to whom we must give thanks, as well as to the previously mentioned authors, for the most exhaustive experimental work on thrombosis—that in a completely finished thrombus, for example in the femoral vein, the variations in the colors are perfectly regular. The first part (Kopfteil) of the thrombus is chiefly of a white color, and represents the so-called white thrombus, and on this a middle part (Halsteil), mixed in color, and a deep red distal and final portion (Schwanzteil) are subsequently laid down. The first part (Kopfteil) may be of the smallest possible size and extent; whereas the final red part (Schwanzteil) often forms the bulk of the thrombus

[1] Cartwright Lecture, 1913. (See p. 340.)

and may measure many centimeters. Thrombi in other parts of the venous system are built up on exactly the same principle.

It is easy to understand that red thrombi occur only where a white thrombus has more or less completely obstructed a vessel, and that they cannot occur where the white thrombus only partially obstructs the lumen. Very long white thrombi can arise only when the blood-stream continues to pass through a vessel. From all these points a rule can be formulated which holds for the majority of all autochthonous thrombi in human beings; namely, that the white thrombus is the determining and peculiar factor in the whole process, and that red thrombi are only, so to say, accidental—they may occur, but not necessarily.

Our interest, then, centers on the question of what this "Kopfteil," or first part of a thrombus, looks like under the microscope. The structure of it will perhaps give us an understanding of its mode of origin.

First of all, we must remember that the much-quoted Zahn's markings on the outer surface of thrombi, the small ripple-like, net-like and linear markings, are only to be seen on the "Kopf" and "Halsteil" of thrombi, whereas in the red part of the thrombus they fade and soon totally disappear. These markings are merely fine, white elevated lines or ridges which are specially well brought out when the furrows between are reddish in color, or where a mixed red and white thrombus, as in the "Halsteil," is present. Along with the explanation of this marking stands or falls the whole problem of thrombus formation, so far as consideration of the majority of cases of autochthonous thrombosis goes. This decision appears at first sight a bold one, but will readily be understood when the microscopic structure has been taken into account. A longitudinal section through the "Kopf" and "Halsteil" of a thrombus shows that the very delicate surface elevation is only the summit of a framework of beams, which in delicate rings like a mass of coral, forms the skeleton of the whole thrombus. When a thrombus at quite an early stage in its development is examined, this framework is seen to be a finely granular mass which consists simply of an accumulation of blood-platelets. All the beams

of this framework are surrounded by a border of polymorphonuclear leucocytes, by means of which they are differentiated even more sharply from the red blood-mass which fills up the numerous spaces between them.

But it is not only the regular and definite separation of the different blood elements which is surprising, but the further fact that all the beams of the framework stand in a very special relationship to one another. The beams follow one another at fairly regular intervals and build up group-like systems, inside of which the direction of the beams is much the same. In addition, however, secondary beams are seen in these groups extending either upward or downward from the primary beam of the framework. It must be admitted that dissimilarities also occur here. The more we approach the pointed outer extremity of the "Kopfteil" the broader become the beams of the framework, the furrows between disappear, until finally the beams unite into a single mass, to form the pure white outer surface of the "Kopfteil."

The most important point, however, in the structure of this whole system is that fibrin practically does not appear. When it is found, however, the strictest regularity governs its situation. The threads of fibrin shoot out first of all along the borders of the framework of blood-platelets just where the red blood touches the framework. Subsequently it penetrates more and more into the blood itself. A structure such as has just been described is the only sure token by which we can recognize microscopically the intra vitam origin of a thrombus.

With this explanation of this structure, we are enabled at the same time to understand the way in which a thrombus is built up. The explanation involves the solution of a complicated physical problem, which I can present here only in a general way, since, in spite of many discussions with my colleagues in the department of physics, I have been unable to get to the bottom of it. What the vital question is, we can state nowadays with certainty. This question is: Does the thrombus arise in the flowing or in the stationary blood stream? So long as the view was held that white thrombi were built up from leucocytes, as Zahn pointed out, it had to be assumed that it was only in the flowing blood that these

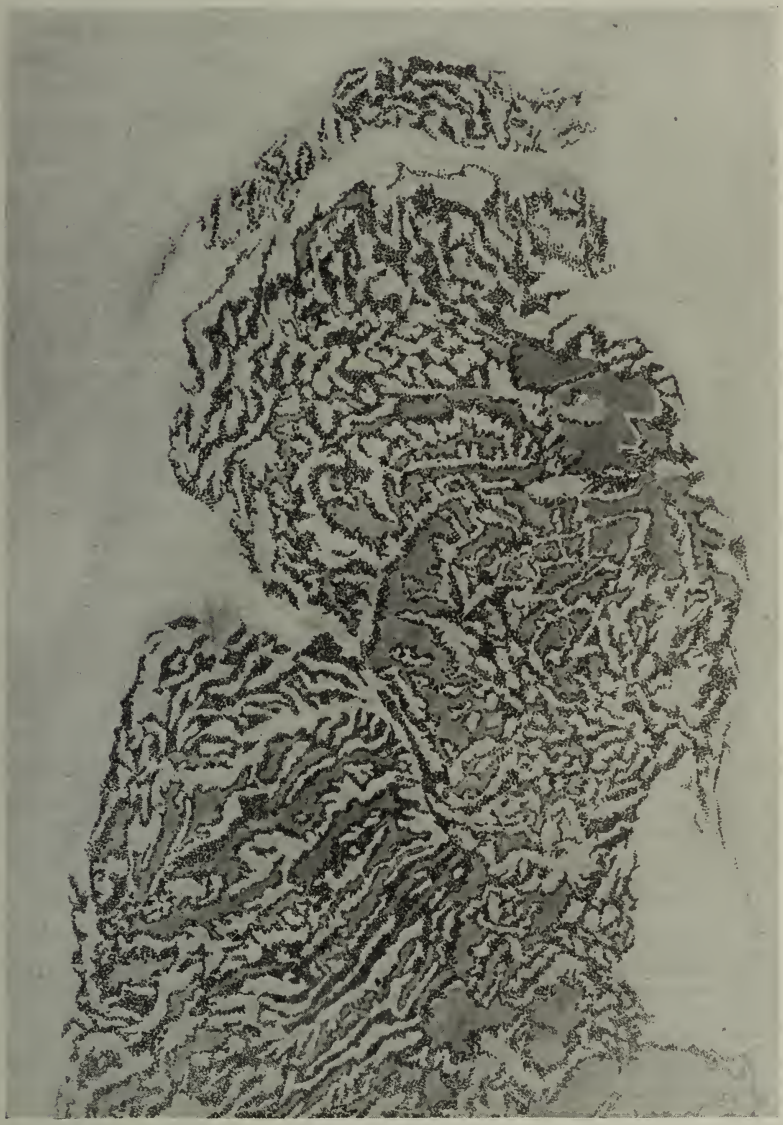

FIG. 21. Structure of a thrombus.

thrombotic masses could be laid down. Zahn himself laid great stress on this point. But when it became practically certain that a thrombus takes origin exclusively from blood-platelets, uncertainty again arose, since the origin and meaning of these platelets was veiled in obscurity. While some observers affirmed the independence of these structures, many more considered them to be merely disintegration products of white and especially of red corpuscles. If the latter theory were true, a thrombus could quite well be considered to be formed from a small mass of dead and disintegrated red blood cells, which had died because of the stopping of the blood stream. But it could not explain why the heap of particles at once proceed to build themselves up into such a beautiful framework and divide themselves off so sharply from the red corpuscles.

Taking it for granted that the origin of blood-platelets is not from leucocytes or erythrocytes, but that they are independent elements existing by themselves in the blood streams (as indeed the excellent researches of Deetjen have already suggested), it becomes quite clear to us that such accumulations of blood-platelets as occur in a thrombus can be deposited only when the blood is circulating. The important question of the blood-platelets can, in my opinion, now be regarded as settled. They take origin neither from white nor red corpuscles, but are, for so long as they circulate in the blood, independent structures. J. H. Wright of Boston was the first to point out their origin from the giant cells of the bone-marrow and spleen. This fact has now been repeatedly confirmed by the numerous investigations of various hematologists of all lands, so that the ever-recurring question whether other elements also participate in the production of blood-platelets, appears to be unjustified.

We have concluded then, that the thrombus arising from the blood-platelets has its origin in the circulating blood stream, and the question yet to be answered is: Why do the platelets build themselves into this peculiar framework? To this important question I can give no final answer. A few interesting points only may be raised. By making serial sections of human thrombi, and subsequently building up models, Ferge, working in the Pathological Institute in

Freiburg, was able to determine with certainty that the platelets do not form beams running in circles, but do form a system of lamellae, more or less parallel and arranged on the vessel wall one behind another. Most of them run obliquely or transversely to the long axis of the vessel. These lamellae grow outward from the vessel wall, and from the flow of the blood through a part of them, they become bent in the direction the blood is flowing. The appearance of this system is strikingly similar to the beautiful figures made on the fine sand of the seashore by the ebbing tide. The water pushes up the fine sand into ridges, until the strength of the flow overcomes the small obstacle, and the water travels on to build new ones further on. In this way then, the beautiful series of ripple lines are drawn on the shore. The blood stream builds up its lamellar system in an exactly similar way from the sand-like multitudes of blood-platelets. Zahn had previously taken notice of the work of de Candolle on the curious sand formations produced by moving water, and had put forward the suggestion that the lines visible on the surface of the thrombus are simply the effect of to-and-fro movements of waves of blood. But the essence of the matter is not that already existing sandy masses are shaped into systems by the movements of the blood, but that solid elements are taken from the flowing blood stream and laid down in the form of specially situated lamellae. I can only mention here in passing that by experiments which I carried out in the laboratory of Professor Rehbock, I was able to find exactly similar deposits formed in running water from a given solid material, when the velocity of the flow was reduced sufficiently by the introduction of a dam or weir. No transformation of already laid down masses of particles was necesssary to make the ridges, but the particles were laid down in such a way from the first. The question, of course, arises from these experiments as to why a deposit of platelets occurs at all, and this will be discussed later on. So long as the blood flows through this framework just as sea water flows beneath branches of a tree of coral, new masses of blood-platelets are laid down on the system already formed, and so new systems are always being built up behind the first one. The first-formed

system naturally grows faster, and finally there comes a time when the openings in the lamellae of the old part of the thrombus (this is indeed the "Kopfteil" which has already frequently been referred to) are so narrowed that the blood stream becomes slower and slower, and finally stops altogether. With this event the building of a primary thrombus is finished, since once the blood stream is at a standstill no new blood-platelets can be carried past, and hence further growth is impossible.

But before the complete cessation of the blood stream occurs, a certain peculiar separation of the red and white corpuscles comes to pass, resulting in the whole system of platelets becoming covered with a layer of leucocytes. The facts of this peculiar separation are best explained by the well-known researches of Eberth and Schimmelbusch, who found that when the blood stream was slowed the white corpuscles, being of lighter specific gravity than the others, tended to travel at the margin of the blood stream, and so were found closely in contact with the vessel wall. By the growing system of platelets which occurs in the formation of a thrombus the main blood stream is divided up into a series of small streamlets. Each small streamlet is, however, subject to the same laws as a larger vessel, and when the slowing of the blood stream occurs, the leucocytes are found close to the sides of each small streamlet, whose wall is in this case composed of the framework of blood-platelets.

Before I can turn to the question of why the blood-platelets are deposited from the circulating blood, I must briefly describe the results which follow in the peripheral part of the vessel, when the stream is completely interrupted through the gradually increasing obstruction of a system of platelets. As soon as the lumen is closed in the region of the white, that is, the primary, thrombus, the whole blood column becomes stationary right up to the place where the next anastomosing vessels enter, and undergoes very rapidly, as experiment shows, a complete coagulation. In this "Schwanzteil" of a thrombus, which is usually of some length and like the rest in color, we can expect, it goes without saying, no definite framework of platelets; and in fact it is either completely absent or occurs only partially. This red

thrombus resembles in its microscopic structure essentially a post-mortem clot, and consists of an irregularly arranged mass of red and white corpuscles, blood-platelets and fibrin. It must be admitted that here the leucocytes and blood-platelets have a tendency to form themselves into masses, but there is no attempt at the formation of lamellae. The fibrin frequently shows striped thickenings running in definite directions. These may be the results of currents in the plasma, for although the column of blood has been checked it is still connected in manometer-like fashion with the rest of the vascular system. They may also merely be the expression of the movements of the fluids induced by the coagulation.]

Thus an essential difference exists between the "Kopfteil" and "Schwanzteil" of the thrombus, which it must be said are connected together by a more or less transitional zone. This difference we know must depend on the fact that the "Kopfteil" is formed in flowing blood, the "Schwanzteil" in blood at a standstill. This brings up the question then of *why a white thrombus is built up from platelets in the flowing stream and a red thrombus when the blood flow has ceased.*

MECHANICS OF THROMBUS FORMATION

After the corpuscular nature of white thrombi was recognized by Zahn, von Recklinghausen directed attention to the important bearing which the slowing of, or rather the formation of, eddies in the blood stream, had on this question. His work has given considerable support to the well-known teaching of Virchow regarding the mechanical genesis of thrombi. When we compare the blood stream with a river which has countless small particles of different specific gravity swimming about in its waters, we are driven to the conclusion that there must be some optimum velocity which will bring about a local aggregation of particles, such as we have seen by the microscope to occur in the building of thrombi. Neither by a rapidly flowing stream nor by complete stoppage of the current can such a heaping-up be brought about. Thus the blood must flow slowly, or, to put it in a better way, must flow differently, from the way it did before. It is noteworthy that deposits of sand in a river occur by

preference where a widening or a deepening of the river bed exists. It is not a uniform slowing, but the inequality of the local conditions which predisposes to this extraordinary deposit. The insertion of a dam or barrier, by introducing counter currents and eddies, is also an important predisposing cause. I have made an effort to explain this building of sand banks on purely physical lines, and in this I have had the assistance of Prof. Dr. Rehbock in whose laboratory the experiments were carried out. If a weir is introduced into a stream of fluid, then by the interference with the current so induced an unusually long "Walze" (or helix), as it is called technically, is produced in which a portion of the fluid flows backward. And not only that, but fine particles suspended in the water (we used sawdust for the purpose) are deposited in ripple and net-like elevations in the regions of this "Walze." By means of obliquely placed weirs two "Walzen" can be produced, the one proximal, the other distal to the obstruction. It is at the point of contact of the two that thrombi arise, and, as Ferge also found, the thrombus is not built close under the valves of the veins.

Finally the question of sand-bank building by the flowing together of two unequal streams must be considered from the physical standpoint. When we study what occurs in a pipe when this state of affairs is brought about, it will be found that a slowing of the stream in the so-called zone of transition occurs. If the stream from the smaller vessel flows very slowly, a sand-bank is formed at its mouth. This agrees very well with what is found in human pathology.

All these experiments are, on account of the number of factors outside our control, merely suggestive. We can take no account of the part played by the living blood and the living vessel wall. We can only prove the gross results and ask what alterations of the blood stream, in the form of sudden slowing, backward-flowing and eddy-making, are found in the places where in the human subject autochthonous thrombi have a tendency to grow.

LOCAL CONDITIONS FAVORING THROMBOSIS

The special tendency to slowing of the blood-stream is quite properly insisted on by every one who has written on

the subject. It is quite clear that some very special and unusual condition must be present in the arterial system to slow the blood long enough to allow a deposit of blood-platelets to occur. As Virchow pointed out long ago, and as is now generally recognized, there are certain situations in the venous systems which are especially predisposed to thrombus formation. Among these, the veins of the leg, the proximal part of the femoral vein where the large valves are present, the pelvic plexus, the venous network of the dura mater and the auricles, may be taken as examples. There are besides, four conditions, each of which, alone or in combination, has to do with the localization of thrombosis. First, there is continued overpressure on the wall of a vein, such as occurs in the veins of the leg from the pressure of the column of blood when the body is upright, or such as is brought about in the venous plexus of the pelvis by downward pressure of the intestines. This overpressure tends to physiological widening, and, finally, may terminate in a physiological thrombosis. I refer to thrombus formation in varicose veins in the lower limbs and to the thrombosis in the prostatic plexus in old age which is so usual as to be practically physiological. Thrombus building in the vaginal plexus, which may be the origin of a spreading thrombosis or be a nidus of secondary infection, has not been given sufficient attention.

A second condition is the widening which obtains in the auricles and also occurs in the veins at each valvular sinus. Ferge's recent experiments have confirmed the work of Kölliker and Epstein, who discovered that the musculature of the vein wall can be practically absent in the region of the valvular sinuses, so that backward pressure must be followed by an ampulla-like widening above the valve. Further, the possibility of a backward pulsation in the veins, the so-called venous pulse, which often is most marked at the proximal end of the femoral vein, must not be lost sight of. Lastly, when the body is lying prone, certain local conditions affect directly certain veins with a known tendency to thrombosis. For example, the femoral vein just where the large valves are present, lies close under Poupart's ligament, and the importance of the bend so brought about must not be underestimated. The iliac vein, shortly after the

junction of the hypogastric vein, also comes into the same category, and its tendency to thrombosis is also to be referred to the bend in the path in which the blood flows.

Naturally, these local factors play an even greater part when any defect in the heart's action leads to a general slowing in the venous system. In such a case the posture of the patient exerts a further and additional influence. In certain conditions the posture has directly to do with the left- or right-sided position of the thrombus, the limb which lies lower having a greater tendency to become thrombosed. When lying on the back the increased compression of the left iliac vein by the arterial trunks (right iliac, middle sacral and left hypogastric arteries) has a direct influence in slowing the stream, and explains the well-known frequency of thrombosis in the left lower limb. Another point, too, is of interest. When a double-sided thrombosis of the veins of the lower limbs occurs, the following characteristic conditions can often be found. The thrombosis on the right side extends up to Poupart's ligament, whereas on the left side it extends up to the point of compression of the left iliac vein by the right iliac artery.

The deposition of blood-platelets in all the above-mentioned examples of thrombosis is easily understood. It is not the stagnation but the retardation which brings about the thrombosis, and must be reckoned as the direct cause of the deposition. Eberth and Schimmelbusch have given to this type the name of conglutination thrombosis. They took this descriptive name from a phenomenon which occurs in the heaped-up mass of platelets, namely, the cementing of the platelets together. This phenomenon can also quite truly be called agglutination, so the term agglutination thrombosis is also a suitable one.

Between accumulation of platelets on the one hand and conglutination or agglutination on the other there exist very special relationships.

We do not know as yet anything of the phenomena which precede agglutination and which are the very earliest factors in thrombosis. We cannot say whether they are of a type long known to workers in bacteriology or serology, or whether they are chemicophysical. We suppose at least that a special

degree of viscosity must be present to allow the masses of platelets to form so easily, whereas precipitation phenomena in the sense of agglutination can also play a rôle. It is also quite conceivable that a mass of platelets, once it is formed, can exert an influence on other platelets flowing past it. The agglutinability of the platelets depends, of course, on the chemicophysical characters of the fluid in which they are suspended—in this case, the blood-plasma.

Thus we see that alteration in the blood stream is only one condition in the making of a thrombosis, the second condition being dependent on the agglutinability of the platelets themselves. Unfortunately, we have no knowledge of spontaneous changes occurring in this property of agglutinability. This question, chiefly from the experimental side, is considered by Achard and Aynaud.

It is evident that the number of the platelets is an important matter to be considered in relation to thrombosis. Judging from the literature it seems clear that the number of platelets—their exact enumeration is no light matter—undergoes great variations in cachectic states. We know too, that after experimental anemia the number of blood-platelets increases rapidly, coincident, as has been shown by Ogata, with increase in the number of giant cells in the marrow. It is, therefore, quite feasible to suppose that subsequent to loss of blood at operations or during parturition, an increased tendency to thrombosis can be brought about, although it cannot at all be said that an increase in the number of platelets can by itself alone bring on thrombosis.

VASCULAR CHANGES AS INFLUENCING THROMBOSIS

We have up to this point considered two of the conditions which have to do with the building of thrombi, namely, changes in the blood stream, and qualitative and quantitative alterations in the platelets. We will now take up a third condition, which used to play the chief rôle in the teaching about thrombosis, but the significance of which was soon greatly limited by Virchow. I refer to alteration of the vessel wall itself. That this is not the decisive, not to say the only cause of thrombosis of the ordinary type, is made very clear when we can think of an atherosclerotic aorta, which in

spite of the most marked changes can remain quite free from thrombi. Here, of course, there is no slowing of the blood stream. On the other hand, the question arises whether the slowing of the stream can alone, without any accompanying change in the vessel wall, give rise to a thrombosis by deposition. Do the deposited platelets remain bound together only when the endothelium is damaged? Is this damage of the endothelium a third condition which must be fulfilled before thrombosis by deposition can arise, and how must the endothelium be damaged? Covering this point of endothelial damage, the importance of which is always accepted without question, and which is always given great prominence in the literature, we know in reality practically nothing. We can affirm only one thing, namely, that chronic changes of slight degree in the intimal lining of a vein, as for example, fatty changes of the endothelium, can by themselves play no important rôle, since one must so often assume this change to be present without thrombosis resulting. Besides, it is very difficult to understand how a fatty change merely of the endothelium can lead to a deposition of blood-platelets. I can find in the literature no well-authenticated cases in which thrombosis has really been brought about by changes in the endothelium, a factor which is regarded by many authors as of special importance. It is naturally quite another story when rigidity of the wall and valves of the vein, brought about by severe and progressive phlebosclerosis, has interfered with the blood flow. Changes in the wall of the vein are then not the direct, but only an indirect, source of thrombus formation. An analogous state is brought about in the numerous experiments carried out to induce thrombosis by means of corrosives, cutting and the introduction of threads or other foreign elements. These experiments were carried out at an early date by Zahn, Eberth and Schimmelbusch, Welch, and more recently by Zurhellen in the institute in Freiburg. Here the rough and mechanical disturbances of the blood stream resulting from the laceration of the vessel wall do not play the entire rôle, but the plasmatic exchanges between the fluids of the blood and the lining of the vessel must also be important. When instead of slow retrogressive changes, the intima is suddenly stripped of its endothelial

lining, then a reaction inevitably ensues, as occurs in all living tissues, accompanied by a pathological flow of lymph. Then it is, indeed, the alterations in the blood stream in the region of the injured area which bring about a thrombosis by deposition. It is not made clear by the previous experiments how and whether a direct influence on the blood-platelets as they flow by can possibly be exerted by agencies of an agglutinative or coagulative nature produced by the tissues (L. Loeb, Achard, Aynaud). Nor is it explained whether the connective tissues or the muscle laid bare by the damage at a surface capable of absorption (Morawitz) can bring about the adhesion of the platelets. At any rate, all these artificially produced thrombi present the characteristic structure of thrombi by deposition of the blood-platelets. We must allow that up to the present we have not been well enough informed concerning the first and absolute beginnings of thrombus formation in the case of autochthonous thrombi in the human subject. Unfortunately, in this connection we can hardly ever obtain fresh enough material, since, of course, we must eliminate all post-mortem coagulation, which naturally can occur in the thrombus itself.

We must endeavor to get a clear idea of why the adhesion of the platelets to the vessel wall occurs in autochthonous thrombosis, since we assume that this deposition of platelets is the first procedure. It may be quite possible that the endothelium dies as a consequence of being covered over by the platelets. Fibrin is in this way set free and cements the masses of platelets to the wall. Or the platelets, after lying on the wall for some time, may themselves die, and then coagulation on and between the endothelial cells can ensue. At any rate, it is necessary that an interaction of a certain duration occur between the platelets and the endothelium in order that the material may remain stationary and, so to say, be fixed there. If slowing of the blood stream and alteration in the conditions of the platelets are to figure as the direct facts in the thrombus formation, then we must consider as indirect factors changes in the wall, alterations in the cardiac action and loss of blood during operations.

In considering the vital question as to why a white thrombus occurs in the circulating blood, and a red thrombus

only when the stream is stationary, I have already attempted to answer the first part and shall now proceed to the second. I have already mentioned that a red thrombus arises only when the lumen of the vessel is sufficiently closed by a white thrombus to bring the blood stream to a standstill in the peripheral portion of the vein. This stationary column of blood coagulates. But under the microscope this red thrombus, dense in the neighborhood of the "Kopfteil," while peripherally becoming more and more spongy, and, finally, almost fluid in consistence, can scarcely be differentiated from post-mortem clotting. The microscope shows, however, that the denser portion is richer in fibrin and leucocytes and suggestions of lamellae can here and there be recognized. As we travel more to the periphery the structure of the thrombotic mass more and more approaches that of the normal blood. Microscopically, it is also true that the boundary between the white and the red portions is as hard to recognize as that between the slowing and final complete stoppage of the blood stream. From these points we can also explain why this column of stagnating blood does go on to coagulation, in contradiction to the well-known findings of Baumgarten, who observed that the column of blood contained in a doubly ligated portion of a vessel did not coagulate. We must take into consideration that, as has been already mentioned, coagulation phenomena can also be observed to have taken place in the blood found occupying the gaps in the white portion of a thrombus. These phenomena very probably must be referred back, judging from the characteristic situation of the fibrin network, to an interaction between the fibrin ferment set free by the death of the platelets and the stationary blood-plasma round about them.

Of course, the amount of fibrin ferment set free in the white "Kopfteil" will be very considerable. It can advance by diffusion into the caudal red portion of the stagnating blood column. We know, as Baumgarten has stated, that the cause of the blood remaining fluid in a doubly ligated segment is that the blood dies relatively slowly. Conversely, we can presuppose a very rapid death to occur in a structure rich in ferment, as the blood-platelets are, and so the clotting of a column of blood in stagnation becomes intelligible. I

will not consider here the processes which precede clotting, and above all I cannot discuss the question of where the forces which bring about clotting have their origin. Nor can I stop to inquire whether the source of thrombokinase is to be sought for only in the thrombocytes and leucocytes, or in the erythrocytes as well. I would prefer to refer to you the well-known and very clearly expressed papers of Morawitz.

I pass over here the finer morphology of the processes preceding clotting, and would only mention that the "centers of coagulation," so-called, are to be regarded in my opinion as acting both chemically and physically. In the origin of the red thrombus we are also dealing, not with the separation of the formed elements of the blood, which practically does not occur, but more especially with crystallization of fibrin as in ordinary clotting. Thus we have a coagulation of the blood as a whole, and not merely the deposition of some parts of it. This view has already been suggested by previous authors, who have put forward the name coagulation thrombosis, in contradistinction to conglutinaton and agglutination thrombosis.

Just as in deposition thrombosis the slowing of the blood stream and the relations of the platelets as to number and viscosity are the essentials, so in clotting en masse the stoppage of the stream and the increase of fibrin ferment are the important factors. It cannot be denied that an intimate relationship exists between the heaping-up of platelets, the agglutination and the clotting, i.e., the coagulation. One must conclude that agglutination is, so to speak, only a means of creating in the circulating blood conditions which are necessary to allow the crystallizing out of fibrin, a process which cannot occur in the circulating blood under ordinary conditions.

But it is quite evident that these two phenomena (agglutination and crystallizing out of fibrin) do not mean the same thing and must be kept genetically apart, since each can occur without the other. In the case of ordinary autochthonous thrombosis with which we have been dealing until now, the deposition and coagulation processes are closely related. The process of deposition brings about the coagula-

tion, and is, so to speak, the indirect source of it. Then the further question arises as to whether coagulation thrombosis can occur apart from the process of deposition, and what may be the indirect causes influencing them both. It is important in this connection to remember that while thrombosis by deposition can be brought about readily at any time, a primary coagulation thrombosis is very difficult to induce. The stoppage of the blood stream alone does not suffice, as Baumgarten's experiments have shown, for the ferment does not develop quickly enough. Also optimal relations must be established between the rate of stream and amount of ferment present, to initiate the process of clotting. Even the flowing blood, however, can be made to clot, if a large quantity of ferment is introduced all at once, either by the injection of pure fibrin ferment or by artificial transfusion. Of course, control by the microscope is essential in such experiments to ascertain whether the solidification of the blood depends really on clotting of fibrin, and is not merely a precipitation, such as occurs when a substance which coagulates albumin is introduced.

To the question of these precipitation thromboses and other related processes, I will return later.

LIGATURE AND INFECTION

Two other processes must be mentioned here which undoubtedly have relationships with coagulation thrombosis. I refer to *ligature* and *infection*. Since, as we shall see, both of these can also induce thrombosis by deposition, we can now inquire how ligature and infection, respectively, act, and what is their significance from the point of view of thrombosis.

The facts in the case of ligature are comparatively simple. If done carefully, so that considerable damage to the intima is avoided, and the portion included by the ligature is so small as not to interfere with the movement of the blood, no clotting need necessarily occur, a fact which we have noticed elsewhere in connection with transplantation of blood-vessels. At other times we find thrombus formation, often quite scantily, however, in the region of the intimal damage,

where the fibrin ferment arising from the injured wall can act on the stationary blood in its neighborhood. Or at the margin of the ligatured part of the vessel a true deposition thrombosis may arise as a result of local eddy formation. In this way the area may finally be separated completely from the blood stream, and the column of blood thus shut off passes into a condition of coagulation thrombosis, like the "Schwanzteil" of an autochthonous thrombus.

In the discussion of spontaneous thrombosis I have thus far omitted from consideration the question of infection. It is well known to you that, for the origin of thrombosis, infection has been considered as playing an important rôle, especially on the clinical side. If, however, you wish to settle this question correctly, you must distinguish between two types of thrombi: namely, that form of thrombosis which arises within the inflammatory area or adjacent to it, and that which occurs at some distance from it. I select as examples the well-known thromboses which may occur as a result of a gynecological or obstetrical operation, or the spontaneous thrombi in connection with septic infections of the uterus. Here we not infrequently see that the branches of the hypogastric veins which drain the infected operative field are filled with thrombotic masses. These thrombi present varied appearances. At times they are white, at others red, and then again of a mixture of colors. Very often they show definite purulent softening. In short they behave exactly as the thrombotic processes of the uterine veins in puerperal sepsis. There is no question that in these spontaneous, just as in the local postoperative septic thrombi, infection plays a great part, and as a matter of fact, is a deciding factor in the progress of the thrombosis. We may therefore, in all justice, assign to infection the most important etiological rôle in this connection. No clinician and no pathologist will dispute this.

It is more difficult, however, to explain the infectious thrombi, individually. In many instances after forcible removal of the placenta, or after operative interference in the pelvic organs, there arise in the torn or ligated vessels numerous small thrombi (due to blood stasis, or ligation) which have been secondarily infected through the invasion

of microorganisms from the placental or operative area. These multiply in the small thrombus and call forth very severe irritation phenomena in the vessel wall. This irritation is followed by the occurrence of a progressive thrombosis by deposition. Concomitant with the increase in the growth of the bacteria and the simultaneous involvement of new sections of the vascular system, the thrombus grows larger and larger. Thus arises the picture of progressive thrombophlebitis with the familiar purulent softening of the thrombotic masses, and the serious sequelae, that of pyemia.

But even under the most favorable operative conditions, where the ligation of vessels is followed by practically no thrombosis, subsequent infection of the tissue about the vessel wall may occur from without, with the possibility of the formation of thrombi by deposition. Then we have a primary phlebitis and a secondary thrombosis, that is to say a phlebitic thrombosis which in its further development and in its microscopic appearance it is impossible to differentiate from a thrombophlebitis.

In contrast to the certainty of the occurrence of such local thrombi stands the uncertainty of deciding the question of how many of the postoperative local thrombi are to be considered as actually arising on an infective basis, and how many as a result of purely mechanical causes. The postoperative infectious thrombi, especially those occurring after gynecological operations, have been especially stressed for the reason that these were looked upon as the chief source of the fatal pulmonary emboli. Before I turn to the problem as to whether fatal pulmonary emboli may at all arise from the pelvic veins, I would like to touch upon the question of the frequency of local septic thrombosis after gynecological operations, etc.

To prove that such thrombi are of septic origin it is naturally insufficient merely to demonstrate that the patient has had a transitory rise in temperature. It is necessary to prove that an invasion of microorganisms into the thrombus or into the vessel wall had actually occurred. This however is impossible in the majority of cases. Frequently such thromboses arise in wounds apparently free from any reaction. Is it not more likely that one might imagine that the thrombus

present had arisen through mechanical means as a result of a general diminution in the cardiac efficiency consequent upon loss of blood, or following tamponade, or perhaps something else? In modern aseptic operations, the number of local postoperative thromboses in the region of the pelvic vessels is as a rule trifling, and their size so small that in my opinion they scarcely play any rôle at all. In spite of that, however, the number of fatal pulmonary emboli has not diminished in proportion to what one would expect in view of the advances in asepsis and antisepsis. This would seem to point to the fact that altogether different phenomena must come into question.

When we examine the cases of fatal pulmonary emboli, it appears that, almost as a rule, they arise through the closure of the main branch of the arteria pulmonalis, or simultaneous occlusion of both main branches, or of all the three branches. When we examine the size of these vessels, it is obvious that tremendously big plugs are required to occlude such large vessels. As a matter of fact a closure of the large pulmonary vessels by such plugs, equally thick throughout, is very rare. Clots so extensive could only arise from the vena cava or from the point of origin of the iliac vein; there however you scarcely ever find such isolated thrombi. As a matter of fact, the plugs which occlude the pulmonary arteries are actually composed of numerously folded thrombi of a finger's breadth, on the average, but therefore very long. The more carefully one removes this embolus, the more successful he is in unrolling the manifold twists, and actually establishing its length. I have done it repeatedly, and have always been able to prove that one is dealing here with blood-clots 35–45 cm. in length. The average thickness of these plugs corresponds to the width of the femoral vein. It is quite obvious that such a long embolus may break here and there in its journey to the right heart and the pulmonary artery and be reduced to smaller fragments. One may, however, reconstruct the whole from the color of the individual parts. This finding shows unequivocally that the fatal embolus can only arise from a very long, medium-sized vessel. The only vessel which comes into play as a possible source is the femoral vein. It is altogether out of the question that a thrombosis

of the pelvic veins alone, even when it spreads to the iliac vein, can bring about a similar effect to an embolus from a femoral vein. It lies within the realm of possibilities that a pelvic-vein thrombosis, by spreading upward into the iliac vein or the vena cava inferior, may ultimately lead to a fatal pulmonary embolus. That however is the exception. The majority of all pulmonary emboli have as their point of inception the vena femoralis. We shall therefore try to pay especial attention to this most frequent form of distant thrombosis. Not only do we see it arise spontaneously in heart disease and in general infections, but also postoperatively after extirpation of myomata, etc. For this reason an infectious origin has also been attributed to it.

The definiteness with which we can establish the occurrence of *local* thromboses in the region of the pelvis after infected wounds and the apparent simplicity and clarity of the related circumstances stand in sharp contrast to the difficulty of the problem of the septic origin of *distant* thrombi. We can establish over and over again that in such operated individuals femoral thrombosis arises without the occurrence of a local thrombosis in the hypogastric vein or its branches. And even in such cases where the latter may be demonstrable, it may be quite independent of the thrombosis of the femoral vein. It is not a question of a primary thrombosis of the hypogastric gradually growing backward and breaking through the iliac vein into the femoral vein. If in such cases the thrombus of the hypogastric vein were actually of an infectious nature, one would naturally have the right to speak of the thrombosis occurring in the femoral vein, as infectious. But when each arises independently of the other, or when a femoral vein thrombosis alone ensues, the relation between infection and thrombosis is all the more difficult to establish. When it was possible at post-mortem examinations to obtain positive cultures from the heart's blood of these cases, one was inclined to consider these thrombi as of infectious origin. At an earlier time it was assumed that the coagulability of the blood was increased by the invasion of the infectious agent, but we now know such diminution in coagulation time does not give rise to thrombosis. Then again it was thought that microorganisms settled on the walls of the vessels and pro-

duced an endophlebitis, with the consequence that thrombosis set in. But just in these very postoperative thromboses of the femoral vein following pelvic operations, it was impossible to demonstrate any such phlebitic process. Finally one had to consider that the invasion of microorganisms into the circulation incited a general reaction of the hemopoietic tissue and thereby also, as far as our experience goes, an increase in the blood-platelets. We know, however, that this increase alone does not presuppose any thrombosis, therefore there is nothing left for us but to assume that the same conditions must hold true for the postoperative thromboses beyond the operative area as for the non-infective thrombi. In view of the fact that these also find their site of predilection in the same location, namely the femoral vein, there remains but one common feature for all of them, namely the static. I hope therefore to have established that the thrombosis of the femoral vein in cardiac disease, in typhoid fever, following gynecological operations or abdominal operations, can always be referred back to the same principal cause, that is to say, the slowing of the blood stream. As a result of these considerations there arises the very important problem of prophylaxis. No matter how carefully one will handle the factor of asepsis and antisepsis, he will not be able to prevent the occurrence of femoral thrombosis until he will provide for the proper circulation of blood in the lower extremities. For this purpose it will suffice if after operative procedures the extremities are raised or passive motion carefully instituted. In examining a large material of pulmonary emboli, following femoral vein thrombosis, I could almost always establish that the patient in question, for some reason or other, shortly before death, had to maintain his or her body in such an unusually cramped position, with the lower extremities on a much lower level, that movement was impossible. I am therefore thoroughly convinced that through systematic manipulations of the lower extremities, the danger of thrombosis and emboli can be reduced to a minimum.

Naturally, everything which I have just said concerns only the *spontaneous thrombosis*. I have already previously referred to the fact that the *local* thromboses in the *vicinity*

of the septic operative field, or of an infected wound, should be regarded from an altogether different point of view. Inasmuch as under ordinary circumstances we rarely have to deal with such severe infection after a general operation, septic thrombosis comes up for consideration only as a result of certain definite septic processes such as that of the uterus, phlegmonous inflammation of the appendix, purulent inflammations of the middle ear and furunculosis of the skin. It is quite obvious that operations in such infected areas must lead to the occurrence of postoperative septic thrombi. This type of thrombosis cannot be avoided as long as a state of sepsis obtains within the organism. In comparison, however, with the number of static thrombi which arise spontaneously, these play an inconsequential rôle. The septic thrombi are serious because of their sequela, namely pyemia, which they may awake; the static thrombi, because of the danger of fatal emboli.

I must not, however, omit the fact that the alleged importance of the static factors in the production of thrombosis has been apparently refuted by the experiences of the Great War. A very careful student of the thrombosis question, the German pathologist Dietrich, came to the conclusion, on the basis of a very large mass of post-mortem material on the western front (1400 autopsies), that the majority of the cases of thrombosis observed by him were of septic origin. In these 1400 post-mortems there were found 155 cases of thromboses; in other words, a total of 12 per cent. An approximately similar percentage, about 14 per cent, of venous thromboses, could be demonstrated by the material from the Pathological Institute of Freiburg, before the war. When you realize that in Dietrich's 155 cases of thromboses, 139 followed gunshot wounds, then there appears to be but a very slight difference between the war-time and peace-time material. When, however, one bears in mind that the majority of the thromboses before the war were wont to occur in individuals after the fortieth year, so that the proportion of thrombosis cases before the fortieth year and those after forty was as 1:2, then Dietrich's statistics have an altogether different connotation. Inasmuch as when dealing with soldiers wounded in the war, it was a question of young individuals, between

twenty and forty years of age, during which years the number of thromboses is apt to be, as a rule, the smallest, one would at most expect 3–5 per cent rather than 13 per cent. The marked increase of cases of thromboses during the war to something like fourfold, was consequent upon the frequency of severe wounds accompanied by infection. It is quite obvious that as a result of this, local septic thromboses arose in greater number. This material therefore can in no way be compared with that of peace times. One should not draw any conclusions as to the genesis of thrombus formation during the war from the findings in the war material, for the type of disease, and the type of thromboses are altogether different. In the peace-time material the so-called spontaneous thromboses by far supercede the traumatic and the operative, as well as the traumatic-infectious, which play a subordinate rôle. Quite the opposite holds true for the war-time material, where the traumatic-infectious thromboses predominate, while the static fall into the background. It is readily demonstrable that even during the war the static thromboses played a definite rôle. In the first place they occurred after blood loss; in the second, following general body debility due to the stress of war and undernutrition; in the third, as a result of bandaging, especially first-aid; in the fourth, consequent upon paralysis following gunshot wounds of the spinal cord where static thromboses were likewise observed. After all, however, the war has clarified for us many important facts concerning the production of the traumatic and infectious thrombi. Dietrich could demonstrate, in his investigations of one hundred amputation-stumps, that, as long as the amputated surface was not infected, the ligated arteries very rarely and the ligated veins only infrequently gave rise to thrombus formation. The frequency and extent of thrombosis increased with the onset of infection. In addition Dietrich called attention to the fact that the thrombi found in the large veins in the severely wounded very often had as their source of origin the very small muscle veins which were situated in the vicinity of a wound produced by the splinter of a shell, etc. Finally he also showed that without any external evidence of a decubitus ulcer, very often widespread necroses were to be found in the

glutei muscles. From these muscle necroses, extensive thromboses arose without any other infection.

Thus we see that no scheme suitable for all cases can be established for the formation of thrombosis. The entire process is by far too complicated to permit one to speak of one single factor or cause. It is more important for us by far, to discover in every individual case, out of the many factors which come into question in the production of thrombosis, that which is dominant. Then only shall we succeed in finding out the proper prophylaxis and therapy for the various types of thrombosis. The information obtained during the war, replete with illustrations of a different type of thrombosis, has more than ever emphasized to us that in the origin of the spontaneous thromboses of peace times quite another factor than infection, namely the static, must play the chief rôle. For that reason, the physician whose thoughts are focused along the lines of prophylaxis should attempt above all to attack the dangers of stasis, and the avoidance of infection will automatically come into consideration.

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XII

THE RELATION OF MUCOSAL EROSIONS TO THE DEVELOPMENT OF ULCER OF THE STOMACH[1]

The difficulties which we encountered, following the World War, in providing ourselves with foreign literature, make it easily comprehensible that one or another problem was worked out one-sidedly by us. This one-sided attitude toward certain problems would have been greater, had we not been liberally supplied with at least the American literature through the magnanimous aid of our American colleagues under the leadership of Dr. Boas. Nevertheless, I must ask your forbearance, if, in the theme to be discussed in this paper, I limit my references to the contributions to this question made by Germans or Japanese under German influence. I shall here assume as familiar the fundamental work of the American, English and Swedish authors, and particularly of Mall, Cunningham and Forsell.

When I was last in New York, in 1913, I had occasion to present to a smaller circle my conceptions of the problem and the genesis of ulcus. At that time I emphasized that we could not obtain a comprehensive understanding of this clinically so important disease, until we had sharply divided and separately considered its two constituent phases, namely, the development of erosions, and the development of ulcer. Unfortunately this hope of mine was not fulfilled. On the contrary, even to this day, at least in Germany, the ulcer problem is, as a rule, evaluated from a single point of view, and accordingly a more or less hasty criticism is passed on the apparently opposed opinions. On more careful consideration, it appears that contrary opinions do not at all exist, but rather that one point of view is valid for the formation

[1] Osler Memorial Lecture.

of the erosion, while the other point of view is valid for the genesis of the ulcus. It is only by a reciprocal supplementing of both points of view that the entire clinical problem can undergo any clarification.

If I have at the very outset insisted on a separation of these two problems, it was as a result of the well-known experience that it is almost never possible artificially to produce defects that become real chronic ulcers, in the gastric mucosa of animals. Rather, almost without exception, there sets in a rapid healing of these artificial defects. Since we may compare these artificial defects of the animal mucosa with the fresh erosion of the human mucosa, it was *a priori* to be expected that in the human being too, the majority of all erosions would result in healing. In fact, the hemorrhagic erosions of the gastric mucosa are so frequent, the actual formation of ulcer so unusual, that one asks in amazement, why, with the marked healing power of the gastric mucosa, ulcers develop at all, and why all erosions of the stomach mucosa do not result in healing (see Nicolaysen). From this consideration, a double problem presents itself:

1. How do spontaneous hemorrhagic erosions of the gastric mucosa originate?

2. What are the peculiar conditions in which hemorrhagic erosions exceptionally develop into real ulcers?

This division of the problem into two parts seems to me to be the more justifiable, since with the eventually different genesis of erosion and of ulcer we must proceed in a different fashion prophylactically and therapeutically. Thus it might be conceivable that though we were unable to prevent the genesis of erosions, we might learn to avert their transformation into a true ulcer. Naturally it should also be our endeavor to prevent the genesis of erosions, since, as we shall see, it is indeed from these that ulcers first develop. However, the phase of erosion and the phase of ulcer formation are consummated under quite different conditions.

I need not go into the various theories concerning the origin of ulcers. First of all, those theories of a malnutrition of the gastric mucosa in anemic patients, or of an insufficient antipeptic content of the tissue as the cause of erosions or ulcer,

are fallacious, because we can today say with great certainty that practically all ulcers arise from an original erosion. It is, however, not comprehensible why a deficient nutrition of the mucosa or a lack of antipepsin (Katzenstein) should lead to erosion formation only at particular places in the gastric mucosa. If we, and other workers (such as the Norwegian, Nicolaysen) reject these theories, we must employ ourselves with the question as to how erosions of the stomach arise at all. By erosion of the stomach we understand a fresh loss of substance of the mucosa, regardless of whether it may have arisen from a disintegration of a circumscribed mucosal necrosis, or from a hemorrhagic infarction of the mucosa with secondary digestion. The characteristic of the erosion is the more or less acute loss of substance and its limitation to the mucosa and the uppermost layers of the submucosa. The muscularis proper is never involved by erosions. Only very exceptionally do deep-reaching, apparently perforating losses of substance occur. These very rare cases have been too little studied for us to be able to form an opinion concerning them. If then erosions develop from an acute digestive process of an anemic necrosis, or from a hemorrhagic infarct, there arises the further question as to how these changes in the mucous membrane come about. On this point there are at present five theories which I shall briefly enumerate:

1. The inflammatory theory.
2. The theory of displacements of mucosa.
3. The spastic theory.
4. The circulatory theory.
5. The mechanical theory.

Of these theories, now the one, then the other, has assumed a dominant position. Originally the circulatory theory, as promulgated by Virchow and Hauser, stood in the foreground. But under the influence of our better knowledge of the vegetative nervous system, this theory was more and more superseded by the spastic theory particularly sponsored by Talma, Bergmann and his pupil Westphal. And recently, the inflammatory theory, under guidance of Moszkowicz

and Konjetzny, has come to the fore with the contention that it is best able to explain the formation of erosions. I consider it proper to begin at once with this last theory. It is doubtless correct, as the above-named authors maintain, that in the so-called ulcer stomachs all kinds of chronic gastritis, particularly the most varied anomalies of the gastric mucosa, are present. Thus, even earlier authors, as Adolph Schmidt and Kokubo, have called attention to the frequent occurrence in the gastric mucosa of the so-called intestinal glands. The occurrence of such glands has always drawn to itself the attention of investigators. Some authors believed that in such changed areas of mucous membrane, a peculiar disposition to the formation of erosion, or indeed of ulcer, must be seen, because such changed islands of gastric mucosa must possess a reduced resistance to the gastric juices.

Unfortunately, we are by no means as well informed concerning the normal histology of the human gastric mucosa as would be desirable. Recently a great deal of work concerning the human gastric mucosa has appeared in Germany and Austria. I shall name only the work of Stoerck, Paschkis and Orator, Oshikawa, Moszkowicz and Konjetzny. I, myself, have endeavored with Oshikawa to make clear the conditions, first in the dog's stomach, and later in human stomachs as nearly normal as possible. The usual subdivisions of the gastric mucosa into a cardiac zone, a fundus zone, and a pylorus zone, is known. It is also known that this zone of pyloric glands extends much further toward the cardia along the lesser curvature than along the greater. One might say they correspond to the zone of the radiation of the pathway of the stomach, later to be described. It is also well known that the boundary between pyloric glands and fundic glands is no very sharp one. This zone of intermixing of pyloric and fundic glands has been designated as the intermediary zone. As is known, the pyloric glands are characterized by their peculiarly clear epithelial cells, which give a mucous reaction, while in the fundic glands we differentiate the more darkly staining chief cells from the coarsely granular parietal cells. The more recent researches of Oshikawa have, however, shown, as Ellinger had previously demon-

strated in the dog, that there is still a third form of glands which should receive the appellation of intermediary glands. These are glands which almost entirely lack chief cells, but which, on the other hand, contain parietal cells in varying numbers. Essentially they are composed of epithelial cells which resemble, but are not identical with, the pyloric cells, and which constitute a special type of epithelial cells, the so-called intermediary or adjacent cells. The transition of intermediary glands to the genuine fundic glands occurs very gradually. Nevertheless, from now on, the normal dog or human stomach must be divided into four parts instead of the usual three, namely, the zone of the pyloric glands which is in general limited to the region of the pyloric canal, the intermediary glands which comprise the region of the infundibulum, the fundus glands which take in the main mass of the corpus, and finally, the zone of the cardiac glands in the cardiac region. In view of this variegated composition of the stomach mucosa, and of the fact that the boundaries run quite differently on the lesser than on the greater curvature, the possibility appears to be given for the displacement of one sort of mucous membrane by another. In fact, the researches of Oshikawa have shown that just on the lesser curvature, intermediary, or indeed pyloric glands, may be found far up in the corpus region, and just in the neighborhood of stomach ulcers. Naturally the thought occurs that such abnormal implantations of the pyloric or vestibular mucosa into the corpus mucosa may predispose to ulcer formation. I believe, however, that such assumptions are wrong. Experience has often shown that, regardless of its structure, the normal gastric mucosa is not attacked by the usual stomach juices. One could at most say that in the normal transportation of food from the fundic portion through the vestibular portion and the pyloric canal, a gradual diminution of the active fundic juices takes place before the pyloric canal is reached, while the action of these juices on the islands of pyloric mucous membrane displaced into the corpus, must be much more intense. We must, however, be very cautious in drawing such conclusions, for we know not how far such abnormal gland formations may have developed under the irritation of the ulcer.

Thus, I return to the presence of intestinal glands in the gastric mucosa. They are so frequently to be found in the stomach with chronic ulcer and with chronic gastritis in general, that a certain disposition toward erosion and ulcer formation has been seen in them. But the question here, too, is in how far these intestinal gland formations are primary, and in how far the sequelae of the formation of superficial erosion formation. While it was formerly assumed that these intestinal glands represent partly physiological displacements, and partly pathological metaplastic processes developing chiefly through migration of intestinal epithelium within the furrows of the stomach, we have more recently come to the opinion that the majority of these formations represent atypical healing processes of inflammatory erosions. Moszkowicz especially has emphasized the frequent concomitance of small mucosal erosions and intestinal gland formation. Since both occur in chronic gastritis, which in turn is found in chronic ulcus ventriculi, Moszkowicz sees the chief source of gastric ulcer in the inflammatory erosions found in stomachs changed by chronic gastritis. I shall in no way question these facts, the less so since I, myself, have been able, through Kokubo, to point out the frequency of intestinal gland formation in stomachs with ulcer. But the question here again is which is primary and which is secondary. Chronic inflammatory changes of the stomach are unusually numerous. They may occasionally lead to the formation of erosions. Conversely, a chronic ulcer with its numerous secondary conditions of gastric disturbance, may of itself be the picture of a chronic gastritis. That all manner of superficial erosion formations may arise under the influence of the disturbed gastric function is to be understood. I should ascribe more importance to the inflammatory erosion and intestinal-gland formation, were they not also found in gastric carcinomata in which we only seldom observe a true ulcer formation. The conclusion consequently, seems justifiable to me that these various anomalies of the gastric mucosa and the different inflammatory changes and erosions have nothing to do with the typical gastric ulcer, but are rather the results of the most varied diseases of the stomach. I do not thereby intend to

deny that under particular conditions, even inflammatory changes of the mucosa may lead to the development of erosions and ultimately ulcers. Indeed there are certain, though rare, forms of erosions and ulcers that are surely of an infectious nature. To this category belong primarily the mushroom (schimmelpilze) type of gastric ulcer, repeatedly described in the literature. Similarly, the tuberculous and other specific ulcers, must be classed here in so far as the infections result from the surface of the mucosa. Since these are, however, rare disease forms, they need not be taken into consideration in our discussion.

The well-known fact that mucosal erosions, particularly of the multiple type, present a fresh character, indicates that other factors besides a chronic catarrh play the chief rôle. The spastic nervous influences have recently been especially mentioned as one of these factors. Before we enter upon this important question, I must here point out that the concept of erosions is by no means a uniform one. The researches of the last few years have again shown, as Langerhans had done previously, that according to their size and their situation, two types of erosions must be differentiated. In recent years, Katayama especially has called attention to this. From my own experience, I can confirm these various statements. One portion of the hemorrhagic erosions presents the so-called stigmata of Beneke. These are almost regularly found in the corpus, localized predominantly in the region of the greater curvature. There is consequently a very large surface area of the stomach covered by these. They may be more or less thickly scattered, so that countless small erosions are found. They are usually of the size of a pin head, or slightly larger, and only exceptionally do they reach a greater diameter. As a rule, they are blood-tinged and show a central loss of substance. In the newborn, during the first few days of life, these losses of substance are not reddish, but definitely jaundiced, because of the concomitant icterus neonatorum. Since the main portion of the body of the stomach is designated as the fundus, these erosions may also be designated as *fundus erosions.*

Opposed to these is quite another type of erosions which may be differentiated from the so-called stigmata by their

relative size and the manner of their localization. These hemorrhagic erosions reach the size of lentils, and may be larger. They occur in smaller numbers only, and are, in the main, limited to the fold system of the pathway of the stomach and its projections into the pyloric canal. The microscopic examination shows that these hemorrhagic

Fig. 22. Erosions of the fundus of the stomach.

erosions, not only in area, but also in depth, reach a greater extent than the fundic erosions. Consequently Katayama, following Orth, has with justice contrasted these hemorrhagic ulcers with the hemorrhagic erosions in the narrower sense. If the appellation "ulcer" is used, it must always be borne in mind that we are considering quite acute destructions of the mucosa, the very earliest stages of ulcer formation, which should not be mistaken for the real chronic ulcer.

They probably represent the early stages of a chronic ulcer, and only under peculiar conditions change into a chronic ulcer, as we shall see later on. This second form may be designated as *erosions of the gastric pathway*. These two forms are in the literature still considered as equivalent, although there can be no doubt that genetically, as well as

FIG. 23. Erosions of the pathway of the stomach.

in their subsequent development, they are to be evaluated as quite different.

Fundus erosions are found in all age periods. They are found especially frequently in infants, but are observed also in adults, following all sorts of abdominal operations, meningitic irritations, brain tumors, etc. It is for the origin of this type of erosion that a spastic influence on the vessels of the gastric wall has been held responsible.

Thus, above all, Beneke and his pupils, Nakamura and Kobayashi, as well as Schmincke, consider a nervous arterial vascular spasm responsible for the development of the small anemic necroses of the mucous membrane. They are supposed to be later perfused with blood, and thus the picture of the hemorrhagic erosion arises. Ricker, too, believes in circulatory disturbances of nervous origin. Others,

Fig. 24. Erosions of the pathway of the stomach (canalis pyloricus). (*After Strohmeyer.*)

and especially von Lichtenbild, have described a spastic contraction of the muscularis mucosae as the cause of the arterial blocking and the anemic necrosis. The claim made by von Bergmann, that the gastric ulcer is found only in vago-sympatheticotonics, and the spasmogenic theory of gastric ulcer initiated by him, have stimulated renewed experimental researches as to the etiology of hemorrhagic erosions. In this connection the work of Westphal, Murata, Nicolaysen, Haeller, and Hayashi should be especially

mentioned. While Haeller finds the cause of the development of fundus erosions more in constitutional, nutritional and circulatory disturbances, the others have advanced striking evidence in favor of the spasmogenic theory. In the first place, they were able to produce typical erosions through the use of pilocarpin, muscarin and picrotoxin. Since no influences causing vascular spasm come into question, and since, moreover, the violent contractions of the stomach could be followed roentgenologically and by the naked eye, no other conclusion remains but that here, due to the cramp-like severe contractions of the musculature, a kinking of the vessels, and thereby a localized anemia with succeeding hemorrhage or local stasis, occurred. Hayashi was able to produce similar spastic erosions in anaphylactic animals. In these investigations of Murata and Hayashi, it was striking that one portion of the erosions was hemorrhagically discolored while the other was not. The former were mainly in the fundus region, the latter predominantly in the region of the gastric pathway. It appears that even here, in animals, there are certain differences between the two types of erosion. It is similarly remarkable that in certain experimental series, only the fundus portion is affected by erosion. There must, consequently, be exceptional conditions which favor the formation of erosions, now in the fundus, and now in the gastric pathway. This variation may only be explained on the ground that the two different portions of the stomach are affected to a varying degree by spastic irritation, so that the fundus erosions appear much more frequently than the erosions of the gastric pathway. In the human, too, we see both types of erosions arising by themselves. Indeed, the combination of both types is somewhat remarkable and unusual. From this, too, we must conclude that there is a certain difference in origin. We shall only acquire a more accurate insight into this situation, when we better understand the nervous system of the stomach (Perman).

The frequent appearance of erosions is comprehensible because the fundus portion of the stomach is, on the whole, more strongly influenced by the spastic contractions. That they are, as a rule, hemorrhagic, probably rests on the fact

that the fundus portion of the stomach is altogether richer in blood. Accordingly, in severe contraction, not only arterial but also venous compression takes place, causing a venous stasis and hemorrhage. Such a possibility is admitted by Murata. Thereby we come to the question as to whether certain circulatory disturbances may not play at least an auxiliary rôle in the origin of fundus erosions. Virchow had already pointed out that these erosions were found with striking frequency, following asphyxia or vomiting. We can thus understand the frequent occurrence of fundus erosions in infants, for example, following peritonitic and meningitic irritation, or following abdominal operations in general. I can only concur in the opinion of Virchow concerning the great significance of vomiting in the etiology of fundus erosions. Doubtless the vomiting act is accompanied by, or better, is introduced by, a hyperemia of the abdominal organs and particularly of the stomach. Then follows the compression of the abdominal contents by the abdominal musculature, and finally the active contraction of the stomach itself, which, as we know from the researches of Klee, ejects its contents. The pyloric canal is tightly closed, while the fundic portion is undergoing the vomiting motions. Consequently two factors, blood engorgement and spasmodic contraction act together in producing a venous stasis hyperemia and a venous hemorrhage on the summits of the fold system. That the venous stasis hyperemia, as such, can actually lead to typical hemorrhages and hemorrhagic erosions, has been shown by the experiments of Hagemann, and especially by the ligation experiments of Yano on rabbits. Though I consider the venous stasis, particularly in vomiting and asphyxia, as primarily responsible for fundus erosions, I do not intend thereby to say that arterial anemic necroses may not arise in other cramp-like conditions of the stomach. These fundus erosions, however, play no rôle in the pathogenesis of the real ulcus ventriculi, as we shall see. Nevertheless I must briefly mention that we considered other circulatory disturbances, especially of an embolic nature, responsible for their origin. Thus Eiselsberg believed that the fundus erosions which set in after abdominal operations were to be explained by retrograde emboli from the venae epiploicae

into the coronary veins. Nevertheless subsequent investigators were unable to demonstrate such emboli. On the other hand, in the so-called fat embolism, arterial emboli with secondary necroses of mucosa and hemorrhage, have been definitely established by Schridde.

More important for us than the pathogenesis of fundus erosions, is the pathogenesis of erosions along the gastric pathway, since it is from them that the later chronic ulcers develop. As I have previously shown, workers have been more successful in producing fundus erosions by using spasmogenic drugs than in producing erosions of the gastric pathway. Murata was completely unable to find any erosions in the gastric pathway. At all events, the gastric pathway takes a peculiar position in this respect. Since we know from the researches of Forsell, Elze and Bauer, that it possesses its own muscle system, independent contractions of the region of the gastric pathway do not seem so incomprehensible to us. It is conceivable that spastic necroses of the mucosa might occur, particularly when the gastric pathway is especially involved in the spasm. It is remarkable, however, that in human, as well as in animal experiments, these erosions of the gastric pathway are, as a rule, larger than in the fundus mucosa. This can, of course, depend only on a special vascular supply of the gastric pathway. Even the casual examination of the stomach shows that the lesser curvature possesses quite a different vascular supply from that of the greater. One could more properly speak of the region of the gastric pathway and of the fundus. In the fundus region, the arterial branches of the right and left gastric epiploic arteries quickly penetrate the stomach wall, and there branch out. The fundus region, however, also receives blood from collateral branches of the gastric artery. These enter the gastric wall, not on the greater curvature, but at some distance from it, at the boundary between the gastric pathway and the fundus region. Consequently the fundus region is nourished from both sides, while the gastric pathway is supplied only through the recurrent branches of the gastric or pyloric arteries. Nagayo called particular attention to this, by demonstrating the more exact relationships by means of injection of dogs.

It is further noteworthy, as I have repeatedly shown, that the boundary between the pyloric canal and the rest of the stomach is characterized by the region of anastomosis of the gastric and pyloric arteries. Here, therefore, from the point of view of vascular supply, there will be a special disposition to the formation of anemic foci. The ligation experiments carried out by Dr. Yano on rabbits have demonstrated that all ligations in the region of gastroepiploic arteries have no recognizable influence on the fundus mucosa. On the contrary, ligations of the gastric or pyloric arteries or of both vessels, lead to localized nutritional disturbances of the mucosa, as can best be shown by subsequent intravenous injections of vital dyes. The mucous membrane areas belonging to the ligated vessels remain more or less colorless. Since these colorless membrane areas correspond broadly with the generally observed hemorrhagic ulcers of the stomach, there can be but little doubt that in the human being, too, arterial blocking must play a particular rôle in the origin of these changes in the gastric pathway. I had formerly believed that, as in the fundus erosions, venous stasis must be held responsible for the erosions in the region of the gastric pathway. The experimental observations however, seem to speak in favor of what I have never denied — that the arterial etiology for these erosions here plays a greater part than the venous. But it may be asked by what these transitory arterial blockings are conditioned. Here, as we have previously shown, peculiar spasm of the gastric pathway may play a part. The remarkable predilection of these erosions for the so-called isthmus region may well be brought into accord with such spasms. I have particularly emphasized such local spasm as isthmus formation. They are in a manner physiological, but may naturally undergo pathological increase. Since the spastic isthmus formations are now tightly narrowed and then widely dilated, the frequent finding of erosions, arranged in rows on the summits of the longitudinal folds of the gastric pathway, is to be explained. And since the branches of the gastric artery going to the gastric wall are segmentally arranged, the border regions between the individual segments are especially injured in spasmodic conditions of the gastric pathway.

It may now be asked how far all erosions of the gastric pathway can be explained by the spastic theory. It must be considered that not only this blocking of the artery indirectly called forth by gastric spasm, but also the direct embarrassment of the arterial supply, may play a rôle. Here we must consider, first of all, embolic blocking, and then, disease of the vessel, particularly of an atherosclerotic nature. I have previously expressed myself as opposed to the great significance of these factors. Erosions of the stomach occasioned by emboli doubtless occur, but they are extremely rare. Arteriosclerotic diseases of the vessels with secondary changes in the mucosa are more frequent. They too are unusual. As a rule, gastric erosions and ulcers develop in youth and middle age, concerning which time one cannot talk of arteriosclerosis of the gastric vessels. Usually the changes found in the vessel walls are to be looked upon as secondary, and as arising as a result of the chronic ulcers. There remains consequently only the spastic contraction of the vessels themselves. I consider it by no means excluded that such vascular spasms occur in the stomach, and in particularly predisposed areas lead to anemic necroses. To be sure, the experimental evidence is lacking. Nevertheless, we must agree that spastic conditions in the gastric wall or the gastric vessels acquire an especial rôle in the origin of erosions of the gastric pathway.

There remains for consideration only the purely mechanical injuries. That the gastric pathway may be unusually easily injured by the introduction of sounds or the gastroscope, that ulcers caused by caustics and hot foods localize particularly along the gastric pathway, is self-understood. But these are such rare etiological occurrences that they may well be left out of consideration in a discussion of the pathogenesis of spontaneously arising erosions.

To summarize what has been said, we may say that two forms of erosions must be differentiated—the fundus erosion and the erosions of the gastric pathway. They owe their origins to quite different conditions, but in neither of the two do infectious, toxic infections, or mechanical factors play a prominent rôle. Circulatory disturbances, however, represent the most important source. These may be either direct or indirect through spasms of the stomach muscula-

ture. In fundus erosions, venous stasis and the spasmodic motions of vomiting play a particular part. In erosions of the gastric pathway, it is apparently peculiar spastic conditions of the pathway itself, or arterial blockings, whether of a spastic, embolic, or arteriosclerotic nature, that call forth the necrosis of the mucosa. What great significance attaches to spastic conditions in the region of the stomach and the gastric vessels for the etiology of erosions, particularly in the region of the gastric pathway, follows from my exposition. For my part, I have always recognized the significance of the spastic theory in this direction, although I attribute a much greater part to purely mechanical circulatory disturbances in the case of the fundus erosions.

The conditions are quite different, however, when we turn to the second question, namely how *chronic gastric ulcers develop from erosions*. I have been wrongly classed as a one-sided advocate of the mechanical, or more properly of the mechanical functional theory of the pathogenesis of gastric ulcer. It had been thereby completely overlooked, that my conclusions had to do exclusively with the problem of the transition of gastric erosions into gastric ulcer and not with the origin of the gastric erosion itself. As long as these two problems are interwoven, the conflict will continue, because what may be correct for the origin of erosion may be false for the second phase, the transition of the erosion into the ulcer. And what may be considered as correct for the second phase need have no significance for the first phase. It is a well-known fact that chronic gastic ulcers are almost without exception found in the region of the gastric pathway. Had I, in conjunction with my pupils, desired to point out this fact only, this would have been a superfluous beginning. It is important rather to explain the origin of the entire gastric ulcer, its development from the erosion, its formation, its localization from the anatomic functional structure of the gastric pathway. Such attempts have often been undertaken. I call attention particularly to the work of A. Schmidt and Bloch, who pointed out the slight movability of the mucosa in the region of the lesser curvature. I believe, however, that the problem is not thereby exhausted, but that the whole structure of the gastric pathway must be taken into consider-

ation to obtain a correct picture of the anatomical and clinical findings in gastric ulcer. As you know, since the thorough researches of Forsell (I cannot go into the earlier literature), we differentiate in every stomach a pars

FIG. 25. Gastric ulcers in the pathway of the stomach.

digestoria and a pars egestoria, the latter characterized by the pyloric canal. The pars digestoria consists of fornix, corpus and vestibulum, which represent a sort of connection between the corpus and the pyloric canal, which, as I showed previously, is to be differentiated, though not sharply, from the rest of the corpus by its peculiar mucosal glands.

Between the infundibulum and the main portion of the stomach we frequently find in the stomachs of human cadavers, the so-called narrow pass of Forsell, which I have designated as isthmus. I must expressly emphasize that we are here considering not an anatomical but a functional structure, which is now present and now absent, now constitutes a small portion of the corpus, now a large, as is best seen from *x*-ray pictures. I have found this isthmus also in the dog's stomach. It represents doubtless a sort of tonic spasm of a definite portion of the stomach. Elze believed he recognized in this a pathological formation which developed mainly under the influence of morphine. I must absolutely reject this point of view since in many of my cases, and in the dog, no morphine had been given. Whether this spastic isthmus formation is really physiological, cannot for the present be determined. The roentgenograms permit of no judgment, because the diet is always pultaceous. I have, however, obtained the impression that it is on a mixed diet that the isthmus takes shape and forms a sort of funnel, through which the fluid contents, rapidly digested in the corpus, are transported to the vestibulum, and from there are evacuated by the contractions of the pyloric canal. This funnel shape presents itself to us just as clearly whether viewed from the cardia, or on section through an isthmic narrowed stomach. During the war, I had the opportunity of fixing a large number of human stomachs relatively soon after death. I was able to convince myself that the isthmus form was no post-mortem occurrence, but must have existed before death. This is a functional attitude of the stomach fixed by death. It cannot be removed even on excessive filling of the stomach with fluid any more than can the spastic closure of the pyloric canal, which I could establish in practically all stomachs. I must at this point call attention to another thing observed in these cadaver stomachs. I have never seen, nor could I artificially produce, a true peristalsis. On the other hand, irritation of the serosa regularly led to localized muscle contraction which produced nodular thickenings of the wall, and which often persisted for several seconds. Similar contractions could not be produced from the mucosal side. Moreover, the surface of the stomach showed a

gradual increase in irritability from the cardiac to the pyloric end. The pyloric canal was particularly irritable. This could be even better demonstrated on the dog. What significance is to be attributed to these localized contractions, I cannot state. Nevertheless they were very striking. On longitudinal section through a stomach with such an isthmus, a very definite difference between the relief of the mucosa of the

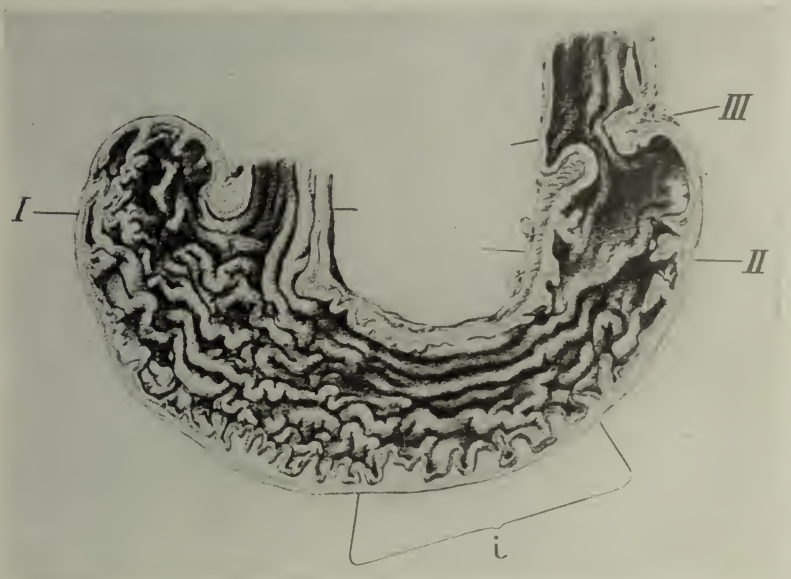

FIG. 26. Longitudinal section of the stomach. I, Limit between fornix and corpus; II, Limit between infundibulum and canalis pyloricus; III, Limit between canalis pyloricus and duodenum; i, isthmus ventriculi.

lesser curvature, that is, the gastric pathway, and that of the greater curvature, i.e., the fundus, can be shown. On the lesser curvature, the mucous membrane folds run quite through the isthmus, as though they were purposely stretched over the site of the curvature of the isthmus. On the greater curvature, however, the mucous membrane folds are definitely arranged in a maze. Similar clear pictures are obtained when a fixed stomach is opened along its greater curvature. One can then quite plainly see the gastric pathway, usually limited by four longitudinal folds, spreading out fan-

shaped into the pyloric canal which presents a sparse irregular network of folds. In contrast to this, the remaining portion of the stomach, which may be called the fundus, is characterized by the active convolution and close approximation of its fold system. In certain cases, the color differ-

Fig. 27. System of folds in the stomach opened at the greater curvature.

ences between the gastric pathway and the fundus are very distinct. From this it develops without further proof that the gastric pathway is not identical with the lesser curvature. The gastric pathway, in its narrower sense, reaches from the cardia to the beginning of the pyloric canal, where it spreads out superficially and goes over into the pyloric canal. One gets the impression throughout that the gastric pathway

and the pyloric canal must be conceived as one sort of functional entity, while the rest of the stomach represents another entity. Therein can still be seen a phylogenetic vestige of the filling pathway of the stomach and the gland division (Bauer). The boundary between the gastric pathway and

Fig. 28. System of folds in the stomach opened at the lesser curvature.

the rest of the stomach is indicated by the course of the fibrae obliquae. These may be looked upon, as Bauer has claimed, as a sort of sphincter muscle of the fundus portion against the rest of the stomach. The striking fact, however, is that with increasing contraction of the stomach, as long as it maintains its closed form, taut folds are to be found in the

main portion of the gastric pathway, particularly in the region of the isthmus. This longitudinal stretching disappears only if the stomach is freshly opened and then fixed. It is only then that the gastric pathway, deprived of its fixation point, puckers up, and the system of longitudinal folds is transformed into a convoluted mass of folds. If, on the other hand, a fixed stomach is opened along the lesser curvature, one is astounded at the complicated mass of folds which the stomach fundus usually presents.

This barring of the gastric pathway against the rest of the stomach can be well recognized, even on transverse sections, throughout a contracted stomach. It can then be seen that the gastric pathway, now better called the gastric groove, is limited by the four familiar folds, while the folds of the fundus lie irregularly one against the other. One gains the impression that the contracted, i.e., more or less empty stomach, drains the juices from the fundus portion, that is, the specific digestive juices into the gastric groove, so that they may flow towards the pylorus. Against this unusual position of the gastric pathway in relation to the rest of the stomach, it has been argued that in the roentgenogram no such gradual opening out of the stomach from the gastric groove can be established. I believe that this objection has been removed through the roentgenologic researches of the Vienna Surgical Clinic wherein Orator[1] has been able to call attention to just such opening pictures. It is also easy to understand that with a marked ingestion of pap, the fold system of the stomach opens up very rapidly, so that these differences are not easy to recognize. Corrosion casts speak more clearly than do roentgenograms for the independent nature of the gastric pathway. The area, corroded especially with acids, corresponds almost exactly with the gastric pathway.

From these descriptions, it follows without going any further that the fate of a loss of substance in the mucosa of the fundus must be quite different from that in the region of the gastric pathway. In one place there is greatest mobility of the fold system, in the others, taut longitudinal stretching; here, discharge of gastric juice, there, its reception as by a

[1] *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* Jena, 1923, XXXVI, 725.

drainage tube; here, hardly any influence on the contour line by the isthmus, there, a purposeful kinking. Thus it appears conceivable from the very outset, that the healing tendency of a defect arising in any manner whatsoever, of a so-called erosion, must be much greater in the fundus region than in the region of the gastric pathway. This it was, that I meant from the very outset, by the mechanical functional explanation of gastric ulcer. I wanted to point out that losses of substance in the gastric pathway continue gaping in a quite

FIG. 29. Characteristic form of ulcer of the stomach. m, mucosa; sm, submucosa; mu, muscularis propria; s, serosa; p, proximal (cardiac); d, distal (pyloric). (*After Strohmeyer.*)

different manner, come into contact with gastric juice much longer and finally are more injured mechanically by the peristaltic motions than is possible in the fundus region. I laid so much stress on the remarkable mobility of the mucosa on the cardiac or oral side of the ulcer, and the adherence of the mucosa on the aboral or pyloric side, because thereby the peculiar funnel-like shape of the ulcer and the development of the roentgenologically important niches are to be explained. That the pulling and pushing effects of the muscular and mucous walls of the stomach during its peristaltic motions would first appear within or just above a spastic isthmus formation is self-understood. I believed that making

use of the anatomic functional peculiarities of the gastric pathway, the following facts could best be explained:

1. The relatively frequent transition of erosions situated just along the gastric pathway into chronic ulcers, i.e., the poor healing tendency of these losses of substance as compared with those of the fundus.

2. The striking location of a great number of ulcers in the isthmus region or relatively close above it, i.e., the development of ulcers far removed from the pylorus in contrast with true pyloric ulcers.

3. The peculiar funnel-like shape of the ulcers; the chronicity in general induced in them by the stasis of gastric content in the funnel.

How much the healing power depends on the mechanical functional protection of the ulcer is shown once more by the latest work of Perman. He adduces numerous clinical and operative cases of this type confirmed by autopsy. All manner of objections have arisen against this conception of mine of the mechanical functional factors in the development of a gastric ulcer from an ordinary gastric erosion. These emanate mainly from Bergmann and his pupils, who will not believe in the unique situation of the gastric pathway and in what I may call the physiological strait-formation of the stomach. They and their adherents have come, first of all to a denial of the mechanical functional theory because they believed that they had at hand sufficient evidence for a spastic origin of gastric ulcer. In answer to this, I must remark that this unique position of the gastric pathway and the presence of an isthmus have been again and again verified by those pathologists who commanded the largest material (Gruber, Kratzeisen, Busch); that, on the other hand, the experiments of the adherents of the spastic theory have dealt mainly with the origin of hemorrhagic erosions, but do not at all, or only very slightly, account for the question which I consider equally important, namely, the question of the transition of erosions into an ulcer. I, therefore, think myself absolutely justified in persevering in my conception of mechanical functional conditioning of the true chronic ulcer, and in permitting myself to submit further proof to you.

You are all aware of the remarkable fact that it is, as a rule, impossible to produce true ulcers in experimental animals through corrosion or mechanical defects of the mucosa. As a rule these losses of substance heal extremely rapidly, so that after a short time—one to two weeks—hardly anything is to be seen of the loss of substance. If then our conception of the functional mechanical disposition of the gastric pathway is really correct, it should also permit of experimental confirmation. There should be found a definite difference in healing capacity of losses of substance in the fundus region and similarly large losses of substance along the gastric pathway. Many such experiments have been carried out on the rabbit by Dr. Yano. They have given the unequivocal result that similarly large losses of substance produced by branding on the gastric pathway, healed with much more difficulty, or did not all result in healing, while in the fundus they showed good healing tendencies and disappeared fairly rapidly, so that only a faint scar in the fundus region could be found associated with ulcers in the gastric pathway. Thereby the well-known disposition of the lesser curvature, or more properly, gastric pathway, to the formation of chronic ulcer is confirmed, since also those losses of substance produced in the pyloric canal heal more slowly than those in the fundus. The questions naturally arise whether in the rabbit, conditions of the type such as we have postulated for the human come into consideration to account for difficult healing of the mucosal defects, and what these conditions are. In the first place, the diminished mobility of the mucosa in the gastric pathway as compared with the fundus region, must be mentioned. In the fundus region extending quite far out from the vicinity of the defect, one sees a rigid tonic contraction of the muscularis mucosae whereby the mucosal edges are approximated. Moreover, the mucosa of the fundus is much thicker than that of the gastric pathway, and by contraction of the muscularis mucosae it is made still thicker. The fundus mucosa shows a remarkable tendency to produce, through metaplastic processes, a sort of thin mucus which is poured out over the wound surface. This mucus formation is usually absent in the gastric pathway. The epithelium of the fundus

mucosa shows a greater tendency to epithelization which could be entirely lacking in the gastric pathway. So it comes about that fundus defects are quickly covered by a sort of protecting membrane, while the defects of the gastric pathway lie, so to speak, bare. And correspondingly, the defects along the gastric pathway show a much more intense reaction than those in the fundus. Naturally the fundus defects are not lacking in leucocytic reaction and in histiocytic and fibroblastic proliferation. Here, too, there develops granulation tissue with increasing thickening of the fibrous framework of the submucosa. Depending on the depth of the defect, the musculature is involved in the fibrous change, so that even after complete healing of the mucosal defect, the old wound site can be recognized in a microscopic section. In defects of the gastric pathway, the reaction processes proceed much more intensely, but without the desired success. There develops quite the picture of a chronic ulcer as we have been accustomed to see it in the human stomach. In succeeding days we find a true digestive necrosis of the superficial layers of the submucosa or of the muscularis, which may be infiltrated by wandering leutocytic masses. Beneath the digestion membrane lies the very strongly developed granulation tissue with the strikingly rapid development of fibrous connective tissue, so that one may almost speak of the callous scar formation with a sort of hyaline swelling which is found even in the base of human ulcers. The intense irritation exercised by the gastric juice on the surface of the ulcer reaches into the submucosa and calls forth marked reactive proliferations. In short, the picture indeed resembles a chronic ulcus ventriculi. Macroscopically, also, the rounded form, the slightly thickened wall, resemble the human ulcer, though it must be noted that, as a rule, in humans, this wall-like thickening of the mucosa at the ulcer edge is not usually as distinct as in the rabbit.

The second question, namely, whether the peculiar localization of ulcers at some distance from the pylorus can be explained by the isthmus formation, cannot be quite definitely decided in the rabbit, because in the rabbit, as a result of the nature of its diet, it appears that no isthmus is formed. Nevertheless, we received the impression that certain defects

produced on the border between the pyloric canal and the rest of the stomach, that is, on the boundary between the areas supplied by the gastric and pyloric arteries, healed particularly slowly. However, this cannot be mathematically proved. Here, therefore, the circulatory relationships in the vestibular region of the gastric pathway would play a rôle.

The third question, however, concerning the formation of ulcer under the influence of the gastric pathway, could be well studied in the rabbit. As is known, a fairly large proportion of human ulcers show a characteristic funnel-like shape with the tip of the funnel directed, not perpendicularly to the wall, but obliquely and toward the cardiac or oral side. This peculiar funnel formation it is which may be visible in the roentgenogram as Haudek's niche. This funnel-like shape of ulcers was formerly attributed to disease of the nutrient vessels. It was believed that the funnel-shaped ulcer represented, so to say, the picture of a wedge-shaped infarct of the stomach wall. It was very easy to demonstrate that the vessels penetrating the gastric wall did not at all branch in the manner which should have been expected from the funnel-shape of the ulcer. To be sure, the branches of the arteries penetrate the muscularis and submucosa in a more or less oblique direction, but not in such large branches as was to be expected from the form of the ulcer. Similarly, it was easy to show that the vessels in a relatively fresh ulcer run in the floor of the ulcer, and only secondarily became eroded, a fact which is familiar to all physicians. Consequently the funnel shape of ulcers must depend on something else. I believed that the mechanical functional burdening of the gastric pathway was to be held responsible for it. Not only the contents, but the gastric mucosa, even in the region of the gastric pathway, is propelled by the peristaltic contractions from the cardia toward the pylorus. This must make noticeable an overhanging of the mucosa on the oral, and a pushing away of the mucosa on the aboral side. As soon, however, as such a roofing over had taken place on the oral side, a filling and a stagnation of the gastric juice could occur under the overhanging mucosa, and then the action of the gastric juices take effect. Accordingly, the ulcer must first penetrate into the depth more quickly on the oral than on

the aboral side, and so bring about the oblique funnel shape. I therefore had demonstrative preparations of fresh ulcers produced in the work of Strohmeyer. I saw in the unilateral filling of the ulcer with gastric juice, the chief reason for the progress of the ulcer and its possible consequences, namely the erosion of the deep-lying subserous vessels. From these observations, I thought it necessary to conclude that the healing of a gastric ulcer could only occur on a diet which permitted of the quickest and most complete digestion of the ingested food, so that such deposits of larger food particles as I had frequently found in ulcer funnels would be impossible, and thus the ulcer be protected as much as possible. We can see from this that the milk diet represents exactly such a protective cure for gastric ulcers.

Against this conception of mine, objections have been raised: first, that a great number of gastric ulcers do not at all show the typical form, and second, that the chronicity of gastric ulcers is conditioned not by the gastric juice but by quite other processes, such as those of an infectious nature. To this I reply as follows: since the peristaltic axial displacement of the mucosa becomes noticeable essentially in the pyloric canal and the region of the narrowing of the gastric pathway, it would be there predominantly that typical ulcer forms would be observed, while in the true pylorus, or on the cardiac side of the corpus, they would hardly make their appearance. In fact, a statistical survey by Oshikawa concerning the distribution of typical and atypical forms of gastric ulcer gives the following figures:

Distribution of Typical and Atypical Forms

	Typical	Suggested	Uncertain	Atypical
Pylorus	1	2	2	2
Pyloric canal	8	1	2	0
Isthmus	3	0	1	5
Corpus	3	1	0	3

Naturally, however, this localization is not the only reason for the presence or absence of typical funnel shapes. We must

rather consider that in a destruction of the muscle wall and extensive callous disease of the subserous region, such as is seen in chronic gastric ulcer, the displacement phenomena would become indistinct. And finally, the healing processes setting in irregularly now here, now there, on the base of the ulcer, distort the picture very considerably. Thus it is quite conceivable that the typical form of ulcers would only be found when no complications had as yet occurred to distort the picture. The question of the form of ulcers is, however, most intimately connected with the question of chronicity. It is usually accepted that chronic gastric ulcers show almost no reaction. This is, however, by no means the case. On the contrary, the latest researches of Askanazy and Perman as well as Nissen and Nicolaysen have shown that practically every gastric ulcer shows at its base a typical triple layer arrangement, namely, a superficial leucocyte-fibrin layer, a necrotic layer lying beneath this, and finally, beneath this, a granulation layer involved in more or less advanced scarring. This inflammatory scarring extends not only through the entire stomach wall up to the serosa, but far into the periphery, as sections through human gastric ulcers show. However, it is often possible to show that these fibrous thickenings of the serosa extend mainly toward the oral side in correspondence with the typical funnel shape of the ulcer. Thus there comes about the powerful drawing up of ulcers of the gastric pathway toward the cardia. Now to what is this intense inflammatory irritation, this necrosis of granulation tissue, to be attributed? Up to the present, it has been generally accepted that it was the action of the gastric juice that killed the reforming granulation tissue. Through this necrotic layer, the leucocytes wandered from below and deposited themselves, while beneath it, new granulation tissue formed. Against this view of the corrosive action of the gastric juice, it has been objected that there should be demonstrable an equal corrosion of the base of the ulcer, whereas in reality very diverse pictures are found. Consequently another cause for the more circumscribed necrosis of the base of the ulcer was sought, and it was believed the cause must be seen in the invasion by the Oidium albicans. This assertion made by Askanazy

has, however, not been verified. Oidia are, indeed, frequently to be demonstrated in gastric ulcers, but they are, so to say, found only as saprophytes in the dead layers, but not in the living tissue itself. More accurate researches show, too, that the irregular formation of necroses on the base of the ulcer are attributable to the varyingly strong influence of the gastric juice, since morphologic remnants of the gastric contents are to be found now here, now there, but especially in the infundibular angle. What results in reference to the question of the structure and the cause of chronicity of ulcers do the experiments of Yano give? They show quite unequivocally that even in the rabbit, the characteristic shifting of the wound edges occurs under the influence of the peristaltic contraction of the stomach. Though these displacements are not always to be recognized in the mucosa, they are the more prominently to be seen in the muscularis proper. This shifting occurs simultaneously with the breaking through of the mucosa. When somewhat larger areas of the musculature are necrotized by the cautery, the necrotic piece is forced straight upward. At the same time, the oral wall shifts sharply upward, toward and right over the ulcer, while in the aboral portion, the musculature does not participate to a like degree, and thus the ulcer, contrariwise, shifts over the musculature. Thus there develops an extremely characteristic picture which becoms more and more distinct, and which is found time and again in the chronic gastric ulcer of human beings in the form already described by Hauser. On the oral side, the muculature tapers out above toward the edge of the mucosa by which it appears to be completely covered, while on the aboral side, the musculature, more or less frayed out, terminates in the ulcer base. I cannot here elaborate on all the particulars of ulcer formation. I believe, however, that from these descriptions, the peculiar working forces of the active stomach are easily recognizable. In the ulcers of the rabbit, furthermore, it may be established that their chronicity depends, not on invasion by fungi, but on the action of the gastric juice itself. At most, it might be believed that continually recurring vascular spasms produced a new anemic necrosis, and thus created a new area for digestion. In the rabbit,

however, such spasms, without any special intervention, are hardly conceivable. In the human, they may perhaps play a part, but this must here remain undiscussed.

I believe that the experiments of Dr. Yano show that, as in the human, the mechanical structure of the gastric pathway must be invoked in explanation of the poor healing and characteristic form of ulcers. Finally there remains one last problem to be discussed, namely, that of influencing the poorly healing ulcer of the gastric pathway, once it has developed. Because of the nature of the diet, we had to dispense with a "protection therapy" in the rabbit. All the more should the problems engage our attention, as to whether the healing of ulcers is in any way to be influenced by an increase or decrease in the contractility of the musculature. From this point of view, the experiments with atropin, which is used in the treatment of human gastric ulcers, were particularly noteworthy. Now, the rabbit's stomach is quite different from that of the human, and pharmacologic data are not directly applicable from one to the other. Nevertheless, this fact is worthy of report, that all artificially produced defects, even those in the region of the fundus, showed a poorer healing tendency under the simultaneous atropin treatment than without atropin. Doubtless, the loss of tone of the whole stomach, and the decrease in its contractility add considerably to the diminution of the healing tendency. In a second experimental series, it could be shown that vagus section also exercised a marked restraining influence on the healing of the ulcer. Such vagus lesions may have a certain significance for the surgeon, in so far as the increased contractibility of particular regions more easily permits operative lesions to become ulcers. Therefore I shall touch briefly on the question of the postoperative ulcer. On the basis of my anatomical experience, I am convinced that some sort of injury must precede the formation of an ulcer. In resections and gastroanastomoses, this injury occurs mainly at the site of suture, or at the sites where the stomach and intestinal clamps lay. Also, in my opinion, the greater or lesser capacity of the sutured mucous membranes to cover and protect the operatively produced defect, no matter how small, plays a great rôle (Oshikawa, Gaza). But in this

covering over, the muscularis mucosae and its muscular system radiating into the very mucosa, is of particular significance. Everything that hinders the covering up of the defects in the mucosa, or that, in consequence of the operation, leads to large necroses or hemorrhages of the mucosa, must favor the development of a postoperative ulcer. Paralyses of the gastric nerves occasioned by the operation belong here. Naturally I am not unaware that an abnormal increase of the action of the gastric juices may unfavorably influence the healing of the defect and thus produce a postoperative ulcer. The striking observations made in Germany by Enderlen, Freudenberg and von Redwitz and others, concerning the influence on the second phase of gastric digestion in the stomach with pyloric exclusion, speak in favor of this. Under the influence of the excluded pylorus, a particularly powerful gastric juice develops in the corpus and, indeed, at the time when the chyme has already left the stomach. It is absolutely conceivable that such an increased powerful gastric secretion may transform mild, slowly healing operative defects into true ulcers. Consequently, in Germany, exclusion of the pylorus is, wherever possible, avoided, and the more extensive resection favored by surgeons.

To return again to our rabbit experiments, drugs such as pilocarpin, adrenalin and ergot, which increase contraction, have no particular effect unless in the sense that with them the ulcers healed somewhat more slowly than when the stomach was left alone. It may well be that as a result of the severe contractions of the gastric wall, caused, for example, by pilocarpin, the vascular supply to the ulcer also suffers, and thus the beneficial effect of approximation of the mucosa is vitiated by the poorer blood supply.

And now I believe I ought to terminate my communication on the latest researches in the field of gastric ulcer, in so far as I have been able to follow them in Germany. From the above it follows that practical medicine has two great purposes: first, the prevention of the so-called erosions or hemorrhagic ulcers in the region of the gastric pathway; second, the prophylaxis against the transformation of these acute ulcers into a chronic ulcer, which is identical with the promotion of healing of these ulcers. As far as the first task is

concerned, doubtless the treatment of the nervous disposition plays a great part. Whether these nervous spastic conditions of the stomach are first precipitated by some other disease, as Roessle assumes, so that the development of gastric erosions and then of gastric ulcer is to be regarded as a secondary disease, appears to me to be questionable. It is just here that the hemorrhagic erosions in the fundus, which we actually see developing secondarily to appendicitis, appendectomies, meningitis, etc., are confused with the erosions of the gastric pathway. They must not, however, be put on the same plane. One must always remember that such spastic conditions of the stomach may be produced in the isthmus region during the digestive period by the irritation of the stomach itself. The character of the diet may play a great part. If the mechanical functional peculiarity of the gastric pathway is of great significance here, then in the solution of the second problem, (i.e., the rapid healing of already formed erosions, so that any ulcer with all its consequences may not develop from the erosion) it is a decisive factor. Only a thorough-going "protection therapy" which avoids a too severe or too prolonged burdening of the gastric pathway, which prevents too marked a spasm of the isthmus, can lead to the goal. Such a therapy, however, is equivalent to a prophylaxis against the development of new erosions, and thus of new ulcers. Therefore, in addition to this general therapy, *proper diet* will always be one of the most important factors in the medical advice to people predisposed to ulcer. From the surgeon, it demands the most careful avoidance of unnecessary losses of substance in the operative field, such as suture sites, the avoidance of operative procedures which enhance the action of the gastric juice, particularly during the empty interval of the stomach, the careful choice of diet for the protection of the sick and the still healthy portions of the stomach. As a pathologist, I fear to utter such sentences, because they are either quite familiar to the clinician or, in the mouth of the pathologist, appear as unfounded on personal experience. Still, as a pathological anatomist, I feel bound to correlate our pathological experimental experiences with the clinical picture, in the hope that

new therapeutic pathways may appear to you, if not new, at least, as old ones better founded.

NOTE. The lantern slides used in this lecture may be ordered through The Bildarchiv, Freiburg i. Br.

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YANO. Künstlüche erzeugung v. magengeschwieren (will be published).

XIII

THE GOITER PROBLEM, ESPECIALLY THE GOITER OF PUBERTY

A MORPHOLOGICAL STUDY

It is something of a venture to talk on the goiter problem in this country where so many distinguished investigators—Gaylord, Marine, Lenhart, Plummer, Kendall and Boothby have worked with such great success on the same problem and on an exceptionally broad basis of comparative pathology, of biochemistry and of internal medicine. The first papers of my friend Gaylord, in whose institute in Buffalo I was privileged, twenty years ago, to share the interesting observations on the goiter of Salmonidae, made a deep impression upon me. These goiters have a remarkable similarity to certain goiters found in man in Basedow's disease, or, as you call it, Graves' disease; and this curious fact, together with the observation that they can be influenced by iodine, sublimate and other antiseptics to a certain degree and can be reduced to the normal, has again and again returned to my mind. When I moved from Marburg to Freiburg in the Black Forest, which is a typical goiter region, I was again induced to turn my attention to this problem. As a pathologist I naturally endeavored to bring order into the varied forms of goiter formations, on the basis of anatomical and histological principles, before trying to solve the problems of the functional significance of the different forms of goiter and their clinical appearances.

Since that time I have had no personal contact with the American investigators of goiter except Gaylord, and have only now, since the war, been able to find out the essential results of their work. We have therefore followed our own path in Germany. I know very well that the results of our investigations cannot be compared with yours, and you will

understand that the conditions of war did not afford the necessary leisure and facilities to solve scientific problems of this kind. If I venture, nevertheless, to bring before you our investigations on goiter I do so mainly because I believe that our observations may supplement your results. As you know, Germany consists of a North German plain, which is apparently free from goiter, and a South German mountainous country, which contains many cases of goiter, and therefore offers us excellent comparative material for the study of the thyroid gland in goiter-free and goitrous regions. If in my observations I do not refer to the American literature in detail it is because I wish to give you an independent picture of our own observation and conclusions.

When, eighteen years ago, I came to Freiburg, I had an opportunity to make a thorough study of extensive operative material supplemented by the investigation of post-mortem material. At that time, in the year 1906, only two forms of goiter were distinguished, from the clinical point of view; namely the Basedow goiter and the mountain goiter proper, with the latter of which cretinism was placed in close relation. For the present I shall not deal with the Basedow goiter, because it is a separate form, and has nothing to do with the true goiter formation. The true mountain goiter appears as a problem of locality, while the Basedow goiter is not localized, but manifests itself all over the world. I shall therefore at first deal only with the mountain goiter, by which I mean the mountain goiter of Baden. You will see later that even mountain goiter is not everywhere the same, but has special varieties that seem to be dependent on the soil on which the goiter has arisen.

No further distinctions in the mountain goiter were made by surgeons or clinicians except that they referred to the varying colloid content, or the hemorrhagic character, or the fibrous character, etc. A main distinction, namely, the separation of the nodular struma from the diffuse struma, was not sufficiently recognized. This distinction seemed to me to be one of the main tasks of morbid anatomy. I have, therefore, from the beginning, demanded a clear distinction between the *struma nodosa* and the *struma diffusa*. On this principle the various forms of mountain goiter have been

studied by my pupils, Kloeppel and Kraemer. We were able to show that the nodular form was not a kind of hyperplasia or hyperplastic condition, as was then believed, but that we were dealing with a definite tumor formation, namely, adenomata. These adenomata were not the result of a development of fetal rests—the so-called adenomata of Wölfler—but in agreement with the school of Langhans, especially with the investigation of Hitzig and Michaud, we found that these nodular adenomata have their origin almost without exception in the ordinary thyroid-gland tissue. Based on the observations of one of my pupils—Kraemer—I was enabled to show that the epithelial proliferations which lead to these adenomata have their origin mainly in the centrally situated follicles of the thyroid lobules. These central follicles are mainly distinguished by their irregular, often elongated, even branching, form. Their epithelium is usually a little higher and more darkly stained than that of the rest of the follicles, and they contain a little colloid. I have designated these peculiar follicles as central canaliculi, and look upon them as rests of the germ material from which the other follicles of the thyroid lobule have developed. One might also call these central canaliculi the germ layer of the thyroid lobules. It is indeed peculiar that it is just from this apparently not fully differentiated epithelium that those proliferations take their origin which lead later to the adenomatous nodules. Recently the derivation of the adenomata from these central canaliculi has been disputed and it has been said that such adenomatous formations may arise in any part of the lobule from any follicle. This led me to reinvestigate this point together with my pupil Dr. Bürkle de la Camp, and I must maintain that only the epithelium of these so-called central canals has a special predisposition to the formation of adenomata, a view which seems rational if we look upon these central canaliculi as incompletely differentiated germ material of thyroid tissue.

The smallest adenomata appear as darkly stained epithelial follicles lying closely together and having practically no content. As they increase, they displace more and more the tissue of the lobule and eventually produce an atrophy by pressure of the neighboring lobules. In this way these

nodules grow, beginning with microscopic size and reaching eventually the size of a fist or of a child's head. As they grow, they form a more or less distinct capsule, which delimits them clearly from the normal thyroid-gland tissue. As long as they have no capsule of their own, as is the case with nodules having the size of a pea or a cherry stone, the distinction is not so simple. It is then possible, if one does not have a good deal of experience, to look upon the whole proliferation as a hyperplastic process and to fail to recognize that one is dealing with a real tumor formation. I lay great stress upon the distinction between simple hyperplasia and tumor formation, because with a simple hyperplasia one must assume at once a hyper-function, while with a real tumor formation there may be hyper-function, or dysfunction, or hypo-function. There is a simple test to distinguish hyperplasia from tumor formation. We know from the study of all other organs that in functional hyperplasia the detailed structure of the organ is maintained. Thus hyperplastic parts of the kidney show the normal proportion of glomeruli and tubules: hyperplastic parts of the pancreas or salivary glands show the typical arrangement in lobules. We may thus expect in a hyperplasia of the thyroid gland that the individual lobules are enlarged, but that the division into lobules as such is maintained. But what do we see in these nodular formations? From the beginning there is a complete absence of division into lobules, and this manifests at once their nature as new growths. These adenomata of the thyroid illustrate beautifully the doctrine of Ribbert of the unicentric growth of tumors. Ribbert had at first applied this theory only to malignant new growths. It could be shown, however, without difficulty, that the benign neoplasms also grow as a rule from a single center (Simpson). It is now a well-known fact that the oldest parts of every tumor, that is to say, the central parts, undergo destructive processes, while growth proceeds at the periphery. It is, therefore, clear that with increasing duration of growth there must be a more or less clear distinction between center and periphery, and this is very markedly represented in the adenomata of the thyroid gland. Further, it can be shown that all the various forms of nodular goiter which one has distinguished as fibrous,

hemorrhagic, cystic, etc., are nothing else but different stages and forms of involution of the center of the growth. Again, it is a well-known fact that in slowly growing tumors the involution or degeneration of the ageing tumor cells in the region of the growth center also proceeds slowly, so that the connective-tissue framework, the so-called stroma of the tumor, has time to adapt itself to this process of involution. In this way we get a gradual disappearance of the specific tumor tissue in the center of the tumor node, and a replacement by abundant stroma, which, as a result of all kinds of secondary changes, assumes a fibrous, a hyaline, or a gelatinous character. We see then microscopically in the center of this struma nodule a whitish, almost scar-like, frequently radiating tissue which may replace the greater part of the node, so that in such a case one speaks of struma fibrosa. Such a struma fibrosa can further, by the deposition of lime salts in the fibrous parts, or by secondary bone formation, be transferred into a struma calcificans or struma ossificans. We see such a transformation produced, as a rule, in the so-called parenchymatous forms of the adenomata, in which there is little tendency to the formation of colloid, and where there are solid follicles or cell accumulations in the form of trabeculae.

In other cases the struma nodosa parenchymatosa is transformed into a struma nodosa colloides by an accumulation of colloid similar to that found in normal thyroid tissue. We find, then, the same picture of rapid or slow colloid formation as we shall see later in the colloid tissue proper. We call such nodes or nodules struma nodosa colloides. They too are subject to the typical involution processes in their center, but here there may be other forms of involution either replacing the fibrous transformation or taking its place. What is the nature of these involutions? Mainly hemorrhages that occur into the larger follicles filled with colloid, or between them, and disintegrate the tissue. We shall see later what the explanation of these hemorrhages is. In any case the occurrence of such hemorrhages is facilitated by the involution processes proceeding in the central parts and destroying the epithelium of the large follicles. This, when followed by necrosis and softening of the whole center, may

lead to the formation of enormous cysts filled with blood. These are, as a rule, not covered with epithelium—so-called false cysts—which may be filled with fresh or old blood, or even with atheromatous pulp. We speak, then, of struma nodosa cystica, struma nodosa hemorrhagica, struma nodosa atheromatosae. All these various forms of struma nodosa are, as I have just been trying to show, nothing else but phases of development and involution of the same kind of neoplasms within the thyroid gland, namely, the adenoma of the thyroid which is usually called struma nodosa. I maintain therefore, that all these nodules without exception represent *true neoplasms* whose significance for the organism is quite different from that of normal thyroid-gland tissue or that of a hyperplastic thyroid-gland tissue. Before I leave the adenomata of the thyroid gland I wish to refer briefly to certain of their peculiarities. I do not wish here to refer to the finer histology of the gland or of the epithelium of the follicles, which has been studied by Scott, Williamson, J. H. Pearce, Nicholson and others. I restrict myself to the goiter problem. We know from other tumors that their blood supply is different from the mother tissue in which they grow. We find this to be true also in the adenomatous nodules. Monogenow could show that the blood vessels enter and leave the nodules as a rule only in one or two places, so that the nodule is hung up, so to speak, on a vascular stem. One can, therefore, readily understand that as the result of external mechanical factors affecting the thyroid gland, such as coughing or other sudden disturbances of the circulation, the circulation within the nodule may be disturbed by congestion or kinking. In this way we can easily understand the great tendency of the struma nodules to hemorrhage. In the same way as the inflow and outflow of blood, the outflow of lymph may be disturbed or inhibited. While in the normal thyroid gland we only exceptionally see the colloid-like substance in the lymph spaces of the tissue, the accumulation of colloid between the follicles of the struma nodosa colloides is a very common occurrence. This, too, manifests at once the true tumor nature of these nodules. It also shows that the specific product of these follicles is retained within these nodules and cannot therefore exert its action on the whole

organism to the degree that corresponds to the size of the nodule. Indeed, it is quite conceivable that such a nodule, in spite of an abundant colloid formation, may have no physiological effect at all on the organism, just on account of these peculiar anatomical arrangements. The possibility that a part of the active substance is carried away by the blood cannot of course be denied, but so far as I know the literature on this point, nothing is known. I believe I am entitled to insist on the basis of these investigations of Kraemer upon the clear distinction of struma nodosa and struma diffusa.

This leads at once to the second question: *What is the primary cause of that which appears clinically as goiter?* Originally goiter meant nothing else but thickening of the neck through enlargement of the thyroid. Is then the mountain goiter due essentially to the adenomatous new formation, or to an increase of the normal thyroid-gland tissue? Clinically, no attention was paid to this distinction. The true mountain goiter was looked upon essentially as a so-called nodular hyperplasia of the thyroid gland, although one knew that there are also diffuse enlargements of the thyroid gland. But the relation of diffuse hyperplasia and nodular tumor formation was not clearly recognized. It seemed necessary, therefore, to carry out a systematic comparison in which use was made of the thyroid material of the North German plain. At my suggestion Dr. Kloeppel carried out such a comparative study in 1909 on the thyroid glands of all ages from Berlin, from Göttingen and from Freiburg. Berlin belongs to a so-called goiter-free region; Göttingen was situated in the North German plain, adjacent to the foothills of the Hartz mountains, so that an influence on the thyroid gland in that region seemed possible. Lastly, Freiburg is the center of a large goiter region. This study led to the important conclusion, confirmed later by Isenschmidt and Hesselberg in Langhans' Institute, that the thyroid gland of the newborn in the so-called goiter countries, that is to say, in Baden and in Switzerland, has a heavier weight than the thyroid gland of the newborn in Göttingen, Berlin and the sea-side town of Kiel. For the other age periods, too, it was possible to show that the average

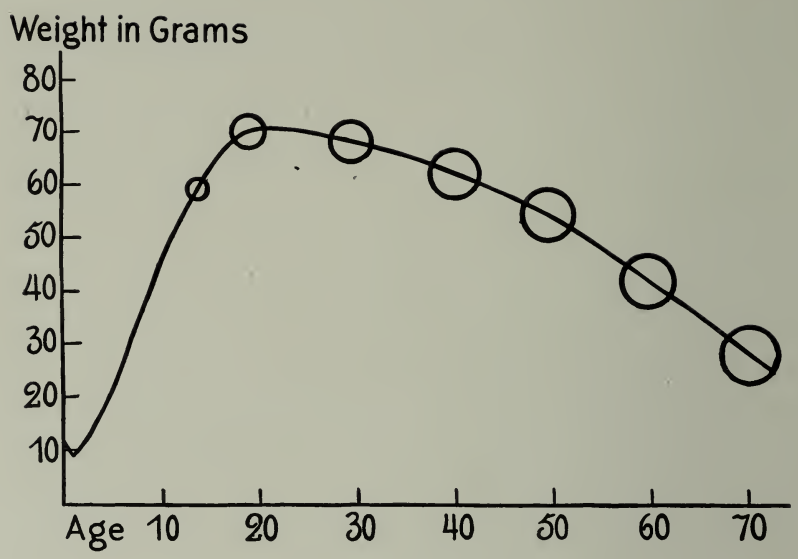

FIG. 30. Thyroid in the so-called goiter region.

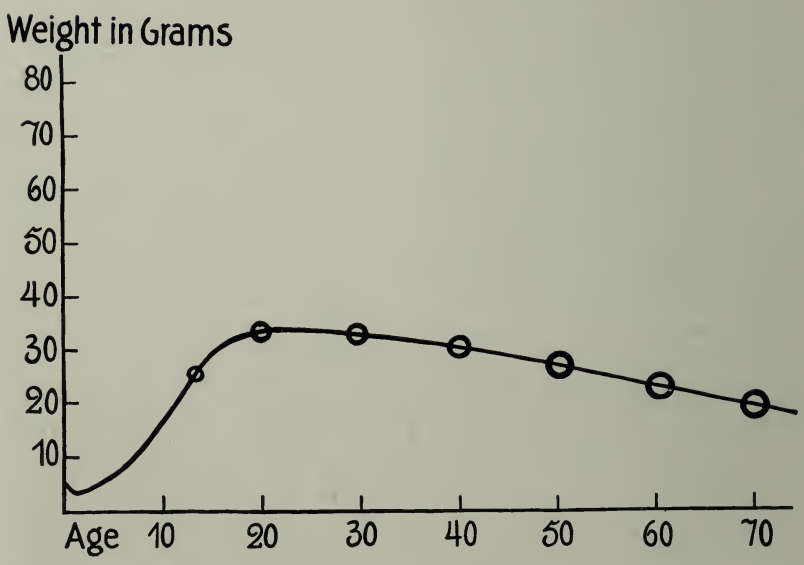

FIG. 31. Thyroid in the so-called goiter-free region.

weight of the thyroid in the goiter countries, even when it had been freed from nodules as much as possible, was heavier than that of the thyroid gland in the plains.

On the other hand, it was found that the thyroid gland from the North German plain showed the same formation of nodules, that is to say, adenomata, as in the so-called mountain thyroids. The number of the nodules, too, was, on the whole, the same in the thyroid glands from the plains and from the mountain countries. But there was this essential difference: that these so-called adenomata of the thyroids from the plains could frequently not be recognized macroscopically and could be seen only microscopically, while in the thyroid glands from the mountainous countries they used to grow to a frequently astonishing size. These investigations led, therefore, to the conclusion that the thyroid from the mountains, that is to say, the thyroid of the goiter countries, has from birth on and during the whole life, on the average, a much higher weight than that from the plains, or the goiter-free countries. Secondly, the adenomata or tumors that develop in both types of thyroid apparently with equal frequency are insignificantly small in the thyroid gland from the plains, but remarkably large in that of the mountains. One had the impression that one was dealing here with a kind of tumor rest that exists in every human thyroid gland and begins to develop at a certain time, but that these tumor rests show virulent growth only when they are, so to speak, sown in a favorable soil. This favorable soil is the thyroid of the mountain countries, which, to judge from its weight, is during the whole life in a state of increased functional activity as compared with the thyroid gland of the plain. The greater development of the adenomatous nodules appears, therefore, merely as a result of an increased functional activity of the mountain thyroid generally. The tumor formation thus appears as a secondary process which does not represent the essential goiter problem. The essential problem is: Why does the thyroid gland in the mountain countries, that is to say in the goiter countries, show a diffuse enlargement during the whole life, even from birth? Indeed, in newborn children we find occasionally the thyroid gland so strongly developed that it

actually embraces the air passages and esophagus, and may, in fact, kill some children through asphyxia, as the result of the excessive enlargement of the gland. This shows at once how important the goiter problem is for us. There is in addition, as a result of the excessively developed adenoma formation, the possibility of all kinds of mechanical disturbances of respiration in later years, apart from the other general disturbances of metabolism related to the diffuse hyperplasia of the gland.

All these considerations lead us to conclude that the goiter problem is identical with the problem of the diffuse hyperplasia of the gland, and not with the formation of the nodular goiter, as was erroneously believed. It is easy to understand that the surgeon is mainly interested in the nodular struma and in the formation of the nodules, since these factors are the immediate cause of the mechanical disturbances; but for the theoretical investigation of the problem, the formation of nodules is of much less importance than the diffuse enlargement. We decided, therefore, in the years before the war, to institute a Committee in Freiburg for the investigation of the diffuse enlargement of thyroid gland by clinical and pathological investigations. I do not wish to trouble you here with all the theories of the cause of goiter. So far as our country was concerned we could not confirm either the theory that the water was the etiological factor, or that the geological formation of the soil was of importance. I shall refer to this point again later. The systematic prophylactic experiments of Marine and Lenhart, as well as the interesting discovery of thyroxin by Kendall, have placed today the iodine theory in the foreground. Numerous physicians in Switzerland and in Germany have attempted to influence goiter by the systematic administration of iodine. As a pathologist I have no personal experience on this point. I can only say that the statements of the Swiss physicians, who have carefully investigated their material, agree with the statements of Marine and Lenhart, that one can indeed induce a diminution of the thyroid by the administration of iodine. Dr. Eckstein of the Freiburg Children's Clinic, has carried out observations over longer periods, which have given us the surprising result that the goiter of children, if

measured by the circumference of the neck, is subject to considerable variations, so that one can never be quite sure to what extent the iodine therapy can be made responsible in each case for regression of the thyroid. On the whole, however, it can hardly be doubted that the iodine does influence the hyperplastic thyroid gland, as indeed Gaylord had already shown in his fundamental experiments. We have tried to study experimentally the action of iodine on the thyroid gland in animals. Unfortunately we could not imitate the experiments of Marine and Lenhart in Germany, because neither in the goiter countries of Germany, nor, as fat as I know, in Switzerland, do the domesticated animals show hyperplastic thyroids to the same extent as man. At my suggestion Büdel has investigated the large material of our slaughter house in Freiburg and has compared the histological results with the material from North German slaughter houses in Dresden and Kiel. Our investigations comprised cats, dogs, pigs, goats, sheep, calves, cattle and horses. Except the calves, all these animals were fully grown. No very great differences were found between the thyroid glands of the animals from the mountain countries and those from the plain. It is possible that investigation on even larger material may reveal greater differences. We could only find that the average weight of the thyroid gland of the animals in Freiburg is a little higher than that of the animals in the North German plain. Unfortunately, we could not always obtain the weight of the animals, so that the relative weights could not always be calculated. Histologically, the thyroid glands in Freiburg showed a slight proliferation with a little thinner colloid, as compared with the quiescent form with relatively small follicles filled with colloid, of the gland in the North German animals. It was also noticeable that in the North German animals colloid was frequently found in the lymph spaces, while it was a rare occurrence in the animals in Freiburg. One had the impression that the colloid of the North German thyroids was more viscous. Only very few cases of adenomatous struma formation were observed. They are undoubtedly a rare occurrence in our Freiburg animals. You see, therefore, that the conditions in Germany are quite different from those in America, where there are

undoubtedly regions in which, as the observations of Marine and Lenhart have shown, the domesticated animals also show a diffuse or nodular enlargement of the thyroid. I can add that even in our trout-breeding places there have never been goiter formations nor an epidemic of goiter, although I have made a special point of inquiring into this matter. And it is interesting that the same mountain water is used by man and animals.

Since our animal material was unsuitable for experimental work, and since even rats kept on the so-called goiter-water of the Black Forest did not show any alterations, we had to rely for the further analysis of the goiter problem on observations on man. Before I deal with this I wish to refer briefly to experiments of Dr. Tanabe which gave the following result. He wanted to see by a comparison of rats from Berlin and from Freiburg how the thyroid gland of these two groups of animals would be affected by food differing in its iodine content. He found that with mixed food and ordinary water both the Freiburg and the Berlin rats showed normal glands, that is to say, fairly large follicles filled with colloid with a low epithelium that did not show any mitotic figures. These glands showed no congestion. The water in Freiburg is relatively poor in calcium. If, now, these rats, either the Berlin rats or the Freiburg rats, were fed with meat, vegetable and barley and received in addition either Freiburg water or distilled water, the animals showed a peculiar change in the thyroid gland which assumed a more parenchymatous character. The colloid disappeared more or less from the follicles, the epithelium became remarkably high and showed almost mitotic figures in varying numbers. These glands were remarkably hyperemic. The effect of this kind of feeding was accentuated by the addition of lime salts. Then the mitotic figures became quite numerous. The whole effect of this feeding with meat, vegetable and barley, as well as the effect of the lime salts, could be prevented by the addition of potassium iodide, that is to say, the *lime salts* and the *iodine salts* have an *antagonistic action*. The formation of colloid now proceeds in the normal manner. Whether the food which imposes upon the thyroid gland a parenchymatous character produces its effect by a relatively

small content in iodine, or whether there are other substances which are concerned in this action, we have not yet been able to determine. This much, however, is certain: that bacterial contaminations of the water cannot be responsible for this peculiar parenchymatous transformation of the thyroid gland, which also leads to an increase in its volume, that is to say, to a real diffuse goiter formation. For we could obtain the same change in the rats that were fed with distilled water. On the other hand, it could also be shown that the enlargement of the gland is determined not only by a relative lack of the common iodine, but also by a relative excess in lime. It does not follow, however, that these two are the only determining factors, for it is probable that the nutrition, on the whole, will also play a part. The antagonistic effect of calcium ions to iodine containing thyroid preparations has also been pointed out by others, especially by Japanese investigators.

I propose now to deal with our goiter material and begin by giving you our classification.

You will find that our division agrees, on the whole, with that which has been worked out by the American authors. The only differences are the frequency of the occurrence of the various forms and the significance we attach to them. The table shows at once that we distinguish a *goiter of the newborn.* In this we have a diffuse enlargement without colloid formation. For these goiters of the newborn, as well as for the thyroid of the newborn generally, a physiological desquamation has been described and a physiological significance attributed to it. It is indeed true that in the thyroid gland of every newborn infant there is abundant desquamation, especially when the baby has died during birth. I believe, however, that this so-called desquamation of the thyroid epithelium in the newborn represents mainly a post-mortem process. The very hyperemic thyroid of the newborn is exceptionally sensitive and suffers so many mechanical injuries as the result of manipulation when it is taken out, that this alone explains a good deal of the desquamation. One can prevent this desquamation when one fixes the thyroid in situ, as Heinemann has done by injecting a hardening fluid soon after the child has died. This shows

quite clearly that we are dealing with a post-mortem process. The struma diffusa parenchymatosa neonatorum shows a uniform diffuse enlargement of the thyroid gland, and not merely a hyperemia.

CHART I

A. Hyperplasia of the thyroid gland.
(Struma diffusa)
1. Struma diffusa parenchymatosa neonatorum.
2. Struma diffusa colloides macro-follicularis.
(*a*) Proliferans. (*a*) Hyperthyroidism (slight and severe degrees). Thyroidism. Thyroidism from therapeusis. Formes frustes. Basedowoid. Thyroidic constitution.
(*b*) Non-proliferans. (*b*) More indifferent, suppression, slight hypothyroidism to cretinism.
3. Struma diffusa colloides microfollicularis (normal mountain thyroid of Wegelins).
4. Struma diffusa parenchymatosa Basedowiana. { Hyperthyroidism of severe degree. (*a*) With Basedow triad. (*b*) Without Basedow triad. }
5. Struma diffusa colloides Basedowificata.
B. Hyperplastic-adenomatous form.
6. Struma diffusa et nodosa colloides hyper- and hypothyroidism (Proliferans or non-proliferans)
C. Adenomatous form.
7. Struma nodosa simplex. Hypothyroidism.
8. Struma nodosa Basedowifacata. Hyperthyroidism.

The second group of goiter is the *struma diffusa colloides*. This type of goiter represents the greatest percentage of operative material from young people, and to it we have devoted special attention. We believe that the designation "struma diffusa colloides" is not exhaustive because it comprises too many different groups. In Germany, Hellwig was the first to distinguish between macro- and microfollicular forms. Both the macroscopic and the microscopic appearances of these glands show differences. Both show the characteristic distinct glistening of colloid *rich* struma as compared with the more fleshy appearance of the struma of the newborn. The difference between these two types of colloid goiter consists in this: that with the macrofollicular

form one can distinguish with the naked eye the relatively large colloid-containing follicles which sometimes show cystic dilatation, while the microfollicular form requires a lens to demonstrate this. Between these two types there are all kinds of transition stages, so that with the naked eye the distinction is not always easy. Nevertheless, as we shall see presently, the distinction must be maintained and can be recognized without difficulty under the microscope. The macrofollicular goiters are, as a rule, heavier than the microfollicular goiters. Microscopically they show remarkably large follicles, although the diameters of the varying follicles show great variations. In addition to exceptionally large follicles there may be others of a medium and small size. The essential point is that, on the whole, the follicles are enlarged, and that their content appears very fluid. As I shall point out later on, Hellwig has found this type of macrofollicular struma mainly during puberty. It was difficult to relate this macrofollicular struma with the clinical symptoms. These difficulties could be surmounted only by a further histological study of these forms. This was carried out by Dr. Bürkle de la Camp and led him to distinguish two subdivisions. He recognizes a proliferating and a non-proliferating form of the macrofollicular struma. The proliferating form is characterized by the development of so-called buds of proliferation in the individual follicles. Even in the normal thyroid it can be seen that the epithelium of the individual follicle does not show a uniform behavior. Its thickness varies, so that on one side of the follicle the epithelium may be a little higher than on the other. This differentiation is even more pronounced in the more rapidly growing follicles, as they occur in the diffuse macrofollicular gland. One gains the impression that each follicle has within its epithelial lining a special germ layer, just as the whole lobule has its germ layer in the so-called central canaliculi. This germ layer of the follicle is distinguished by the existence of a cubical or almost cylindrical epithelium, while the remaining circumference of the follicle exhibits a more flattened epithelium, especially on the side opposite the germ layer. One is almost forced to the conclusion that the follicle, as it grows on one side, is undergoing a pressure atrophy on the other

side. Personally, I have no doubt that with a specially active growth of the follicles, such as one sees in the adenomata, which, as we shall see, are particularly rich in follicles, there is a rupture of the follicles through the increasing tension, so that the contained colloid is being poured free into the tissue. As this one-sided growth of the follicles proceeds, the germ layer, or the germ spot of the follicle, is bulged slowly forward into the lumen, and forms a kind of wart-like bud, within which a further segmentation of the epithelium and new formation of smaller follicles may occur. Their continued growth, together with the subsequent formation of new growth buds leading to new thyroid tissue, slowly brings about a great enlargement of the whole gland. We have here a repetition of the new formation of thyroid-gland follicles as it accompanies the growth of the gland of the newborn. The only distinction is that we are dealing here with a new formation in fully formed follicles, and only in certain places of these follicles; while in the gland of the newborn a uniform and diffuse segmentation leads to the formation of new follicles from old follicles, in such a way that only the central canaliculi remains as material which has not been completely used up. It is probable that this process of proliferation is particularly active in the large follicles derived from the central canaliculi. We base this view on the more central situation of the follicles that show growth buds, but it must be clearly understood that the ordinary follicles also participate in these growth processes. We propose to call this type of the macrofollicular goiter the "*struma diffusa colloides macrofollicularis proliferans.*"

This form differs from the other form of the macrofollicular struma merely in the absence of these processes of proliferation. Only here and there one can see a growth bud. One has the impression that the growth energy of the thyroid gland is exhausted and that the final stage has commenced. But this struma too is built up of large follicles with thin colloid and cannot therefore be readily distinguished macroscopically from the other form. We call it the *non-proliferative form of diffuse macrofollicular colloid goiter.* We wish to emphasize that we have not found any special colloid in the lymph spaces of these goiters.

We come now to the *microfollicular form of the colloid goiter*. The thyroid gland is, on the whole, enlarged and rich in colloid. The follicles are larger than in the normal gland, but not so large as in the macrofollicular form. The colloid is thickened. We look upon this form as identical with Wegelin's mountain goiter.

In addition to the diffuse colloid goiter we have to recognize as a further form the diffuse parenchymatous goiter. It is essentially an enlarged struma of the newborn infant in which the formation of colloid disappears and the follicles consist merely of a narrow lumen with a high, almost cylindrical epithelium. The lobules are enlarged and the number of the follicles is increased. In the central canaliculi with their elongated form, one can often see conditions resembling the gland of Basedow's disease. In this form the new formation of the follicle follows a type of the newborn gland. The differentiation of the individual follicles has not yet taken place to the same extent as it is found characteristically in the diffuse colloid goiter. The lack of colloid, too, indicates a more infantile type of this struma. We mention it here as the fourth form, because in our material it is comparatively rare.

The so-called *Basedow thyroid* must be clearly distinguished from this diffuse parenchymatous goiter, because the Basedow gland does not represent a real goitrous enlargement, but merely a hyperplastic condition of the gland, associated not so much with new formation of follicles as with a peculiar transformation of them. I need not here refer to the characteristic peculiarities of the Basedow thyroid with its transformation of the epithelium to a high cylindrical epithelium and its tendency to the formation of papillae. These characteristics and the abundant presence of lymphoid tissue in the Basedow gland are well known. I may point out, however, that lymphoid tissue is found also in the diffuse colloid goiter, especially in the proliferating form, but it is not as abundant as in the Basedow gland.

We must distinguish between the *Basedow gland* and the *Basedow goiter* proper. In the Basedow goiter proper we have a real increase in the thyroid-gland tissue which represents, as a rule, the struma diffusa colloides which has subse-

quently undergone a partial or complete transformation to the Basedow thyroid. These glands are larger than the ordinary Basedow thyroid, but resemble the latter in their fleshy appearance and in their microscopic structure. If the remains of the old colloid struma are still present in such a gland the microscopic picture will, of course, be very varied. I have never seen a transformation of the diffuse-parenchymatous goiter into a genuine Basedow thyroid, but such a possibility cannot be excluded and certain observations of the Vienna school are in its favor.

So far I have dealt only with the diffuse types of goiter which I regard as being of special importance. This diffuse type may now be complicated by the formation of adenomata which may be more or less abundant and more or less typical. If the diffuse enlargement of the thyroid is the outstanding change we speak of a "struma diffusa et nodosa." If, on the other hand, the formation of nodules dominates the picture, the designation "struma nodosa simplex" is more appropriate. I have already dealt with the various types of the formation of these adenomatous nodules. One should distinguish two main forms: first, those where the formation of adenomata is still proceeding. According to their structure, one would distinguish here struma nodosa parenchymatosa or struma nodosa colloides, and in the latter one would again have to distinguish the proliferating and the non-proliferating form. In contrast to these progressive forms of the adenomata one would, secondly, have to separate the involution forms as struma nodosa fibrosa, struma nodosa cystica, hemorrhagica, etc. If I add that in these adenomatous nodules changes of the Basedow type may appear, so that we can speak of a struma nodosa Basedowificata, I have exhausted the various types of goiter formation. The so-called malignant goiters I do not consider at all, because they represent a chapter of their own.

If we now try to interpret the *functional significance of these different goiters*, it will be best to begin by considering the various ages within which these various types appear. This will give us, so to speak, the life-cycle of goiter and will enable us to relate it to the life-cycle of the normal gland. From my observations on the material in Freiburg I have

arrived at the following results: The struma diffusa parenchymatosa simplex, that is to say, the goiter of the newborn, is found mainly in the newborn. Very rarely we have seen it also appear before puberty, or even after puberty. This type is rapidly replaced in our population by the struma diffusa colloides, mainly by its macrofollicular form. During the first few years of infant life until the changing of the teeth, we have never seen goiter, so that we may conclude that the goiter of the newborn rapidly disappears and that a new goitrous growth of the gland sets in only when the pre-puberty period is reached, that is to say between the eighth and the twelfth year. This growth period shows a further rapid increase during the puberty period between the twelfth and the eighteenth year. As the table shows, we find during this period mainly the diffuse macrofollicular proliferating colloid goiters. For Baden, the Black Forest and the neighboring Odenwald, they represent a genuine goiter of puberty. This type preponderates over all other types, especially over the nodular forms which, in fact, we have never seen in the pre-puberty period and which only begin to make their appearance during puberty. It looks as if, under the influence of the diffuse swelling of the gland as represented by the puberty goiter, the adenomatous germ centers become more distinct and grow more rapidly, without, however, as yet dominating the picture.

In the following post-puberty period from the nineteenth to the twenty-fifth year there is a gradual transition of the proliferating form of the macrofollicular colloid goiter into the non-proliferating form. Occasionally one even sees the microfollicular form. As with increasing age the growth of the skeleton ceases, there is, therefore, a gradual change in the appearance of the type of goiter. Macrofollicular colloid goiter becomes more and more rare, although it does not altogether disappear, and in certain cases it may be observed even in old age. The rule, however, is that the microfollicular forms and especially the adenomatous forms, become more and more frequent.

In the later periods of life, that is to say, after the forty-fifth year, the diffuse macrofollicular colloid goiters are very rare and are only found in very old age, as if there was a kind

of flaring-up of the juvenile functions of the organism, just as we find also the transformation of the bone marrow from the fatty type into the red-blood-forming type in old age. During the later age periods only the microfollicular forms of the colloid goiter persist. The parenchymatous type is rare, but the nodular types become now, more and more distinct, more particularly because the normal thyroid tissue undergoes a kind of regression with increasing age, after having been subjected to a goitrous proliferation. This age atrophy does not affect the adenomatous nodules, which, as we have seen, are of the nature of typical neoplasms.

The thyroid gland of Basedow's disease does not, of course, belong to the goiter forms, but I may point out that the Basedow thyroid can be found from the period of pre-puberty uniformly right up to middle age, but it is rare in the declining period of life, that is to say, from forty-five years on.

Having thus subdivided the different types of goiter and distributed them over the various age periods, how can we picture to ourselves its development? We have already pointed out that the so-called *nodular* goiter formation is, so to speak, a secondary effect. It is dependent upon the *diffuse* goiter formation, so that the question which we have to answer first is: *What is the origin of the diffuse goiter?* Here, too, a comparison with the thyroid gland of the goiter-free countries, especially the North German plain is necessary. We have already shown that the average weight of the glands is higher in Baden and Switzerland than in the glands from the plain. This refers to the period from fetal life to the middle of life. This, however, does not mean that in the plains we do not have changes throughout life in the thyroid gland, corresponding to those found in the hilly countries. References to the literature and our own observations have shown us that in North Germany the thyroid gland shows the same increase and decrease during life as in the mountainous countries. One does not describe these swellings as goitrous, probably because they are not so extensive and do not induce a lasting injury to the gland; but there can be no doubt that in the plains, too, the thyroid glands show an increase in the newborn and also during the pre-puberty and puberty period. This therefore leads to the generalization

that for all glands in all countries, both in the plains and in the mountains, there are definite life-cycles which can be best described thus:

1. Thyroid enlargement of the newborn.
2. Regression during infancy.
3. Thyroid enlargement during pre-puberty and puberty.
4. Regression in post-puberty.
5. Normal gland of the adult during the height of life.
6. Age atrophy of the gland in the decline of life.
7. Possible rejuvenation of thyroid function in old age.

If this conception is correct, it is easy to understand why in the goiter countries the real diffuse goiters appear especially during those periods when there is normally a hyperfunction of the gland, that is to say, firstly in the newborn, and then during the period of pre-puberty and puberty. The whole difference between goitrous and goiter-free countries is that the physiological enlargement of the gland reaches an unusually high degree in the goiter countries, so that they are recognized clinically as diffuse goiters.

One might express this view in this way: in the goiter countries the thyroid gland is sensitized so that it reacts especially strongly under the influence of the physiological stimuli which lead to enlargement and proliferation. Since the adenomatous rests are developed, as we have seen, in all thyroid glands, both in the goiter-free and in the goiter countries, and particularly during the pre-puberty age, it is easily seen that the more active enlargement of the thyroid which takes place during puberty in the goiter countries leads also to a more active development of the adenomatous rests. The regression of the puberty enlargement of the gland, which occurs in the post-puberty period, will, in the goiter-free countries, also lead to a regression of the adenomatous rests that have been subjected to a slight stimulus only. They will, therefore, show only a slow growth and be hardly perceptible in later life, and will in any case not produce clinical symptoms, but only be demonstrable anatomically and histologically. In the goiter countries, on the other hand, the more active enlargement during puberty of the gland will produce a more powerful stimulation of adenom-

atous rests which will now show an active development, will not participate in the regression during the period of post-puberty, and will continue to grow during the whole life, so that eventually they dominate clinically the whole picture. This comparative consideration shows at once that the proper cause of the disease is not to be found by a consideration of the nodular goiter, but is centered in the diffuse goiter (Kloeppel, 1910).

It follows from what we have said that the goiter problem is centered in the problem of the diffuse goiter, and further, that this diffuse goiter is intimately related with the physiological variations of the development and functional activity of the thyroid gland. Two problems must therefore be considered in dealing with the goiter problem. First, what is the cause of the regular physiological enlargements which take place in all countries, even in the goiter-free countries, at certain age periods, to which we may add the periods of menstruation and pregnancy in the female sex? The second question is, why are these physiological enlargements of the thyroid so accentuated in the so-called goiter countries that, as a result, we get the disease which we know as goiter? I believe it is necessary to begin by solving the first question, which deals with the physiological enlargements, before one can attack the second problem of the goitrous change.

One might object that the ordinary enlargement of puberty is a very different thing from the enlargement of the puberty goiter in the goiter countries. It can be shown, however, that the puberty enlargement of the goiter-free countries, which may sometimes be so pronounced as to require operation, shows the same histological picture as the puberty goiter of the goiter countries. This shows that the goiter of puberty is nothing else but an exaggeration of the ordinary physiological enlargement of adolescence What now is the cause of the latter? What are the factors which set it going? Are these factors to be found outside the thyroid gland, perhaps in the gonads or elsewhere in the body? Are the thyroid changes a primary or a secondary effect? Is there an increased demand by the body for the specific thyroid secretion, or does it form too much of its specific secretion? Is the secretion of the thyroid of puberty

real thyroxin, or something else? Is the excitability of the age of puberty related to the processs of increased growth or to the increased activity of the thyroid gland? Is there a parallelism between the increase in basal metabolism and the rate of growth? Can the increase in basal metabolism that occurs during this period be referred to an increased thyroxin content of the body? Which of the two groups of thyroxin is particularly active during the age of prepuberty, the iodine-containing group which favors metamorphosis, or the acetyl-containing group which increases metabolism? We know that the age of puberty has to be divided into two periods: one a period of growth in length, which one might call the "period of growth proper," and a subsequent period of growth in width which one might perhaps call the "period of metamorphosis." Does thyroxin act in the same way in these two periods of puberty, or does it act in the one through its iodine-containing group, and in the other through its acetyl group? I do not know whether American investigators have approached these questions. In Germany no work of this kind has been carried out, so that I am not in a position to answer these questions.

The only definitely known fact is that one can influence the goiter of puberty by continued administration of small doses of iodine. This has been shown by Marine and Lenhart, and has been confirmed by Swiss investigators and also by more recent investigations in Germany. These observations have so far been carried out in goiter countries, not in goiter-free ones. We do not know, therefore, how a slightly increased iodine supply may affect the development of the normal enlargement of puberty, but we may assume that such an effect can be demonstrated. How can it then be explained? The histological picture teaches us that the introduction of iodine leads to a change in the thyroid colloid which becomes more viscous and, so to speak, concentrated. How this concentration is brought about, we do not know. One might conclude therefrom that the increased activity of the thyroid gland during puberty is the more marked the less iodine is available at the time for it; in other words, one might say that there is an insufficiency of iodine during puberty. One could then understand that in so-called goiter countries,

where the iodine deficiency of the food is supposed to be the cause of goiter, the physiological iodine deficiency of the puberty period undergoes a pathological exaggeration which manifests itself in the formation of a diffuse goiter.

During the age of puberty there are other peculiar conditions of increased excitability, the so-called conditions of hyperthyroidism. They may appear, of course, quite independently of the goiter of puberty, and we were thus brought up against the following problem, which we tried to answer: Are there any relations between the goiter of puberty and hyperthyroidism? The observations of Hellwig and Bürkle de la Camp on our material have, I believe, proved that the conditions of hyperthyroidism in so far as they are not due to a definite Basedow disease, are related exclusively to the proliferating forms of the struma colloides both in its diffuse and in its nodular form. Our figures showed us that it is particularly the diffuse and the mixed forms of proliferating colloid goiters that elicit the *clinical* picture of hyperthyroidism and not so much the nodular forms. The most marked symptoms were present with the diffuse forms. Hellwig has shown also that these proliferating forms of the goiter of puberty are associated with an increased basal metabolism, while in the non-proliferating form of colloid goiter the symptoms of hyperthyroidism were not present. The observations on basal metabolism, however, have not been carried out sufficiently extensively on this point. If we include the well-known observations on the thyroid gland of Basedow's disease, we can come to the conclusion on the basis of histological and clinical observations, that there are three different forms of so-called clinical hyperthyroidism:

1. The hyperthyroidism or disthyroidism of the Basedow gland. This is the most severe form of hyperthyroidism. It is not geographically localized and extends with its clinical symptoms especially over the ascending period of life.

2. The thyroid gland of puberty, and corresponding to it in goitrous countries, the struma diffusa macrofollicularis, when both are in the proliferating stage. They produce less pronounced symptoms of hyperthyroidism than the Basedow gland, but they represent a large part of the formes frustes of Basedow's disease. As enlargements of puberty they are not

definitely localized geographically; as goiter of puberty they are localized. They appear during the age of pre-puberty and puberty and only rarely during the later age periods.

3. The struma nodosa colloides macrofollicularis proliferans. This also shows, with the exception of a few cases, only slight degrees of hyperthyroidism which may be even less pronounced than the diffuse form of the proliferating colloid goiter. It is geographically localized and appears mainly in the period of post-puberty and the later ascending period of life, but is seldom seen during the declining period of life.

We may contrast these conditions with those cases of goiter that are not associated with any indication of hyperthyroidism and are rather inclined to show hypothyroidism. This is found in the non-proliferating form of the macrofollicular colloid goiter, in the regression stage of the microfollicular colloid goiter or in one of the ordinary nodular goiters with more or less distinct atrophy of thyroid-gland tissue. We wish to emphasize particularly that the parallelism between hyperthyroidism and certain forms of goiters is applicable only for the age of puberty and the ascending period of life. It does not apply to the period of infancy or the period of old age. In these periods the organism seems to be so strongly influenced by other factors that it does not react to altered functional activity of the thyroid gland in the usual way. In any case one can observe in children diffuse parenchymatous goiters—indeed genuine Basedow goiters—without noticing any clinical symptoms of hyperthyroidism.

Through the kindness of clinicians in North Germany we have been able to compare their material with ours. The number of thyroid enlargements that have to be operated on in North Germany is very much smaller than that in the South German goiter countries. Nevertheless, it can be shown that the distribution of the goiter forms over the different periods of life is almost the same as in Freiburg. This again shows that we are dealing here with a fundamental biological process related to the development of the thyroid gland and accentuated in the goiter countries as a result of factors as yet unknown to us. The only exceptions are the observations of the Vienna school. They found during puberty mainly diffuse parenchymatous goiters instead of the diffuse

proliferating colloid ones. One may perhaps look upon the former as a less advanced stage of the latter. Why the diffuse renchymatous type predominates only in Vienna we do not know. Until we know the endogenous and exogenous factors which determine the function of the thyroid gland in the various age periods, we shall not be able to solve the problem of the enlargement of puberty and the goiter of puberty, which is the most important of all goiter forms.

SUMMARY

These, briefly, are the results of goiter investigations in Baden during the past eighteen years. You will see that in many respects we have come to a conclusion similar to that of our American colleagues, especially as regards the classification of goiter. The American investigators also make the main distinction between Basedow goiter, the diffuse colloid goiter and the toxic adenoma. I have read with great interest the papers of my colleagues Marine and Lenhart, Kendall, Plummer and Boothby, and have convinced myself that their histological interpretation does not essentially differ from ours. But a remarkable difference is to be found in the clinical interpretation of the three groups. With you, only the Basedow gland and the toxic adenoma, which correspond with our nodular proliferating and parenchymatous colloid goiters, are concerned in hyperthyroidism. We deliberately also include the diffuse colloid goiter, but only the proliferating form of it. I believe that such a division into the proliferating and non-proliferating forms is necessary in order to come to an agreement on the problem of the thyroid gland of puberty and of the adolescent goiter. If we should succeed in this, it would open a path for the understanding of the toxic adenoma and the Basedow gland. We should then be able to decide whether the three forms associated with hyperthyroidism are not much more closely related than we believe today, where we are under the influence of the important investigations on the action of thyroxin. Today we make a sharp distinction between the thyroid gland of Basedow's disease and the toxic adenoma. If the three hyperthyroid diseases of the gland do not have

their origin in a primary disturbance of the gland itself, but in some stimulus situated elsewhere in the body, then we would have to assume for each of the three forms a separate predisposition; for the Basedow gland a nervous predisposition; for the puberty gland a predisposition of growth which, in the case of the puberty goiter, would be exaggerated in certain geographical localities; and lastly for the toxic adenoma, a tumor predisposition arising on the basis of an exaggerated enlargement of puberty.

Hyperthyroidism is not simply a goiter problem, with which it has frequently been identified, but a special problem of the irritability of the organism. Goiter, again, is not simply a geographical problem, but also a growth problem. In the goiter of puberty the two problems meet, and for this reason this form will always remain the most attractive of all goiter problems.

NOTE. The lantern slides used in this lecture may be ordered from The Bildarchiv, Freiburg i. Br.

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The American literature will be found in the papers of Marine and Lenhar and in the publications of the Mayo Clinic (Kendall, Plummer, Boothby)

XIV

RENAL SECRETION AND RENAL DISEASES[1]

When last in New York, in 1913, I devoted one of the Cartwright lectures to an analysis of my views on the structure of the kidney and the various forms of nephrosclerosis. Some of you may remember the lecture and it may perhaps be a matter of surprise to you that I should choose the same subject today. But in the interim so many new facts concerning the physiology of the kidney have been revealed, that it becomes necessary to reconcile our knowledge of the morphology of the organ with these newer views.

First of all, the book by Cushny must be mentioned, which again restores some confidence in the old filtration theory of Ludwig. According to this theory, the glomeruli play the chief rôle, the total urine being formed there by a simple filtration process. Then in passing through the contiguous convoluted tubule, there occurs a certain amount of resorption of those substances that are needed in order to maintain their normal threshold level in the blood—for example, sodium chloride. There is little or no resorption of substances which are not needed to maintain such a threshold level, nor of substances which are normally foreign to the body. This filtration theory necessitates a renewed study of renal morphology and of its relation to renal function.

As is, perhaps, well known, vital staining has proved itself a splendid aid for the study of renal secretion. In 1913, I was able to make a detailed report concerning the excretion of carmine through the kidney, based upon Suzuki's studies. If I may be permitted to digress for a moment, I should like to repeat the salient facts revealed by this investigation because they represent the basis for subsequent histologic investigations.

Since the experiments of Heidenhain, the long-known fact that the epithelial cells of the kidney can be stained with the

[1] Harvey Lecture.

help of dyes has been interpreted repeatedly, in the sense that the staining of the epithelial cells, or more correctly, the formation of colored granules within the cells, is the visible expression of a secretion. The dye is said to be excreted from the renal epithelium in the form of colored granules. The peculiar fact that the different urinary tubules are stained

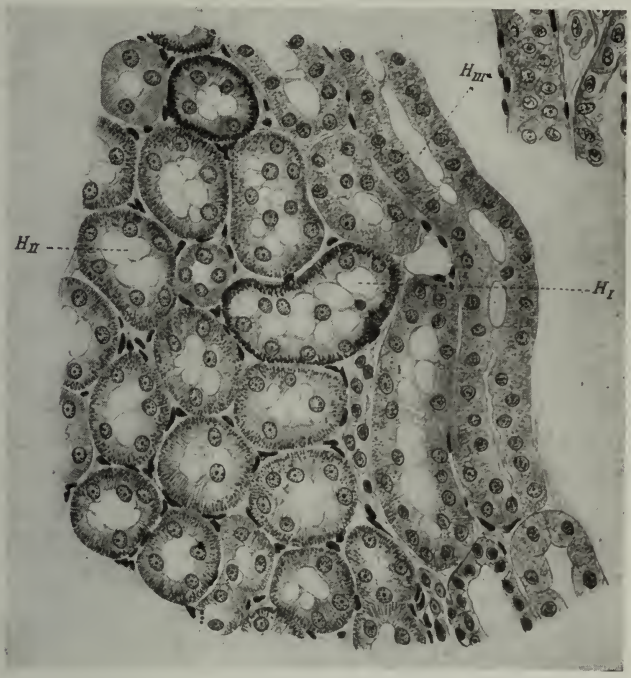

FIG. 32. Intravital staining of the convoluted tubules of the kidney with lithium carmine. Advanced stage of excretion. The various parts of the tubules are stained differently. (*After Suzuki.*)

with varying intensity was thought to mean that the different tubules *function* with varying intensity—a part working while another part rests. The investigations of Suzuki have shown that the formation of pigment granules within the cells has nothing whatever to do with the secretion of the dyestuff itself, and is rather a purely accidental accompaniment, a sort of storage process that catches up a part of the dyestuff passing through the epithelium. It is only a sort of indicator of the passage of the dyestuff through the cells, and

does not itself represent the process of excretion. According to Suzuki, the unequal staining of the tubules does not depend on their varying activity, but rather on the fact that the primary convoluted tubules store the dye to a great extent, and indeed mostly, in the proximal portion close to the point

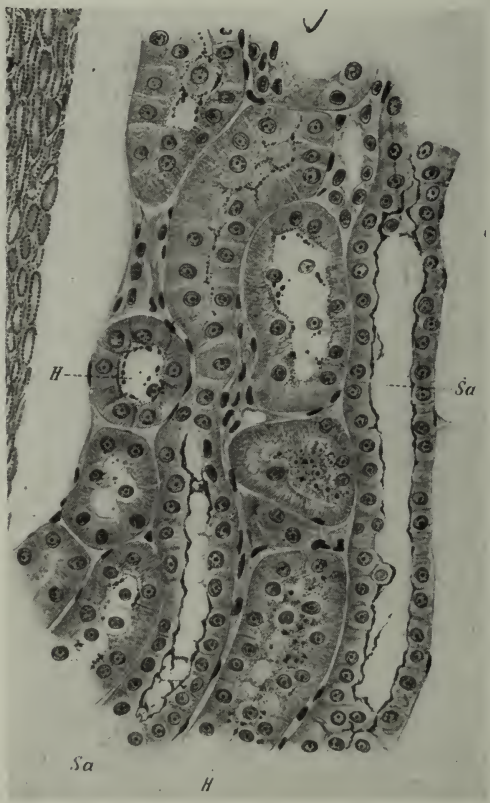

FIG. 33. Earliest evidence of excretion of lithium carmine in the kidney. Fine granular deposits in the brush border of the epithelial cells. (*After Suzuki.*)

of departure from the glomerulus, and least in the distal portion at the transition of the loop of Henle. The primary convoluted tubule can therefore be divided into four sections which gradually merge with one another and which were designated by Suzuki as the proximal, intermediary, distal and transitory portions. Finally, Suzuki was able to deter-

mine that the earliest evidence of secretion consists in a very fine granular precipitation of the dyestuff on the brush border of the epithelial cells, and that the granular staining of the cells themselves only occurs later.

These investigations have since been confirmed by others, but the question has not as yet been conclusively answered concerning the exact mechanism responsible for the remarkable storage of vital dyes within the renal epithelium. Suzuki and I felt that the dyestuff first of all passed through the glomeruli in the manner of a filtration, but that simultaneously there also occurred a very much feebler passage of dye through the epithelium of the primary convoluted tubule in the manner of a secretion. We interpreted the above-mentioned fine granular precipitate in the brush-like marginal membrane of the renal epithelium as the earliest evidence of this secretory process. At this early period, the epithelium itself was still entirely free of carmine granules. We believed that the granular deposit of dye within the cell bodies developed only very gradually in the course of the prolonged passage of dyestuff through the epithelium. Even at that time, however, we were obliged to admit the possibility that the reverse route, a resorption of dyestuff from the lumen, might conceivably lead to the same intracellular pictures. We were unable to solve the problem solely with the aid of vital staining, and at that time expressed ourselves more in favor of a secretion theory. For this reason, we named the primary convoluted tubule, the secretory portion of the renal tubular labyrinth.

On the other hand, the occurrence of carmine-colored casts in the Henle loops impelled us to assume that resorption of fluid took place at this site. Peter claims to have observed that those animals whose kidneys possess conspicuously long Henle loops, excrete a markedly concentrated urine. This served to confirm our belief that a concentration of the urine took place within the Henle loops. For this reason the narrow limit of the Henle loops was designated the resorptive portion of the renal tubular labyrinth.

This represented the general status of the subject at the time when the recent work at the Pathological Institute of Freiburg was begun two years ago by Professor Mitamura.

Suzuki having conclusively demonstrated that the appearance of vitally staining intracellular granules did not coincide with the curve of renal excretion, it now became desirable to ascertain whether the intracellular deposit of dyestuff within the epithelium of the primary convoluted tubules was the result of a secretory or of a resorptive process. The mooted question as to whether the filtration or the secretion theory was the correct one was therefore subjected to reanalysis from the standpoint of morphology.

The investigations received their first stimulus from the observations of Moellendorff, who confirmed the essential findings of Suzuki, but demonstrated that the deposits of dye within the epithelium of the primary convoluted tubules did not coincide with the vital granules, the chondrikones and chondriosomes; and in fact that the degree and type of the deposits were entirely independent of the chondriosome structure of the various cells. As a result of the work of Dr. Oka, I myself had pointed out that the mitochondria and the vitally stained granules respond to autolysis quite differently. We could very easily distinguish that the mitochondria, the so-called Altmann granules, very rapidly succumb to cadaveric autolysis, whereas the carmine-colored granules resist autolysis for a remarkably long time. Also, the arrangement of the mitochondria and of the carmine granules, although they superficially seemed to show some structural resemblances to one another, present important differential characteristics. The carmine granules are densest in arrangement in the neighborhood of the nucleus, and do not extend as far into the basal portion of the cells as do the mitochondria. This doubt concerning the identity of mitochondria and of the vitally stained granules has been referred to in the work of Schulemann, Evans, Moellendorff and others. Of these observers, Moellendorff was able to demonstrate that granular vital staining is the result of a condensation process which takes place quite independently of the mitochondria, and in fact, occurs outside of or between them. These observations can be accepted as at least applying to the *acid* dyes. Moellendorff even pointed out that the carmine granules seem to move their position from the marginal membrane downward toward the base, an

observation which would certainly speak in favor of a resorptive process.

In Cushny's publication, which appeared in 1917, a careful critical analysis was made of all the contradictory observations which had appeared in the literature. He attempted to reestablish Ludwig's filtration theory in a modified form, and has again actively renewed the discussion of secretion versus resorption. Since the publication of Cushny's book, quite a confusion of viewpoints has again appeared.

In the light of the present knowledge concerning the excretory mechanism of the kidney it becomes increasingly important to attempt to solve this problem of renal function by means of all possible methods, physicochemical, physicopharmacological and pathological. I have, therefore, taken up the subject again in cooperation with Professor Mitamura from a pure morphological standpoint. In choosing a method of study, we decided upon what is perhaps the oldest one, the investigation by means of dyes, and confined ourselves exclusively to the use of lithium carmine. This substance possesses many advantages, such as permanency of its solutions, simplicity of composition, the possibility of colorometric titrability, and the absence of a leuco (colorless) base.

When I was in Philadelphia a short time ago, Professor Richards told me of his most noteworthy attempt at the chemical investigation of the contents of the glomerular capsule on the one hand, and the urine on the other. These investigations bring an unequivocal proof of the correctness of the modified filtration theory. My elucidation might, therefore, appear superfluous, were it not a welcome addendum from a purely morphological standpoint. I feel myself the more justified to do so as a paper of Stieglitz in one of your leading journals points out just an opposite opinion.

These physiological investigations upon the normal carmine excretion in rabbits demonstrated that, just as with phenolsulphothalein, carmine was excreted in very much larger amounts and greater concentration in the first few hours than subsequently. The greater the concentration of carmine in the blood, the greater was the excretion of carmine in the urine. On the other hand, the concentration of carmine

in the urine may be more than ten times the concentration in the blood. Furthermore, after the first few hours, the excretion of carmine in the urine is uninfluenced by the volume of urine. This is evidence that carmine belongs to the group of substances which Cushny classifies as belonging to the group possessing no threshold value.

From these observations, Mitamura concluded that the excretion of dyes occurs with greatest constancy within the first few hours following their administration. Mitamura could also confirm Suzuki's observation that the first evidence of dyestuff excretion in the kidney, as far as it can be morphologically recognized, consists in a finely granular precipitate deposited along the brush-like marginal membrane of the epithelium of the primary convoluted tubules. The injection of larger doses, as well as the reduction in the volume of urine, results in increased precipitation at this site. This precipitate, which one would judge from its color, consists of pure masses of carmine, is deposited only in the primary convoluted tubules, never in the loops.

Another important finding concerned the formation of the intracellular granules of dye. The very first traces appeared relatively early, within fifteen minutes after an injection. At this early stage they appear as exceedingly fine deposits which can be recognized only with difficulty, and which lie immediately beneath the marginal membrane of the cells. In the course of the next few hours these granules increase in size, in number and in intensity of their color. They then appear very definitely to be migrating gradually deeper in toward the base of the cell. After twelve to twenty-four hours, in other words, at the height of this granular, intracellular deposition, they are situated for the most part at about the level of the mid-line of the nucleus, or even deeper in toward the base of the cell. During this period, when the carmine granules are moving toward the base, they begin to arrange themselves in rows so as to give the appearance of the rod-like arrangement of the mitochondria. For this reason one can so easily confuse them with mitochondria which have undergone granular degeneration, although as a matter of fact they really lie in between the mitochondria. Later, that is to say, after forty-eight hours, there occurs a clumping

together of granules of dye, such as Suzuki described in detail. The agglutinated masses eventually come to lie within vacuoles of the cell, as evidence of regression of the vital storage phenomenon.

During the entire period of excretion of the dye there never occurs, not even in the early stages of excretion, any diffuse coloration of the epithelium of the primary tubules, such as one might expect to see during secretion; so that one must conclude that only an extremely dilute concentration of the dye could have permeated the cell. This observation agrees with the conception expressed by Suzuki, that the dye is for the most part excreted through the glomeruli and only a small portion passes through the tubules. The above-described morphological pictures, such as the appearance of granular precipitate in the marginal membrane, the appearance of dye in dust-like granules beneath the marginal membrane and the gradual migration of these granules toward the base of the cell, all indicate that the dye is absorbed in extreme dilution from the lumen of the tubules. It passes within the cell in a contrary direction to the blood stream, comes to lie between the mitochondria, and eventually condenses into coarsely granular shapes.

The question now arises, what rôle do the glomeruli play in normal animals stained with carmine? In spite of the fact that he employed as fixation a lead acetate solution, Mitamura was never able to find any carmine deposits within Bowman's capsule. In other words, the dye must be excreted here in extreme dilution.

One is very much tempted to assume from these pictures that carmine is excreted by the glomeruli in extremely dilute form, and that a concentration takes place within the primary convoluted tubules as a result of the resorption of water and of certain salts. However, other evidence is needed to support this view. For this reason, Mitamura performed two other groups of experiments, in one of which he experimentally induced a glomerular damage, in the other a purely tubular destruction. In the first group of experiments he employed Habu-toxin, the poison of a Japanese snake, which damages the glomerular capillaries, similar to the injury which according to Pearce, Flexner

and Noguchi is induced by the poison of the American rattlesnake. For the purpose of producing a tubular damage, he employed chromium and bichloride of mercury. A remarkable fact was revealed by these experiments, namely, that the interference with carmine excretion was quite similar in both groups. Both series of experiments presented all gradations, from the mildest to the severest forms of disturbance, in the staining of the tubules. It was therefore necessary to assume that in both instances the disturbance in carmine excretion was dependent upon a common factor. Whenever the carmine excretion was entirely suppressed, by damage of the glomeruli, no vital staining of the epithelium of the primary convoluted tubules took place, in spite of the fact that the mitochondria were, as a rule, well preserved, at least in the proximal portions of the primary tubules. There was, therefore, no obvious reason why these epithelial cells could not excrete carmine and take the vital stain. One must rather assume that the carmine never reached them because of the fact that it was not excreted by the glomeruli.

On the other hand, in some of the animals whose tubules had been destroyed, and in whom a marked polyuria was produced by means of large doses of sodium chloride, a very good excretion of carmine took place, and yet the epithelium showed absolutely no vital staining. In these animals 40 c.c. of urine was excreted in one hour, about ten times the normal volume. If only a small part of this volume had passed through the epithelium, one would have expected them to have taken the vital stain. But here the resorption through the epithelium had been interfered with by the concentration of sodium chloride and for this reason no vital staining occurred. We are therefore obliged to assume that when there exists a severe injury, either to the glomeruli or to the tubules, the resultant disturbance in dye excretion must always be ascribed to a disturbance in the function of the glomeruli and not of the epithelium.

The third group of Mitamura's investigations concerned the result of section of the spinal cord. In rabbits on whom such an operative procedure had been performed, all possible diuretic influences were excluded by a period of observation varying from seventeen minutes to one hour. When the blood

pressure of these animals fell to 30 mm. of mercury (100 mm. being the normal), no carmine precipitate could be observed in the primary convoluted tubules. Vital staining of the epithelial cells also failed to occur.

On the other hand, similar experiments on cats gave contradictory results. In these animals the blood pressure usually sank only to 70 mm., seldom to less than 45 mm. of mercury. Under these conditions very distinct precipitates and a decided vital staining of the epithelium were observed, and yet the excretion of carmine in the urine was very small. When the blood pressure in the cats, after section of the spinal cord, was lowered still further by means of amylnitrate and other agents to as low as 20 mm. of mercury, the dyestuff precipitation and the granular staining of the epithelial cells failed to occur.

We lay great stress upon these experiments dealing with artificially lowered blood pressure because one would anticipate that filtration through the glomeruli would be more easily influenced by blood pressure variations than would secretion through the epithelium. But since, in addition, an adequate lowering of the blood pressure results in an absence of vital staining in the primary tubules, one is justified in concluding that the epithelium is not concerned in the excretion of dyes.

Naturally, such conclusions must be confined by further evidence. For this purpose, Mitamura employed the old Nussbaum preparation of the frog's kidney. As is well known, the glomeruli of the frog's kidney are supplied by the renal artery, whereas the primary tubules are supplied by a special vessel, a renal branch of the portal vein. One can, therefore, assume that tying off the renal artery would interfere with the function of the glomeruli, but not of the tubules. Similar experiments have been performed by numerous other investigators but have not led to any uniform results. The chief difficulty has always been that anastomoses exist between the arterial system of the glomeruli and the venous supply of the tubules, so that the passage of some blood from one to the other could not be entirely avoided. There is another great objection to all experiments in which an attempt is made to study the function of the tubules by

tying off the renal artery, leaving intact the blood supply via the renal branch of the portal vein. It could be said that by cutting off the stream of filtrate from the glomeruli one also interferes with the secretion from the tubules, for the tubules are thereby deprived of a fluid solvent for the secreted masses of material.

Mitamura tried to overcome these difficulties and objections, first, by perfusing each of the vascular systems with different fluids, and second, by simultaneously varying the pressure within them. If the renal artery is tied off on one kidney and the animal subsequently injected with carmine, the operated kidney will show no carmine deposits within the tubules and no vital staining. It is an easy matter to demonstrate that blood from the portal vein reaches the glomeruli through the anastomoses. If in spite of this no excretion of carmine occurs, it may only be due to the fact that the blood pressure in the portal vein is too low and is therefore inadequate to produce a filtration of urine.

In order to confirm this assumption, the renal artery and the renal branch of the portal were simultaneously perfused with Ringer's solution of a H. ion concentration of 7.6 to 7.7. Under such conditions, the kidneys will retain their normal mitochondria structure for at least two hours. The carmine was employed as a 0.04 per cent solution in this Ringer's fluid. Usually the urine was collected by means of a bladder catheter and the drops counted. The normal rate of urinary flow was about one drop every ten minutes.

The results were as follows:

1. Normal arterial and normal venous pressure; perfusion of the artery with carmine, and of the vein with plain Ringer's solution; result, always an excretion of carmine in a concentration equivalent to that of the perfusion fluid.

2. Normal arterial and normal venous pressure; perfusion of the vein with carmine and of the artery with plain Ringer's solution; result, never any excretion of carmine in spite of the fact that the volume of urinary flow remained normal.

3. Normal arterial pressure but hypertension in the vein; perfusion of the vein with carmine and of the artery with plain Ringer's solution; result, extremely variable.

4. Arterial hypotension and venous hypertension; perfusion of the vein with carmine and of the artery with plain Ringer's solution; result, usually no urinary flow and no excretion of carmine.

In so far as the staining of the epithelium is concerned, it is in similar experiments only found in those cases where an excretion of the dye in the urine is also observed.

One can positively conclude from the experiments of Series 1 and 2 that carmine is only excreted through the glomeruli and that the primary convoluted tubules are not concerned in the process. As far as the excretion of carmine is concerned, the theory of a secretion through the tubules must be abandoned. Series 3 indicates that anastomoses must exist between the renal branch of the portal vein and the renal artery. Series 4 proves that venous hypertension is unable to compensate for an arterial hypotension, and cannot result in any filtration.

Mitamura's experiments present both morphologic and physiologic proof that the excretion of vital dyes, or at least of carmine, takes place exclusively through the glomeruli. This excretion occurs in extremely slow concentration. But as a result of resorption of water within the primary tubules, there occurs a concentration of the urine and a resultant precipitation of carmine masses in the region of the marginal membrane. The resorbed fluids carry some dye with them into the epithelium of the primary tubules, and in this fashion there occurs the vital staining; in other words, a condensation of the resorbed dye into granular particles.

We shall henceforth designate the glomeruli as the filtration apparatus and the primary convoluted tubules as the resorption apparatus. I am therefore obliged to change the opinion I expressed ten years ago that the depositions within the primary tubules are evidence of a secretory activity on the part of these cells. If, on the basis of Ludwig-Cushny's theory and of Mitamura's observations, we must now consider Suzuki's deposition phenomenon as the result of a resorptive process, the question then arises, what rôle does the third important apparatus in the kidney, the system of loops, play?

As already mentioned, we find numerous casts at a certain period of dye excretion, and for this reason we originally named this part of the tubular labyrinth, the resorptive portion. But if resorption is chiefly confined to the primary tubules—a fact also attested to by the presence of the unique marginal membrane—it would seem quite improbable that the system of loops which possess a totally different structure should exert the identical function. One must rather think of some other purpose for them. At any rate, our observations are solely confined to the thin limbs of the loops, for here the peculiar casts are found. Similarly, in human pathology, casts are regularly found obstructing the curved ends of the loops. Here, then, must be a point of predilection. But how could casts form at this site, unless an inspissation, a resorptive process took place? Mitamura believes that these casts form in the thin limbs essentially as a result of precipitation which occurs in the primary tubules, but which are gradually carried downward into the loops by the urinary stream. The loops are placed like a syphon between primary tubules and intercalary tubules. It is permissible to surmise that the system of loops acts as a sort of pressure regulator which perhaps has some relationship to the pressure in the vascular system. But these are only guesses which need careful experimental study and a resorption process of quite another nature, as in the primary convoluted tubules, cannot be excluded.

With regard to the function of Henle's loops, certain observations made by American and German investigators appear exceedingly important. The primary tubules of every glomerulus are of equal length; on the other hand, the loops are of variable lengths. This would indicate that the filtration and resorption apparatus are exactly balanced. The system of loops, however, must exert some common influence on the two other systems. And yet the length of the loops must also be dependent upon some other factors, such perhaps, as the position of the glomerulus within the cortex.

In view of this newer conception that a tubular labyrinth is composed of a filtration system, a resorption system and a pressure regulating system, we must alter our conceptions concerning renal disease. We must first attempt to explain

the action of certain parenchymatous poisons upon the tubules. We know as a result of Suzuki's investigations that the important parenchymatous poisons damage the primary tubules and, in fact, pick out different parts of it. Chromium chiefly damages the first portion, uranium the third portion and sublimate and cantharidin the terminal transition piece. How can this be explained? If indeed the excretion of all these poisons took place exclusively in the glomeruli and only a resorption occurred in the primary tubules, one would naturally expect that all of them ought to attack the first portion with greatest intensity, the portion in which the vital staining is most distinct. But, on the contrary, as we have seen, these poisons attack entirely different sites. This can only be explained as follows: that the structure of the epithelium and of its marginal membrane varies in the different portions of the primary tubule, and that the resorption of molecules of different sizes and of various colloidal suspensions occurs at different rates. But unfortunately, we know nothing about the manner in which the various poisons occur in solution in the provisional urine, so that we are unable to express an opinion on this important problem. Only one thing must be mentioned. Endogenously formed substances are also excreted through the glomeruli and then resorbed by the epithelium of the primary tubules where they are often stored—as for example, the yellow iron salts in hemosiderosis, the green bile pigments, the reddish-brown hemoglobin. All of these substances are deposited most markedly in the proximal portion of the primary tubules.

On the other hand, this is not the case with glycogen. Dr. Baehr has been able to demonstrate that in human beings with diabetes a precipitation of glycogen occurs in the marginal membrane, exactly duplicating the picture seen in the carmine animals. This would indicate that here there occurs a resorption of glycogen from the glomerular filtrate. But, unlike the observations made on the carmine animals, the intracellular deposition of glycogen occurs in the terminal straight transition portion and not in the proximal parts of the convoluted tubules. We are still entirely at a loss for an explanation of this phenomenon. Future investigations must concern themselves with a solution of this problem concern-

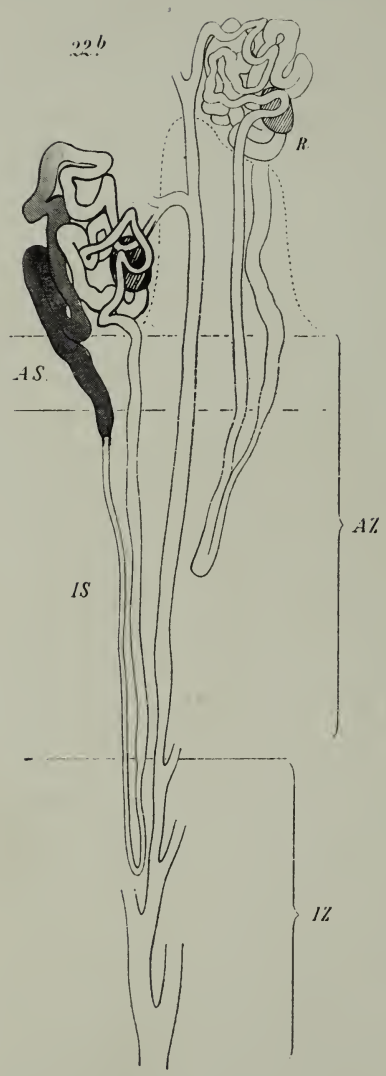

FIG. 34. Localization of the epithelial damage in the convoluted tubule after injection of cantharidin. (*After Suzuki.*)

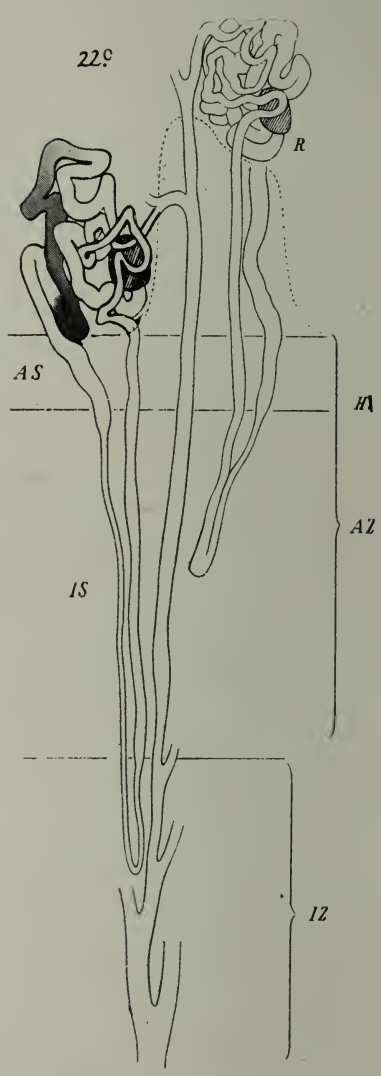

FIG. 35. Localization of the epithelial damage in the convoluted tubule after injection of chromium. (*After Suzuki.*)

ing the various localization of resorbed substances in different parts of the primary tubules and especially with a reason for the localization of the effects of different poisons.

In view of the fact that parenchymatous, that is, tubular, injury to the kidney produced by toxins and poisons will play a very great rôle in such studies, I believe it now desirable to touch upon another question, namely, the fact that renal epithelium seems to be able to develop some immunity, or at least increased resistance, to such poisons. Suzuki called attention to the fact that animals which had been poisoned with uranium and had recovered, could later withstand the re-injection of what would otherwise have been lethal doses. Examination of the kidneys in the course of these experiments revealed a surprising observation. The *renal epithelium*, which ordinarily would have been severely damaged by such large doses, was perfectly well preserved. This seemed to indicate that it might be possible to induce a certain amount of immunity of renal epithelium to such poisons. Personally, I consider this particular question of extreme importance because upon it must hinge our conception of parenchymatous nephritis.

According to Metchnikoff, Adami and others, an essential characteristic of inflammatory processes consists in the fact that it essentially represents a defense mechanism. In the case of infections, this defense mechanism is, as a rule, associated with a process of immunization. If a tissue or a cell develops an increased resistance against a bacterial or other poison, it is safe to assume that these particular cells have taken part in the process of defense. I am therefore prepared to express the belief that parenchymatous or tubular nephritis represents a reaction of the kidney to some poison, and that in the case of this reaction the epithelium itself takes part in the chemical transformation of the poison and in its detoxication. The kidneys of an animal which has survived a parenchymatous, i.e., a tubular, nephritis, produced by a poison, must show an increased resistance of the epithelium to furher administration of the same poison.

Such observations have actually been made in the course of investigations by Dr. Gil-y-Gil. Animals which had survived a single injection of 0.01 gms. of uranium could be

given eighty times the dose subcutaneously or ten times intravenously without the development of any evidences of poisoning, provided that in the interim the animal had received gradually increasing doses. It was possible to ascertain by means of urinary examinations that during the course of these immunization experiments the uranium was not retained in the body, but was actually excreted through the kidneys. In other words, the uranium was able to pass through the kidneys of an immunized animal without damaging them. This can only be due to the development of a local immunity of the renal epithelium.

Another interesting fact revealed by some of these experiments was that just those portions of the primary convoluted tubules which ordinarily are damaged by the first injection of uranium (the middle and distal portions) are entirely unaffected by subsequent injections of uranium, whereas the proximal portions now present the most marked changes. On the other hand, instances occurred in which repeated injections of large doses damaged the epithelium of the primary tubules most severely but did not produce the glomerular changes which were produced by Baehr with uranium. Here again it is necessary to consider the possibility of an immunity of the glomeruli.

Injection experiments on such acutely or chronically poisoned animals whose kidneys had developed more or less of an immunity, demonstrated also that the injury produced was not distributed uniformly throughout the kidneys. The damage appeared to have occurred rather in small spotted areas, so that some of the glomeruli still remained permeable to the dye, whereas others were entirely impermeable. Just those tubules which belong to the permeable glomeruli presented the severer types of epithelial damage. It is therefore necessary to assume that the poison is essentially excreted through the glomeruli, and only damages the epithelium on being reabsorbed from the lumen of the tubules. These observations are entirely in accord with Cushny's theory and with the anatomical findings of Mitamura. Pathological findings speak therefore in favor of a close relationship between glomerulus and primary tubules, since together they represent a unified filtration and resorption apparatus. We

must therefore re-analyze all renal function tests in the light of this new viewpoint. It is impossible for me to enter into a consideration of all the experiments of this character, such as those using the various methods by Schleyer. The division of all nephritis into vascular and tubular varieties which he advocated, has found ample critical refutation in the work of Suzuki and more recently in the publications of Cushny, and yet I would like to describe very briefly some new experiments upon the excretory ability of the kidney made by means of determinations of the hydrogen-ion concentration of the urine.

We know that the acid or alkaline reaction of the urine is dependent upon the food and the metabolism of the body, and can relatively easily be varied from the acid to the alkaline side. The question then arises, how does this ability to excrete more or less acid or base influence diseases of the kidney? The experimental observations of Rehn and Mitamura would lead us to believe that all glomerular diseases are favored by a high acid concentration of the urine, whereas tubular damage is favored by an increased alkalinity. These observations were correct whenever the functional test was made by administration of hydrochloric acid or sodium bicarbonate. These observations have been repeatedly confirmed both experimentally and clinically, but we are still unable to explain them with any degree of assurance. If we assume that a resorption of the "threshold" salts occurs in the region of the primary tubules, it is easy to understand that in the presence of a marked tubular damage such resorption might not occur; for as a matter of fact just those salts which are responsible for the alkalinity of the urine do not appear to be resorbed.

I am, therefore, able to conclude my report upon these newer investigations of the filtration and secretion theories as far as they have been carried from a morphological standpoint. I am well aware that in this country the problem is being attacked most industriously. These functional tests represent a very important and welcome addition clinically, to the purely physiological and histological investigations of the kidney. They afford the possibility of separating, more sharply, clinically also, the diseases of the filtration appara-

tus from those of the resorption apparatus. It is well known that the question whether there is in man a purely tubular-inflammatory disease of the kidneys in the sense of a defensive reaction, and whether such tubular or parenchymatous nephritides may lead to similar forms of contraction, such as the much more frequent glomerular nephritides, is as yet not solved. I am, however, convinced that such tubular nephritides do occur in man, that is, such changes as can be produced experimentally with small doses of uranium, chromium, submese, etc. Such tubular changes can and undoubtedly do lead to some contraction of the kidney. I therefore must agree to the existence of pure tubular contracted kidneys as described by Ophüls and Dickson. How often they occur in human beings it is extremely difficult to say in view of the fact that it is almost impossible to recognize a primary tubular damage when the process has reached the stage of a markedly contracted kidney. However, our investigations in chronic uranium poisoning have revealed exquisite examples of this type of contracted kidney. In view of the fact that we now have this experimental method of producing contracted kidneys, one ought to study more carefully the effect of such contracted kidneys upon the heart and the vascular system. We may, therefore, hope that the better knowledge of the function of the individual portions of the kidney system and the possibility now furnished of testing the function of these individual portions on the living body, will lead to a sharper delimitation of the diseases of the kidney, and especially to the recognition of the clinically interesting, though rare, parenchymatous nephritis and its contraction form.

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INDEX

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