THE INTERNAL SECRETIONS

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THEIR PHYSIOLOGY AND APPLICATION TO PATHOLOGY

BY

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PREFACE

Professor Gley's book, of which a translation is here offered, is believed to fill a gap in our literature on the physiology and pathology of the endocrine glands. It appears that the few available books on the subject are, in many cases, too extensive for the busy practitioner who wants to inform himself about the present status of the theory of internal secretion and its application in every-day practice. Many, also, it would seem to the unbiased critic, err by having too optimistic a viewpoint, especially when discussing organotherapy. Professor Gley's study treats the subject in a thoroughly scientific, critical, yet not ultra-conservative, spirit, pointing out not only what we actually know in this very promising field, but also being careful to indicate what we do not know and suggesting the proper methods to be pursued if we are to learn enough of the subject to make these glands, and their products, available in rational therapeutics. For these reasons Gley's book is given to those who are not prepared to read it in the original French.

The translation has been made quite freely; no literal rendering of the French text has been attempted. Great care has, however, been taken to express the spirit of the author in clear and simple English. No additions of any consequence have been made because it was deemed best to leave the text as originally presented by the author. Several additional paragraphs sent in by Professor Gley, especially for this edition, have been incorporated with a view to bringing the work up to date, and to elucidate some points which needed amplification. Also, an index has been added.

M. F.

New York,
April, 1917.

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The subject of secretions has always formed one of the most important chapters in physiology. The glands which manufacture the digestive ferments, and those which serve to eliminate the waste products of nutrition, are essential to the organism. It may be stated that there is not a single secretion whose rôle does not appear to be at least very useful, if not absolutely necessary, to the integrity of the vital functions. The recognition of the vast importance of the glandular organs and their products has been practically universal for the past twenty-five years. Only within this period, as a result of the inspiration of Brown-Séquard's fundamental work published in 1890, have physiologists undertaken the study of the glands having an internal, or endocrine, secretion; i.e., glands distributing the products of their activities, not through the cutaneous surface or gastro-intestinal mucous membrane and out of the body, but directly to the tissues, through the agency of the blood stream.

I

THE CONCEPT OF INTERNAL SECRETION; ITS ORIGIN AND DEVELOPMENT

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"Nothing about a science is more interesting than the progress of that science itself." —(*Laennec.*)

Complete knowledge of a physiological problem, like that of a living being, can be acquired only by grasping the problem at its very origin and following it through all its successive phases of development. In order to connect physiological facts, which are usually so complex, with one another, to coordinate and systematize the ideas which may be engendered by the facts, it is essential to distinguish the evolution of theory from accumulated data. In other words, nothing is more useful in studies of this sort than a good historical review of the subject.

To the doctrine of internal secretions are inseparably attached the names of Claude Bernard and Brown-Séquard; the one the initiator, the other the resurrector of the doctrine, as I was the first to show.[1]

I. THE PRECURSORS OF THE DOCTRINE

But Claude Bernard and Brown-Séquard had their precursors; in fact, they are found in medical literature.

1. In 1897,[2] I called attention to a work

[1] "Conception et classification physiologiques des glandes" (*Revue scientifique*, 1893, LII, 8-17); "Exposé des données expérimentales sur les corrélations fonctionnelles chez les animaux" (*L'Année biologique*, 1897, I, 313-330).

[2] In my article in *L'Année biologique* quoted above. It is not without interest to know that Claude Bernard had read Legallois (a French physician and physiologist, celebrated for his investigations of the action of the heart and the nervous system; died in 1810). "It has been recognized for a long time," says Bernard, ("Leçons sur les . . . liquides de l'organisme," 1859, I, p. 321), "that although it were possible to admit the

of Legallois, hitherto apparently forgotten, in which it is seen that, more than a century ago, this physiologist had clear notions of the connection which must exist between the various secretions, and the complexity of the composition of the venous blood. The text runs thus: "Considering the homogeneity of the arterial blood and the heterogeneity of the venous blood we may conclude that . . . it would be a supreme triumph of the chemistry of the living body to find connections between the arterial blood, the substances so secreted in each organ and the corresponding venous blood, in the normal as well as in the pathological states of various animals; to find differences between the various kinds of venous blood; finally to discover that these

homogeneity of the arterial blood, the venous blood cannot be regarded as having the same composition throughout its course. Legallois, examining this question in a purely speculative work, had already concluded that the arterial blood is everywhere identical in composition, but declared that the venous blood was not so constant."

differences vary as do the corresponding secretions.

"Once arrived at this degree of perfection, it would often be possible to solve for the unknown in the equation: *arterial blood = a secretion + the corresponding venous blood;* [3] that is, given the left hand member of the equation, and the composition of the corresponding venous blood, chemical science could almost determine what would be the character of the secretion." [4] However keen it may have been for a physiologist of that time (1801) to recognize intuitively an essential part of the problem of the mechanism of secretion, it must nevertheless be noted that the ideas of Legallois are not specific and that they apply to all glands, not differentiating those which have since been designated as

[3] These words were underscored by Legallois.

[4] LEGALLOIS, "Le sang, est-il identique dans tous les vaisseaux qu'il parcourt?" Inaugural dissertation given before the School of Medicine in Paris, Sept., 1801 ("Œuvres de Legallois," II, 209-10).

glands of internal secretion. The importance of this last reservation in the study of the origin of the theory of the endocrine glands is evident.

2. Following a suggestion of Max Neuberger,[5] Biedl wishes to attribute a similar conception to another French physician, Théophile Bordeu, who lived even before Legallois. Biedl says: "In his treatise on 'L'Analyse médicinale du sang,' which appeared in 1775, Bordeu expresses the opinion that each organ serves as a center for the preparation of a specific substance which is discharged into the blood, and that these substances are useful to the organism and necessary for its integrity. The specific substances coming from their particular organs perhaps reach the blood through the medium of the lymphatics. It seemed to him to have been conclusively demonstrated that the venous blood of

[5] Max Neuberger, Théophile Bordeu als Vorlaufer der Lehre der Inneren Sekretion" (*Wiener klinische Woch.*, Sept. 28, 1911, XXIV, 1367).

various regions presents important qualitative differences.''[6] As a matter of fact, Bordeu did not express himself so clearly. The ''Analyse médicinale du sang,'' which Biedl quotes, is a booklet whose title is rather too ambitious. I shall quote several typical passages from which it will be clear that the author's thoughts were very vague. After a series of truisms on the characteristics of each part of the living body, the author concludes: ''I believe it to be certain that every organ keeps its own particular place, as I have just said, and that it lives its own independent life . . . and always diffuses around itself, in its atmosphere and province, exhalations and odors; emanations which have taken on its manners and its ways, which are, in short, true parts of the organ itself.

''I do not regard these emissions as entirely useless and therefore only of

[6] A. Biedl, ''Innere Sekretion,'' 2nd Ed., Berlin and Vienna, 1913, I, p. 5.

mechanical utility; I think they are useful and necessary for the existence of the entire organism. The seminal fluid imparts, as is well known, a manly and firm bearing to all parts of the body, since it is in a position to be pumped into and come back from the mass of humors and solids, by the work of its natural organs; it confirms anew the living nature of the individual, partly subjected to the action of this fertile fluid. . . . Examine the blood that returns from each of the principal regions of the body, that from the head, from the breast and from the abdomen; it is evident [7] that the blood from each of these regions has particular qualities that it has acquired in the tissues of the parts from which it returns. Finally, I accept as a fact, which has been medically verified, the assertion that each organ is continuously diffusing emanations into the blood;

[7] It is useless to add that these words were uttered without observation and *a fortiori* of all analysis.

and if it were possible to base a deduction on some part of the anatomists' discovery of venous lymphatics, I would say that this gelatinous liquid has particular vessels so that it may be more surely brought back into the blood-stream with the individual qualities that it has acquired in the internal tissues of each organ, in order to instil into the chyle, into the thoracic visceral tract, the properties and characteristics peculiar to the parts of which it is composed. Some one has found lymphatic veins in the testicles and has ascribed to them the function of returning the seminal fluid into the blood. It was not necessary to know of the existence of these veins to realize the fact that absorption of the seminal fluid takes place."[8]

We can easily see from the above how much clearer were the ideas of Legallois. But once on a pathological basis—and this

[8] Théophile Bordeu, "Œuvres complètes," édition Richerand, vol. II, pp. 942-943, Paris, 1818.

has not escaped Neuberger or Biedl[9]—Bordeu's progress appears to be a little more certain. "The flowing back of the bile," he says, "for example, its elaboration in the blood, its diffusion through all the tissues of the body, the color that it gives to solids and to liquids, are well known phenomena. We may indubitably conclude from this . . . that throughout life, and even when in the best of health, a constant interchange is going on between the liver and all the humors and solids of the body. The superabundance of humors present in some of the diseases to which their organs are subject, is proof of the existence of passages by which the humors pass when the organism is in a normal condition. . . . The diversity of temperaments was formerly, not without some semblance of

[9] "That Bordeu has presented the pathological significance of anomalies of excretion, is shown by his remark: 'Physicians should follow and classify the various refluxes which take place through the fault of each organ in particular' " (A. Biedl, *loc. cit.*, p. 5).

truth, attributed to an oversupply of humors. I have elsewhere indicated that the various temperaments have some connection with the greater or lesser activity of certain organs when compared with that of others. Thus the liver has within its domain the bilious temperament. . . . This remark may be applied to all other organs; each of them is master of the temperament which it governs. . . . Each organ has a marked influence on the solids, the vessels, the cellular tissue and the nerves. Each also serves as a home and laboratory for a particular humor which it sends back to the blood after having prepared and impregnated it and given it a definite character . . .

"I distinguish as many cachexias, as many minglings or principal mixtures of humors, as there are important organs and distinct humors. . . . All glands derive from the cellular tissues which surround them a large quantity of serosities, pumping them on, to follow the terminology of the Hippocratic school. These serosities mix with the humors specially formed and separated by the glands. Now, these serosities, not being pumped away as they should be, become superabundant; a cachexy that flows back into the humors and inundates all the neighboring parts, even as the bile is stopped in its course. It is a problem for physicians to trace and classify the various refluxes that come on because of the faulty working of some particular organ.''[10] From this it may be seen that the *refluxes* of which Bordeu speaks are not solely of glandular origin, as Biedl would seem to have him say. The context of the sentence which Biedl cites only goes to show that the XVIII century physician had crude views of the possible relations between secretions and pathological disorders. It is no less curious to observe—and this, above all, is the object

[10] TH. BORDEU, *loc. cit.*, pp. 947-949.

with which I have reproduced the preceding quotation, although it is rather long—that he may be considered a precursor of those contemporary pathologists who hold that a certain morbid syndrome may depend on the hyperactivity of the nervous system which, in turn, is caused by the presence of an excessive amount of a product of secretion in the blood. Such is, as is well known, the theory or vagotonia, or *hypertony of the sympathetic nervous system,* which is attributed by the Viennese school to an excessive secretion of adrenalin.

In 1845, J. Müller wrote in his celebrated "Text-book of Physiology": "The ductless glands are alike in one particular: they either produce a definite change in the blood which circulates through them, or the lymph which they elaborate plays a special rôle in the formation of blood or of chyle. In every instance venous blood or lymph are the only substances which pass from the gland into the general economy."[11]

3. Here and there in the works of several biologists of the first part of

[11] J. MÜLLER, "Lehrbuch der Physiologie," 1844. There is a little difference between this purely hypothetical statement and an earlier pronouncement by Burdach: "The vascular or blood glands are agglomerations of vascular ramifications united by the primordial mass, which have neither excretory ducts nor an immediate connection with the mucosa and which can be concerned only in the metamorphosis of the blood without the agency of an external medium. This metamorphosis may occur as the result of the passage of the blood through the glands, for it is inconceivable that that passage should be unattended by some change in the proportion of the secondary elements; or it may result from nutritional processes within the organs, or from a deposit of substance within their tissues; or it may be due to formation in the tissues of a liquid which is afterwards resolved." (C. F. BURDACH, "Traité de physiologie considérée comme science d'observation." Translated into French by A. J. L. JOURDAN, Paris, Baillière, 1837-41, vol. IV, p. 83.) It is evident from this that it is hardly possible to consider Burdach and Müller as the precursors of the theory of internal secretion. The same may be said in regard to Henle, Kölliker, and even more emphatically in regard to Bordeu. (See: "Relations entre les organs à sécrétions internes et les troubles de ces sécrétions," Int. Congress of Medicine, London, 1913. Section Physiology, Part I, pp. 2-5.)

the nineteenth century we note rare allusions to the functions of the vascular glands. Thus, Henle affirms that these glands "have no influence on animal life; they may be extirpated or they may degenerate without sensation or motion suffering in the least," and he adds: "Nothing, then, would be more natural than to assign them a place among the organs which take part in the chemical processes of nutrition or of hematosis. Many facts bear witness that diseases of the spleen and thyroid are connected with general disturbances in the composition of the blood and with nutritional disorders. This justifies us in thinking that the blood undergoes a change in the vascular glands; that while it circulates through their interior it throws off certain substances which undergo some sort of elaboration in the parenchyma, as in the secretory glands. The difference consists in this: that here the products of secretion are not carried out from the gland through a duct . . ., but reenter into the blood vessels or lymphatics, either by absorption or exchange or by the establishment of a temporary means of communication between the vesicles and the blood vessels.''[12] But it is easy to see that this is not the distinction between the two kinds of glands recognized by anatomists, for he differentiated them according as to whether they have or do not have ducts conducting the secretions to the exterior. Kölliker says no more about it: ''*Gewebe der Blutgefässdrüsen.* Unter diesem Namen fasst man am passendsten eine Reihe von Organen zusammen, deren Uebereinstimmendes darin liegt, dass sie in einem besonderen drüsigen Gewebe aus dem Blute oder anderem Safte gewisse Stoffe bereiten, die nicht durch besondere bleibende or zeitenweise sich

[12] J. Henle, ''Traité d'anatomie générale,'' translated into French by A. J. L. Jourdan, Paris, 1843, vol. II, p. 586.

bildende Ausführungsgänge sondern einfach durch Heraussickern aus dem Gewebe abgeführt werden und dann in dieser oder jener Weise dem Organismus zu Gute kommen.''[13] Finally, nothing further is given in the most important contemporary physiological treatises, for example, those by J. Müller, Longuet, and Béclard, nor in Milne-Edwards's great work, which was devoted to physiology and comparative anatomy.

In all that period there was only a single attempt at experimental investigation, that by A. A. Berthold, of Göttingen,[14] who in 1849 removed the testicles from cocks and grafted them upon other parts of their bodies. He observed that ''the animals retained their male characteristics in

[13] A. Kölliker, ''Handbuch der Gewebelehre des Menschen,'' p. 74-75, Leipzig, 1852.

[14] Quoted by A. Biedl, *loc. cit.*, sec. edit., 1913, p. 6. Berthold's work has been published in the *Archiv für Physiologie*, 1849, pp. 42-46. The experiment was only carried out on four cocks.

regard to voice, reproductive instinct, fighting spirit, and growth of comb and wattles.'' From his experiments Berthold concluded that ''the *consensus* is maintained by the productive influence of the testicles; that is to say, by their effect on the blood and, through the blood, upon the entire organism.'' Biedl is therefore correct in saying that ''A. A. Berthold was the first to demonstrate experimentally the nature and activity of a true ductless gland; he showed the influence which an organ through which the blood stream circulates can exert upon the composition of the blood, and thus upon the entire organism.'' With Biedl I will add, moreover, that this discovery, far from attracting any attention, remained hidden in obscurity and hence had no consequences; it stimulated no further research along the same lines.

II. THE FOUNDERS OF THE DOCTRINE

The true founders of the doctrine of internal secretions, such as it is, are Claude Bernard and Brown-Séquard; and in the establishment of the theory each played a part different from that of the other.

1. I believe myself to have been the first to bring to light, in 1893, and above all in 1897 (*loc. cit.*), the texts, often quoted since then, showing that Claude Bernard had clear ideas about the glandular organs which distribute their secretory products by means of the blood stream—into the interior part of the body, as he said—and these ideas came, indeed, not from inferences based on vague observations or from mere suppositions and assumptions reached through *a priori* reasoning, but, on the contrary, from a mass of experimental facts, solidly demonstrated. The facts which he used concern the production of grape sugar by the liver and the

passage of this sugar in the hepatic veins and from there into the general circulation; and once having firmly demonstrated the existence of this internal secretion, the author of this discovery is immediately led to the inevitable generalization:[15] "For a long time a false conception has been current as to what a secretory organ consists in. It was believed that all secretions must be poured upon an internal or external surface, and that all secretory organs must necessarily be provided with an excretory duct for the purpose of conveying to the exterior the products of secretion. The case of the liver establishes in a most lucid manner that there are internal secretions, i. e., secretions which, instead of being carried to the exterior, are diffused directly into the blood." Further on (p. 107), he says: "It is now firmly

[15] "Leçons de physiologie expérimentale," I, 96, Paris, 1855.

established that the liver has two functions of the nature of secretion. The first, the external secretion, produces the bile, which flows to the exterior; the second, the internal secretion, forms sugar which immediately enters into the blood of the general circulation."

Thus we see that Bernard clearly understood the functional significance of the liver in producing sugar, and the physiological significance of this sugar, a product of secretion; and, at the same time, founded a new theory of secretion on these premises.

This is not all he accomplished. The idea of internal secretion, which he understood clearly at the very start of his work, appeared to be immediately connected in his mind with his conception of the nature of the blood, which he came to consider as the resultant of all the internal secretions. "All the fluids which have been examined up to the present time," he said in 1859,[16] "are what are known as excreted or secreted fluids, that is, liquids manufactured by organs which take from the blood the elementary substances necessary for the preparation of the products of their secretions. All these organs pour their secretions outside of the blood. And there is another category of organs which resemble the glandular organs, but differing from the latter in that they are not provided with excretory ducts; they must dispose of the products of their secretion into the blood itself. These are what we have designated by the term *internal secretions,* in order to distinguish them from the *external secretions,* which are not poured into the blood.

"I have shown that the liver is, in some ways, intermediary, because its secretions are of both types; the external secretion

[16] "Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme," vol. II, pp. 411-412, Paris, 1859.

being represented by the bile and the internal by the sugar produced. The organs whose mode of secretion are exclusively internal are the spleen, the thyroid, the adrenals, the lymphatic ganglia, etc.

"It is beyond all doubt that these organs modify the blood which passes through them and when leaving them contains substances not present before it entered. We may therefore consider that the blood constitutes the sum total of all these secretions and it should, in my opinion, be regarded as a true product of internal secretion."

Bernard attaches himself so strongly to this conception that we may wonder if he did not consider all these organs, which he classified among the internal secretory glands, as blood forming organs. In his lectures of 1859-60 at the Collège de France,[17] he says: "The various glands distributed throughout the entire body

[17] "Leçons de pathologie expérimentale," 2nd Ed., p. 100, Paris, 1880.

must be divided into two great classes: those which extract from the blood certain particular principles which impart to each secretion its individual characteristics; and those which, on the contrary, appear to secrete the blood itself, if I may use the expression, or those which are intended to enrich the circulating blood with products manufactured in the interior of their own tissues. Such are the hematopoietic glands, among which are included the spleen, the thymus, the suprarenal capsules and other glands rich in blood vessels, and which do not possess excretory ducts. The lungs, within which the great work of oxygenating the blood goes on, represent the most complete type of this last variety of gland. Also the liver, which, if we consider the biliary secretion, belongs to the first class, is equally allied to the second group by the glycose it produces." The expression of Claude Bernard's opinions on the subject is in no wise different, nor is it more precise and complete in his famous "Rapport sur les progrès de la physiologie générale en France";[18] I have quoted the entire passage in my study in *L'Année biologique* of 1897 (p. 315), mentioned above. It reads as follows: "The secretory cell itself attracts, creates and elaborates all the products of secretion which it pours either on the mucous surfaces without or directly into the blood stream. I have termed those that flow to the exterior, external secretions, and internal secretions are those which are diffused into the vital interior of the body. . . . The internal secretions are far less known than the external. Their existence has been more or less vaguely suspected but is not as yet generally admitted. However, in my opinion their existence is no longer doubtful, and I think that the blood, or, in other words, the vital interior of the body, must be regarded as a product of secretion

[18] Paris, 1887, pp. 73, 79, 83, 84.

of the internal vascular glands. . . . I consider the liver, in the form that it is present in the higher vertebrates, as a two-fold secretory organ. It combines, in reality, two distinct methods of secretion, and it represents two secretions: The first is the biliary secretion, which is external and flows through the bile duct into the intestine; the second is the internal secretion of glycogen and is poured into the blood stream. . . . That part of the liver which secretes glycogen is composed of a large vascular gland, i. e., a gland which has no external excretory duct. In it are produced the sugar constituents of the blood, perhaps also other albuminoid products. But there exist many other vascular glands, such as the spleen, the thyroid, the suprarenal capsules and the lymphatic glands, the functions of which are as yet unknown. However, these organs are generally regarded as playing some rôle in the regeneration of the blood plasma, as well as in the formation of the red and white corpuscles which float in this liquid."

To sum up, we owe to Claude Bernard the first direct demonstration [19] of an internal secretion—the passage into the blood of sugar formed in the liver—and the general conception of these secretions, which he understood as serving to maintain the composition of the blood. Throughout his entire work I find no text which would seem to indicate that he meant anything else by the expression *sécrétions internes* than the concept he first expressed, viz., that they serve to maintain the composition of the blood. How different this is from the true conception! How remote are the ideas represented by this expression to-day from those held by Claude Bernard! A word has no more meaning than the thought it expresses.

2. In order to grasp the exact value of

[19] Berthold's experiment, mentioned by Biedl, only constitutes an indirect proof.

the ideas that Claude Bernard introduced into medical science, it is necessary to state that absolutely no interest was aroused by his work. And it is curious to note in this connection how very differently scientific ideas fare with Fortune. Some, notwithstanding that they are based on insufficiently demonstrated premises and hasty deductions, at times have a rapid and brilliant rise to fame; others, though securely based on a sure foundation, remain in oblivion for long periods or are slow to attract and retain attention, until they are finally resurrected by the light of fame. The doctrine of Claude Bernard under discussion belongs to the latter category. I am well aware that the theory of the glycogen-producing function of the liver was assailed and severely criticized by many physiologists for many years; but it was also very much admired and amply verified by many others, so that, in quite a short space of time, its acceptance was forced upon physiologists, with the exception of several rebellious spirits, as Longet.[20] And beginning with 1855, the year in which the "Leçons de physiologie expérimentale" appeared, considerable work was produced which would naturally be coordinated with the experiments on the glycogen normally produced by the liver. I refer to the researches of Brown-Séquard on the physiology of the suprarenal capsules (1856-58);[21] the observations of Vulpian (1856) on the coloring matter of the

[20] See the last (third) edition of LONGET's "Traité de physiologie," Paris, 1867-69, reprinted 1873, vol. II, pp. 290-296.

[21] It is important to recall that Brown-Séquard, in his first manuscript (*Arch. gén. de méd.*, 1856), wrote very clearly: "The absence of the secretions of the suprarenal glands is therefore more rapidly fatal than the suppression of the urinary secretion . . ." "The question of the function of the suprarenal capsules therefore depends on the following: What are the substances which, when carried to these glands by the blood, are there modified, and what are the products of this modification which are carried away by the blood when it leaves the capsules?"

medullary substance of the suprarenal capsules and the passage of this matter into the venous blood of the capsules;[22] Schiff's researches on the connection of the spleen with the digestive (proteolytic) function of the pancreas (1862). But no one coordinated these facts, not even Claude Bernard. This would be most surprising were it not called to mind, in accordance with what I have just shown, what, in reality, was his conception of the nature of the "internal secretions." It is therefore, possible that it was this, somewhat narrow, conception which concealed from him the general connection existing

[22] Vulpian had well noted the general interest of this statement: "I always noted that the droplet of sanguineous liquid issuing from the venous orifice (of the capsular vein in the sheep in Vulpian's experiments) produced the indicated reaction with sesquichlorid of iron. This proves for the first time, and in a most decisive manner, the hypothesis which regards the suprarenal capsules as being like the glands termed vascular, i. e., glands pouring their products of secretion directly into the blood" (*C. R. de l'Acad. des sc.,* Sept. 27, 1856, XLIII, 663).

between these newly discovered facts and the normal glycemia.

Towards the end of that period, however, there came a biologist who understood the importance of the question. "The action of the glands which do not have excretory ducts," says Charles Robin,[23] "can only be studied from the physiological point of view. The nature of the products of this action can only be definitely established by the comparison of the arterial blood with the venous blood that leaves these organs, or by comparing the ingoing lymph with that which has already passed through the gland. Unfortunately, the direct comparative analysis of the liquids which these organs receive and those which issue from them has not been done anywhere in a suitable manner; no more than it has been done with the

[23] Ch. Robin, "Leçons sur les humeurs normales et morbides," 2nd Ed., Paris, J. B. Baillière et fils, 1874, p. 316.

secreting parenchyma cells themselves." Further on,[24] Robin writes: "Each of these various glands furnishes one or more special principles of its own to the blood carried away by the corresponding vein to the principal organ to which it is connected. Just as the blood which enters the liver does not contain the sugar which the departing fluid holds, it is likewise found that the formation of the substances which are most certainly found in the returning blood must be attributed to the tissues of the vascular glands, which have poured them into the blood exactly as the liver unburdens itself of sugar into the hepatic veins."

"These facts are quite closely associated with the study of the constitution of the blood and lymph.[25] The studies of M.

[24] *Ibid.*, p. 318.

[25] It is thus to be seen that this idea of the constitution of the blood and lymph is always dominant. It is found in Liégeois ("Anatomie et physiol. des glandes vasculaires sanguines," Paris, 1860), as is proved by the

Claude Bernard support them, he having given the name of *internal secretions* to the products poured into the blood itself by the vascular glands, in order to distinguish them from the *external secretions*, the products of which are deposited without the blood." In a note he adds: "As far back as 1837, furthermore, Burdach, who considered the spleen, thyroid, suprarenal capsules and thymus as agglomerations of vascular ramifications, thought that the vascular glands could only serve for what he termed the metamorphosis of blood." Great as was the authority of

following passage: "From all these experiments (Liégeois has just cited Vulpian's experiments on the suprarenal venous blood and those of Béclard, Funke, Lehmann, and Gray on the splenic venous blood), we have the manifest result that in the spleen and the suprarenal capsules, modifications take place which change the constitution of the blood" (*loc. cit.*, p. 53). "The vascular glands," says Liégeois further (p. 59), "have for their principal function pouring into the circulation materials which change the microscopic and chemical constitution of the blood." Moreover, this work lacks facts and also a critical spirit.

Charles Robin at that time, above all in France, these considerations, supported by those of Bernard, in his "Rapport sur les progrès de la physiologie générale en France," did not stir many to a clear realization of their value, or provoke any experimental researches.

A little later we again find the term "internal secretions," from the pen of Paul Bert.[26] "These are," he says, "products of secretion which are emptied into the blood."[27] To this he adds nothing but these lines (p. 254): "The liver gives us an example of a gland which not only manufactures a liquid destined to be expelled, but also substances which are poured into the blood." So brief is this notice that we would be justified in thinking that Paul Bert did not appreciate the importance

[26] "Leçons de zoologie," Paris, G. Masson, 1881. This was a work written with a view to the secondary instruction of young girls. I am indebted to Prof. V. Pachon for indicating to me this source.

[27] *Loc. cit.*, p. 248.

of the question from the point of view of general physiology, did we not reflect that the work in which it occurs is an elementary textbook.

Several years after the death of Claude Bernard, Schiff published his great work "On the effects of the removal of the thyroid body,"[28] a labor inspired by the observations of J. L. and A. Reverdin (1883) and Kocher on postoperative myxedema (1883), which recalled in a most striking manner the experiments of two English physicians, W. Gull (1872) and W. W. Ord (1878), on spontaneous myxedema. It is known, further, that Schiff in 1859 had already pointed out several of the successive accidents of thyroidectomy. Did he include the thyroid among the vascular glands? He puts the question thus: "We may wonder if the thyroid body produces in its interior . . . a substance which it de-

[28] *Revue médicale de la Suisse romande,* Feb. 15 and Aug. 15, 1884.

livers to the blood stream and which constitutes a nutritive element for another organ (nervous), or whether it acts mechanically by its anatomical position. To decide between these two alternatives, it is necessary to find a means of transplanting it, by grafting it into another part of the body. If, after this has been done, the accidents resulting from its removal are avoided or reduced to a minimum, it is evident that the action of the thyroid is due to its composition and not to its anatomical relations; this will prove the thyroid to have a chemical function. . . ." He then states that the grafts he attempted disappeared by resorption; nevertheless the animals in which the thyroid body was transplanted suffered from less severe effects, from which he concludes that "the substance of the grafted organs, taken up by the blood, serves to counterbalance the untoward effects of thyroidectomy."

"It would be curious to investigate if

the macerated extract of the thyroid, introduced into a serous cavity, or injected into the rectum, has the same immunizing power.''[29] This is all that is said. Schiff did not attempt, in the presence of all these facts, to connect them with what was already known about the suprarenal capsules and the formation of grape sugar in the liver. As I have said elsewhere:[30] ''Schiff, although always so close to the work of Claude Bernard, and whose investigations on the connections between the function of the spleen and the digestive activity of the pancreas furnish some of the most favorable arguments for the doctrine of internal secretions, never even used these terms.''

3. Since the time of Brown-Séquard everything has been changed. The notion of internal secretions has spread every-

[29] Several years later this experiment was carried out by G. Vassale and myself, independently of one another.

[30] E. Gley, ''Essais de philosophie et d'histoire de la biologie,'' p. 255, Paris, Masson and Co., 1900.

where, is understood and accepted throughout, although its significance has changed in some respects. It is, in fact, possible that Brown-Séquard retained the conception introduced into science by Claude Bernard; namely, the realization that the glands "without external secretion" have a special influence on the blood, inasmuch as they secrete substances necessary to its constitution; he even adds that the tissues play this rôle of "blood modifiers." But he did not stop at this point. By his experiments on the therapeutic action of testicular extract,[31] and by the generalization he induced concerning the

[31] BROWN-SÉQUARD, "Des effets produits chez l'homme par des injections sous-cutanées d'un liquide retiré des testicules frais de cobaye et de chien." (*C. R. de la Soc. de biol.*, June 13, 1889, XLI, pp. 415-449); "Second note sur les effets produits chez l'homme par des injections sous-cutanées d'un liquide retiré des testicules frais de cobaye et de chien" (*Ibid.*, pp. 420-422). The origin of Brown-Séquard's researches on the therapeutic effects of extracts of the genital glands is to be found in these two initial communications which were received with derisive skepticism.

analogous action of other organic extracts, he was led to the idea that many organs secrete into the blood principles which have the property of acting in an elective manner on neighboring or distant organs. "We have called attention . . ." he says, "to a new method of therapy which consists in the use of subcutaneous, intraperitoneal or intravenous injections of special principles obtained by the maceration . . . of one or another of the glandular organs of the body. We find in a note relating to our communication published by M. Gley facts confirming our ideas on one of the vascular glands, the thyroid. . . .

"All the tissues, in our opinion, modify the blood by an internal secretion taken up by the venous blood. From this conclusion it necessarily follows that, if the subcutaneous injection of the juices extracted from these tissues produces only inadequate effects, it is necessary to inject the venous blood of these parts under the skin. . . .

"We admit that each tissue and, more generally, each cell of the organism, secretes for its own use special products, or ferments, which are poured into the blood and which influence, through the intermediary agency of this liquid, and not through the mechanism of the nervous system, all the other cells, thus rendering all of them mutually interdependent."[32] The last sentence is characteristic and contains the germinal form of the entire theory of functional correlations of humoral origin, or of a chemical nature, as we say to-day. "These particular soluble products," writes Brown-Séquard further,[33] "penetrate into the blood and influence, through the intermediary action of this liquid, the

[32] BROWN-SÉQUARD and D'ARSONVAL, "Additions à une note sur l'injection des extraits liquides de divers organs comme méthode thérapeutique" (*C. R. de la Soc. de biol.*, April 25, 1891, XLIII, 265-68).

[33] BROWN-SÉQUARD and D'ARSONVAL, "Recherches sur les liquides retirés des glandes et d'autres parties de l'organisme et sur leur emploi, en injections sous-cutanées comme méthode thérapeutique" (*Arch. de physiol.*, 1891, 5th series, III, 491-506; see p. 496).

other cells of the anatomical elements of the organism. The result of this is that the various cells of the economy thus form a solidarity, and this is accomplished by a mechanism other than that of the nervous system." "All the tissues—glands or other organs—have special internal secretions and thereby give to the blood something other than the products of their nutritive disassimilation. The internal secretions, either by a direct favorable influence, or by preventing the occurrence of noxious reactions, seem to be of great value in maintaining the organism in its normal state."[34]

Brown-Séquard added to the doctrine of Claude Bernard the notion of the action of "specific substances" secreted into the blood-stream by the various organs and, as a consequence of this, the no less important concept of functional humoral correlations. This greatly enriched the theory

[34] *Arch. de physiol.*, 1891, 5th series, III, 506.

of internal secretions. And hence the reason why Brown-Séquard is called the founder of the doctrine of internal secretions. It is certain that, had the concept of internal secretion not already existed, these new ideas, as I have already mentioned,[35] could never have come to life, and from this point of view there is a direct connection of Claude Bernard to Brown-Séquard, but the latter certainly discovered something new; he took a long stride in advance, a step in the determination of the causes of the functional mechanism.

Certainly, the study undertaken by him on the dynamogenic influence of testicular extract is imperfect—I showed why in 1897 [36]—and does not constitute a good example of the action of these "special internal secretions" whose importance he foresaw.

[35] "Traité élémentaire de physiol.," p. 1143, Paris, 1900.

[36] *Loc. cit., Année biologique.*

This example was soon furnished by the researches of G. Vassale (1890) and Gley (1891) [37] on the amelioration of the grave disorders resulting from complete thyroidectomy in the dog by injections of thyroid extract, as well as the application of this method to the treatment of myxedema (by G. R. Murray, 1891, followed by many other physicians). It was then no longer possible to doubt the sound foundations of Brown-Séquard's views on the rôle of internal secretions in "maintaining the normal state of the organism," or in reestablishing that normal state when it is altered by disease. This was the more

[37] I will avoid overburdening these pages with bibliographical notes by advising the reader to refer to A. BIEDL's work—capital for the study of the internal secretions—where they will be found easily ("Innere Sekretion," Berlin and Vienna, Urban and Schwarzenberg, 1910; 2nd Ed., 1913), or also two articles by SWALE VINCENT, "Innere Sekretion und Drüsen ohne Ausführungsgang" (*Ergebnisse der Physiol.*, 1910, IX, pp. 455-586, and 1911, XI, pp. 218-327). I will naturally give references which are not given in these two bibliographies or which are not easy to discover there rapidly.

strongly established several years later when there appeared the experiments of G. Glover and E. A. Schäfer (1894-1895) which immediately attracted attention. Also the work of N. Cybulski and Szmonovicz (1895), J. P. Langlois (1897), W. H. Howell (1898), etc., on the action of suprarenal extract on the cardiovascular system; those of N. Cybulski (1895), J. P. Langlois (1897), A. Biedl (1898), G. P. Dreyer (1899), etc., on the action of the venous blood of the suprarenal capsules and the numerous observations relative to the reduction in the intensity of metabolism in myxedema, or conversely, the increase in the metabolic activities of the body under the influence of preparations of thyroid extract or iodothyrin. Finally, it is of importance to recall that at the time when Brown-Séquard, in 1889-1890, was giving such an impulse to the theory of internal secretions, J. von Mering and O. Minkowski discovered the important rôle that the pancreas plays in the metabolism of sugar, and many immediately attacked the problem from other angles and showed that these changes in the carbohydrate metabolism are due to an internal secretion of the pancreas (R. Lépine, 1889, 1891;[38] E. Gley, 1891;[39] E. Hédon, 1892;[40] Vaughan Harley, 1892;[41] O. Minkowski, 1892;[42] J. Thiroloix, 1892[43]).

[38] R. LÉPINE, ''Nouvelle théorie du diabète'' (*Lyon méd.*, Dec. 29, 1889, LXII, p. 621); ''La pathogénie du diabète'' (*Revue scient.*, Feb. 28, 1891, p. 273); ''Sur la question du ferment glycolytique'' (*C. R. de la Soc. de biol.*, April 25, 1891, XLIII, 271). Lépine was the first to write the words ''pancreatic internal secretion.''

[39] E. GLEY, ''Sur les troubles consécutifs à la destruction du pancréas'' (*C. R. de l'Acad. des sc.*, April 6, 1891, CXII, 752); ''Les découvertes récentes sur la physiol. du pancréas'' (*Rev. gén. des sc.*, July 30, 1891, 469-76).

[40] E. HÉDON, ''Diabète expérimental'' (*Nouveau Montpelier méd.*, Jan. 2, 1892, p. 27).

[41] V. HARLEY, ''Pathogenesis of Pancreatic Diabetes'' (*Brit. Med. Jour.*, Aug. 27, 1892).

[42] *Berl. klin. Wchs.*, Feb. 1, 1892.

[43] J. THIROLOIX, ''Étude sur les effets de la suppression lente du pancréas'' (*Mém. de la Soc. de biol.*, Oct. 22, 1892, XLIV).

I have therefore not exaggerated the part played by Brown-Séquard in representing him as one of the founders and the resurrector of the theory of internal secretion. Such is also the opinion of numerous physiologists. I will only quote that of Biedl, one of those who has studied the question most completely: "In establishing the doctrine of internal secretions, Brown-Séquard has opened to physiology a new and fertile field of research, he has paved the way to the comprehension of many morbid disorders and has shown us a method of therapeutics which is both rational and, in many cases, remarkably successful."[44]

III. THE PRESENT CONCEPTION OF INTERNAL SECRETION

From the initial works which followed the publications of Brown-Séquard from 1889 to 1891, it was easy to see how rapidly

[44] *Loc. cit.*, p. 6.

the notion of specific functional excitants of glandular origin would develop. The original idea of Claude Bernard, that of glandular products modifying the composition of the blood, on the contrary, made no progress at all.[45] The ideas of Brown-Séquard having been experimentally verified, as he had foreseen, are taking possession of physiology and penetrating into pathology. It may be said that these ideas have not as yet been set forth with great precision and that they lack the necessary support of numerous and thoroughly studied facts. But they are quickly acquiring this precision while facts are rapidly accumulating which give them both

[45] It might be maintained—though vainly—that the two ideas can be confused, in the sense that from the passage into the blood of active specific products coming from certain glands, there would result an actual modification in the composition of this liquid. However, Claude Bernard's sole idea seems to have been that this modification is of a chemical nature. The new notion, since added, is that of the specific, elective power of various products of glandular origin. This is properly a physiological idea.

solidity and a wide scope. And the new knowledge is of an entirely new sort. "What there is characteristic about this," I said in 1897,[46] "is that we are now dealing with functional actions which have neither cause, nor reason, nor an end of their own; but each one of these acts depends on another physiological action, and this dependence appears to be always of a chemical nature, be it direct or indirect, being accomplished through the intermediary action of the nervous system. It is found, for example, that a substance formed at a certain point in the organism is of such composition that it constitutes the excitant adapted to stimulate action in another organ." The same year, in the report that I was charged with presenting to the XII International Congress of Medicine, at Moscow, on the pathological physiology of myxedema, I wrote: "Nothing can convince us that iodothyrin has not a

[46] *L'Année biol.*, p. 330.

direct influence on the metabolism. If, therefore, the thyroid gland, atrophied or attacked by some form of degeneration, no longer secretes that substance, nutritional disorders promptly follow, due only to the organism's lack of a principle which normally augments the intensity of the metabolic processes. And thus the regulation of the intracellular chemical phenomena appears to us as possibly of a directly chemical nature. There exist substances which enhance, others that moderate, these phenomena. Through the elective action of these bodies, nutritional equilibrium must be mechanically arrived at. Iodothyrin is one of these substances. . . . Are not the ferments secreted by the pancreas, which regulate the production of sugar by the liver and the oxydizing ferments . . . similar substances, acting in the same direct manner on the anatomical elements? . . . Furthermore, are there not still other substances, as the one, probably from the genital organs, which, according to the ingenious experiments of Mironoff, stimulates the secretion of milk at the necessary time, independently of all action of the nervous system?" Two years later, in 1899, I qualified with "specific glandular products" the "substances which result from the normal activity of many glands and which appear to play a considerable part in the regulation of the circulation. . . . Many have in fact been led, since we have understood the great importance of the internal secreting glands, to investigate if small quantities of the products of these glands, which pass at different times or continuously into the blood, do not exercise a more or less important influence on the vasomotor centers.

". . . The fact that substances of glandular origin, endowed with a stimulating or depressing cardiovascular action, are normally found in the blood, shows that they play an important part in the regulation of the blood pressure; and as the activity of the glandular organs often varies in an abnormal manner, being either excessively increased or diminished and sometimes even suppressed, the regulation of the circulation may be proportionately disturbed. Herein lies an indispensable labor to be undertaken; namely, the determination of the relations which exist between the normal variations of the circulation, and more especially between the blood pressure and functions of the glands like the adrenals, the thyroid, etc., the quantity of active principles they send out at various times or continuously into the blood, and the conditions which are antagonistic to the action of these substances. . . .

"From all these facts it follows that the tone of the muscles of the blood vessels, in so far as it depends on an automatic stimulation, either direct or indirect, is maintained not only by nervous stimulation, variations in the gases contained in the blood and by the products of the katabolic processes, but also by specific substances normally formed in various glands.''[47] To specific functional excitants in general, Starling gave, in 1905, the happy name of hormones (from ὅρμαω, I excite).

The notion of specific functional excitants, or hormones, led quite naturally to that of functional correlations of humoral cause. Because these same ''special soluble products,'' as Brown-Séquard said, are poured into the blood and ''influence the other cells of the organism,'' these cells ''are thus rendered into a solidarity—acting in unison—and by some mechanism other than the action of the nervous system'' (Brown-Séquard, see above). Many occupied themselves with determining these *functional correlations of a chemical nature,* connecting them with one another

[47] E. Gley, ''Mécanisme physiologique des troubles vasculaires'' (in ''Traité de Path. gén.'' by Ch. Bouchard, III, 133-211; see pp. 165-172).

and at the same time differentiating them from the correlations of *nervous origin,* already studied for many years. It was also recognized that there are still others, which form an intermediary class, the *neuro-chemical correlations,* or functional manifestations provoked by nervous action, this nervous action determining a chemical excitation which is carried to some part of the nervous system.[48]

During this time investigations followed one another, in which facts relative to the internal secretions and the action of these on the organism and its functions were examined and classified. In proportion as they multiplied, the facts assumed their true value and their meaning became more precise.[49]

[48] This is the classification which I presented to my classes of 1908-1909 in the College of France and that I have adopted for the outline study of functional correlations that is given in my "Traité élémentaire de physiologie," Paris, 1906-1909, p. 1142; 2nd Edit., 1910, p. 1167; 3rd Edit., 1913, p. 1181.

[49] It would not be out of place to cite here the first

While the work on functional correlations just indicated was being carried out,

of these studies as well as the most important of those which were published later:

E. Abelous, "La physiologie des glandes à sécrétion interne, corps thyroïde et capsules surrénales" (*Revue gén. des sc.*, May 15, 1893, IV, 273-278); E. Hédon, "Les travaux récents sur la physiol. des glandes vasculaires sanguines" (*Nouveau Montpellier Médical*, 1893, II, 467-468); E. A. Schäfer, "On Internal Secretions" (*Lancet*, Aug. 10, 1895, 321-324); E. Gley, "Exposé des données expérimentales sur les corrélations fonctionelles chez les animaux" (*L'Année biol.*, 1897, I, 313-330); "Le néo-vitalisme et la physiologie générale" (*Revue scient.*, March 4, 1911, 257-265); W. H. Howell, "Internal Secretions Considered in their Physiological, Pathological and Clinical Aspects" (*Trans. of the Congress of American Physicians and Surgeons*, 1897, IV, 70-86); H. C. Wood, "The Ductless Glands" (*Amer. Journ. of Med. Sc.*, 1897, CXIII, 505-13); Francis P. Kinnicutt, "The Therapeutics of the Internal Secretions" (*Ibid.*, 1897, CXIV, 1-23); James P. Putnam, "The Clinical Aspects of the 'Internal Secretions'" (*Ibid.*, 1898, CXV, 31-49); H. Boruttau, "Über den jetztigen Stand unserer Kentnisse von den Functionen der Blutgefässdrüsen" (*Deutsch. med. Woch.*, Sept. 21, 1899, XXV, 625-27); E. de Cyon, "Les glandes régulatrices de la circulation et de la nutrition" (*Revue gén. des sc.*, Sept. 30, 1901, XII, 828-35); "Die Gefässdrüsen als Regulatorische Schutzorgane des Zentralnervensystems," Berlin, J. Springer, 1910; A. Biedl, "Innere Sekretion" (*Wiener Klinik*, 1903, XXIX, 281-283); "Über innere Sekretion" (*Verhandl.*

the nature of the humoral excitants was more completely determined.

der Gesellschaft deutscher Naturforscher und Aertzte, 1911); C. E. de M. Sajous, ''The Internal Secretions and the Principles of Medicine,'' Philadelphia, 1903; G. Coronedi, ''Secrezioni interne e loro chimismo'' (*Arch. di fisiologia,* 1904, II, 36-59); W. M. Bayliss and E. H. Starling, ''The Chemical Correlation of the Secretory Process'' (*Proceedings of the Royal Soc.,* 1904, LXVII, 310-322); E. H. Starling, ''The Chemical Correlation of the Functions of the Body,'' Croonian Lectures, June, 1905 (*The Lancet,* 1905); A. Magnus-Levy, ''Organtherapie und Innere Sekretion'' (Berlin, 1906, pamphlet of 40 pages); ''Der Stoffwechsel bei Erkrankungen einiger Drüsen ohne Ausführgang'' (in ''Handbuch der Pathol. des Stoffwechsels,'' 1907, II, 311-354); Swale Vincent, ''Internal Secretion and the Ductless Glands'' (*Lancet,* August 11 and 18, 1906); ''The Ductless Glands'' (*Science Progress,* January, 1909); L. Fredericq, ''De la coördination organique par action chimique'' (*Scientia,* 1909, vol. V, Third year); L. Hallion, ''Les fonctions de sécrétion interne'' (*Revue scientifique,* May 8, 1909, 583-588); C. Parhon and M. Golstein, ''Les sécrétions internes'' (Paris, A. Maleine, 1909); A. Pi y Suner, ''Correlationes fisiologicas'' (*Association española para el progreso de las sciencias,* Valencia, 1910); S. J. Meltzer, ''Animal Experimentation in Relation to our Knowledge of Secretions, Especially Internal Secretions'' (*Proc. of the Pathol. Soc.* of Philadelphia, Sept., 1910, N. S., XIII, 170-196); I. Ott, ''Internal Secretions from a Physiological and Therapeutic Standpoint'' (Philadelphia, E. D. Vogel, 1910); G. Fano, ''La coordinazione umorale''

"The exciting substances mentioned," says, for example, Starling,[50] "so far as they are known to us, are not assimilable and exert a dynamic influence on the living cells. In this respect they are analogous to substances which form the usual remedies of our pharmacopeias. Since it is their rôle to be frequently excreted, in virtue of a normally organic function, into the circulatory system by which they are conducted to each of the organs on which they exercise their specific action, they cannot therefore belong to that class of complex compounds, animal or vegetable in

(*Atti della Soc. Italiana por il progresso delle sc.*, Naples, Oct., 1910); R. G. HOSKINS, "The Interrelation of the Organs of Internal Secretion" (*Amer. Jour. of Med. Sciences,* March and April, 1911).

For original views or remarks filled with new information, see above all the works of BAYLISS and STARLING, E. DE CYON, G. FANO, E. GLEY, S. J. MELTZER and E. H. SCHÄFER. To this list must naturally be added Biedl's book and SWALE VINCENT'S two studies (in "Ergebnisse der Physiol."), mentioned above.

[50] Address delivered at the meeting of the Gesellschaft Deutscher Naturforscher und Aerzte, Stuttgart, 1906.

origin, which we term toxins." And through the study of the remarkable properties of several of these exciting substances (Reizstoffe, hormones), as for example the active principle of thyroid,—iodothyrin?—adrenalin and secretin, physiology has discovered an entirely new field of investigation, which is as yet far from being completely explored.

Pathology did not fail to participate considerably in all these researches and the progress of our knowledge of the endocrine glands. Some important contributions by pathologists helped directly in the upbuilding of the doctrine of internal secretions. Let us but recall what those who labored to raise this doctrine obtained from the observations of Lancereaux (1877-79) on the pancreas in diabetes and the profound studies of diabetes in its relations to lesions of the pancreas, beginning with the researches of J. von Mering and Minkowski (1889-90); from the comparison (F.

Semon, 1884) between the description of the clinical phenomena of myxedema made by English clinicians, and the observations of Swiss surgeons, J. and A. Reverdin, Kocher, on post-operative myxedema, as well as the effects of thyroid medication on this syndrome; from the pathological anatomy of acromegaly; from Addison's disease and the study of the toxic effects of adrenalin, etc. What a light is thrown by physiological experiments on all these clinical and anatomo-pathological facts, and how, reciprocally, the latter strengthen the conclusions arrived at through animal experimentation! Medicine has drawn its profits from this cooperation of physiology and pathology: hemophilia is explained; many of the anomalies of growth are also elucidated; the pathogeny of diabetes is cleared up; the pathology of the thyroid apparatus has been worked out; that of the hypophysis and thymus undertaken with success; the discovery and definition of new syndromes in which the suprarenal capsules or reproductive glands are concerned. Such is the sum total of the main acquisitions acquired through this work. "The following two factors," Meltzer says rightly,[51] "are responsible, I believe, for the marvelous progress of this new branch of experimental medicine. In the first place, the recent investigations on the ductless glands were carried out purely by biological methods of research. The second factor is to be found in the important fact that these investigations had the great advantage of an harmonious cooperation of critical animal experimentation, scientific clinical observations and the intelligent analysis of surgical results." There is an underlying reason for this cooperation, which I recalled in my Report on Myxedema at the XII International Congress of Medicine at Moscow, to wit: "For the savant," as

[51] *Loc. cit.*, p. 171.

Claude Bernard said, "neither medicine nor physiology is distinct; there is only one science of life, there are only the phenomena of life which must be explained, in the pathological state as well as in the physiological."[52]

[52] CLAUDE BERNARD, "Introduction à l'étude de la médecine expérimentale," p. 257, Paris, 1865.

II

DISTINCTIVE CHARACTERISTICS OF THE INTERNAL SECRETORY GLANDS AND THE PRINCIPAL PRODUCTS OF THEIR ACTIVITIES

II

DISTINCTIVE CHARACTERISTICS OF THE INTERNAL SECRETORY GLANDS AND THE PRINCIPAL PRODUCTS OF THEIR ACTIVITIES

Knowledge of the nature and functions of the internal secretory glands can only be based on the precise determination of the conditions which make of these glands a special system, and then on the discovery of the distinctive characteristics of the products resulting from the activities of these organs. Herein lies the primary and fundamental problem.

I. CONDITIONS ESSENTIAL TO INTERNAL SECRETION

Three conditions suffice to determine an internal secretion as such, but these three conditions are absolutely necessary: The first is of an histological nature; the second results from chemical considerations; and the third is of a physiological order. That is, the cells of the vascular glands in question must present the characteristics of granular elements and these elements must be in close relation to the efferent vessels of the organ; in these cells and in the venous blood of the gland or in the efferent lymph, a specific substance must be chemically determined; finally, the venous blood of the gland must have the physiological action and properties of this specific substance.[1]

Undoubtedly, for many of the organs included among the endocrine glands, all

[1] For technical reasons which are easily understood, the investigation of specific products in the lymph is even more difficult than in the blood. Up to the present, we have only been able to determine the presence of specific substances in the venous blood of some glands; on the other hand, the attempts that it has at times been possible to make on the lymph have always resulted negatively. (A. J. CARLSON and A. WOELFEL, "On the Internal Secretion of the Thyroid" (*Amer. Jour. of Physiol.*, 1911, XXVI, 32-67); A. J. CARLSON and F.

these conditions have not been satisfied. Several of the latter category are, however, most certainly such glands, even to the most exacting critic. In the case of these glands, in lieu of all the conditions mentioned above, we have a collection of facts which permits us to recognize them as endocrine glands. In science as in all human activities, we cannot always follow implicitly the dictates of logic. No one would think, for example, of contesting the right of the thyroid gland to a position among the endocrine glands, although there has not as yet been discovered in the venous blood of that organ any specific chemical or physiological property (Carlson, Coronedi, Cunningham,[2] Gley). But so spe-

M. Drennan, "The Alleged Discharge of the Internal Secretion of the Pancreas into the Lymph" (*Proc. of the Soc. for Exper. Biol. and Med.*, 1914, XI, 71-72). This, however, is no reason why we should not recognize, as does R. Lépine (*Revue de Médecine*, Feb. 10, 1914, XXXIV, p. 81-88), that it would undoubtedly be interesting to undertake studies of this sort.

[2] Cunningham has unsuccessfully used as much as 30

cific are the effects of extirpation of this organ and so characteristic is the action of thyroid extract in counterbalancing the harmful effects of this deficiency, that we are forced to admit that substances contained in thyroid extract have an elective influence on the internal medium.[3]

By an analogous, but not as yet so well founded, compromise, we are led to consider the spleen and the thymus as internal secretory organs, the reasons being purely physiological: The spleen because it furnishes the blood passing through it with a substance which transforms trypsinogen into active trypsin, as was shown by the experiments of A. Herzen (1888, 1893);[4]

to 50 cc. of thyroid venous blood for the investigation of an action on the arterial pressure. Further mention of this work of Cunningham will be found on p. 216.

[3] See also p. 111.

[4] A. Herzen, "Appunti di chimica fisiologica" (*Annali di chim. med. e farm.*, 1888, VIII, IV series, Torino); "Rate et Pancréas" (*C. R. de la Soc. de biol.*, July 29, 1893, XLV, pp. 814-817). Herzen's opinion finds support in the experiments of Lafayette B. Mendel and Leo F. Rettger (*Am. Jour. of Physiol.*, 1902,

the thymus because its extirpation results in disordered development of the skeleton (experiments of K. Basch, 1896; Cozzolino, 1903; Sommer and Floerken, 1908; Ugo Soli, 1909; M. Lucien and J. Parisot, 1910); and, furthermore, because in castrated animals the thymus is larger (A. Calzolari, 1898;[5] J. Henderson, 1904; Ugo Soli, 1906 and 1909), while in animals whose thymus has been removed, the development of the male genital glands is arrested (Ugo Soli, 1909).[6] But the spleen and the thymus are neither histologically nor em-

VII, 387-404), who have stated that injections of splenic venous blood increase the proteolytic power of the pancreas. The defibrination, it is true, might be a cause of error, if we admit that the destruction of the leucocytes liberates kinase. But this objection can be answered by recalling GACHET's experiments (in Pachon's laboratory, *Thèse,* Bordeaux, 1897)—which were negative—with defibrinated arterial and venous blood.

[5] The thymus, according to Calzolari, diminishes in weight at puberty, when the generative organs begin to function.

[6] NOEL PATON (1904) has obtained results which are the reverse of these; that is, an increase in weight of the testicles after thymectomy.

bryologically glandular organs; they are hemolymphoid in nature. With this reservation, we may state that they discharge into the blood products akin to the internal secretions.

(1) Histological Conditions. — Although without any relation to the exterior, being without excretory ducts, the glands called vascular, internal secretory or endocrine, are penetrated by numerous blood vessels with which their cellular elements are in intimate connection and into which they deposit their secretion.

Exceptions are the liver and the pancreas, which are provided with excretory canals, but which are also glands of internal secretion; their cells, so to speak, are pointed in two directions, towards the excretory canals and towards the blood vessels.

We find the same double orientation in the duodenojejunal mucous membrane, the cells of which discharge a digestive juice into the intestinal cavity, i.e., to the exterior, but they also, under certain conditions with which we are thoroughly acquainted, deliver to the blood the substance which stimulates the pancreas to secretion, namely, secretin. Moreover, we may remark that it is not as yet known definitely how secretin is formed and whether this substance is really a product of glandular origin. Furthermore, it is not only in its rôle of secretin producer that the pancreas behaves like an endocrine gland; it is also an absorbing organ. The histological process of the absorption of fats consists in intraprotoplasmic elaboration; in other words, it is a secretory process, and perhaps this is no less true of the absorption of albuminoid substances. These are the products of the decomposition of those materials which reach the intestinal mucous membrane on its free side, and the cells of this membrane deliver, by their internal side, fats and perhaps also albuminoids to the blood.

It is also not without reason that R. Heidenhain, Oppel, Pflüger and others have compared the phenomena of absorption to those of secretion. In fact, as several histologists have shown, the epithelial layer of the intestine behaves like a true granular element; it is a "granular element with two surfaces," physiologically speaking. Through its cavitary, or external, surface, it receives and elaborates the materials to be absorbed; through its internal side pass out, after having been elaborated, the materials which then pass into the vascular or lymphatic circulation. These two acts undoubtedly take place, respectively, in the supranuclear and infranuclear zones of the cell. The physiological polarity of the cell imputes a morphological bipolarity and also the presence, in both zones alike, of the organisms indispensable to glandular secretion. This appears to be verified by the observation which shows the same mitochondrial formations in both zones, while the ordinary glandular cell is only provided with one of them. (Champy.[7]) Absorption is thus only a particular case of the general process of secretion. And the essential result of this secretion—the formation and passage into the blood of the specific albumins of the plasma[8]—is of the highest importance. "We may say," Champy remarks[9] "that the intestinal epithelium secretes the plasma,—the internal medium,—or at least the principal part of it, and it is indeed the most highly differentiated secretion of the organism, for this internal

[7] A. PRENANT and P. BOUIN, "Traité d'histologie," vol. II, p. 823, Paris, 1911.

[8] It is known that the rôle of the intestinal wall in the formation of the proteid substances of the blood plasma can not actually be considered as beyond question.

[9] CH. CHAMPY, "Recherches sur l'absorption intestinale et le rôle des mitochondries dans l'absorption et la sécrétion" (*Arch. d'anat. microscopique*, 1911, XIII, 55-170).

medium is to the highest degree specific."

There are, therefore, glands with a double secretory function, external and internal.

We can make still another distinction between the various endocrine glands, and one which is not devoid of interest from the point of view of the physiological significance of these organs. It has been demonstrated that the cells of the choroid plexuses are granular cells the activity of which regulates the composition of the cerebrospinal fluid,[10] contained in the cere-

[10] J. W. FINDLAY, "The Choroid Plexuses of the Lateral Ventricles of the Brain, Their Histology, Normal and Pathological" (*Brain*, 1897, XXII, 161-203); J. GALEOTTI, "Studio morfologico e citologico della volta del diencefalo in alcuni vertebrati" (*Riv. di patol. nervosa e mentale*, 1897, ii, 480-517); H. OBERSTEINER, "Anleitung beim Studium des Baus der nervösen Central-organe im gesunden und kranken Zustande," Fourth edition, pp. 651-53. Leipzig and Vienna, 1901; A. PETTIT and J. GIRARD, "Processus sécrétoires dans les cellules de revêtement des plexus choroïdes des ventricules latéraux, consécutifs à l'administration de muscarine et d'éther" (*C. R. de la Soc. de biol.*, July 27, 1901, LIII, 825); "Sur la fonction sécrétoire et la morphologie des

bral ventricles and in the central canal of the spinal cord. And it is known, furthermore, that the cerebrospinal fluid thus formed returns to the blood by the perivascular sheaths (lymphatic path) and the blood vessels of the dura mater. This cerebrospinal fluid, first secreted into an exterior cavity, and then reabsorbed, is an example of an externo-internal secretion; and it might be said that the choroid plexuses are glands of external secretion, but having an internal destination (A. Pettit and J. Girard).[11]

Conversely, there are internal secretory glands having an external destination, or, in other words, there are *interno-external* secretions.[12] A typical member of this last

plexus choroïdes des ventricules latéraux du système nerveux central'' (*Arch. d'anat. microscopique,* 1902, V, 213-264); F. K. STUDNICKA, ''Unters. über den Bau des Ependyms der nervösen Centralorgane'' (*Anat. Hefte,* 1900, pp. 303-431).

[11] This means that the secretion, made on the exterior, is intended to be reabsorbed.

[12] Biedl has used a somewhat indefinite name—negative

class is urea, formed in the liver, excreted into the blood and taken up by the kidneys to be eliminated to the exterior. Such also are the phenylsulphates, if we admit that they are formed in the liver; there are also substances excreted into the hepatic blood and intended for ultimate renal excretion. No matter which gland is in question, whether properly internal or mixed (having a double secretion, internal and external), or a transitory external secretion (an external secretion having an internal destination, mentioned above), or a transitory internal secretion (finally destined for the exterior), there is not one with cellular elements which can not be characterized as glandular. In all these cells the nucleus and a part of the protoplasm (upper mitochondrial protoplasm, or ergastoplasm) participate in the elaboration of the secretory products in the

internal secretion—for such a secretion. Swale Vincent has also used this terminology.

same manner as in the cells of the glands that have been best studied histologically.

In brief, it is the morphological condition—cellular structure and relations of the cells to the blood vessels—that is best satisfied by the endocrine glands.

(2) Chemical Condition. — Every product of secretion is a cellular differentiation, the morphological expression of a chemical elaboration. This differentiation is a result of cytoplasmic activity; the product must be recognizable by certain chemical characteristics, both in the glandular cell itself and outside of it. This means, in the case of an internal secretion, which is what we are primarily concerned with at present, that the products of secretion must be found in the efferent blood of each gland.

The presence of the products of secretion in the glandular cells has only exceptionally been demonstrated. It has been shown, indeed, that there are fat globules in the intestinal cells and in the cells of adipose bodies,[13] and that adrenalin exists in the suprarenal cells; in the thyroid cells, it is true, the presence of a complex product of colloid matter has been demonstrated, but do we know if this colloid matter contains only the active principle of the secretion, or if it contains at all the active principle?

Likewise, only in a small number of instances have the specific principles of the endocrine glands been identified chemically

[13] Although the adipose bodies are not made up of epithelial cells, the adipose cell is nevertheless a glandular cell and has the closest connection with its capillary plexus. This undoubtedly explains the ease with which deposits of fat are accumulated when the organism has need of them, as, for example, in jaundice. The following observation furnishes a very clear proof of this fact and at the same time of the glandular nature of adipose bodies: Prenant has seen mitochondria formed in three days throughout the protoplasm in the cells of adipose bodies in the nape of the neck of kittens rendered athreptic by defective alimentation; the cell was thus brought back to its initial condition and all the fat disappeared from it, being collected in the vessels. (Prenant told me this interesting fact by word of mouth.)

in the venous blood of a given internally secreting organ. Fatty bodies have been found and even quantitatively determined in the veins of the intestine and in the thoracic duct; in the blood of the hepatic veins glycose and urea have been found, and in the blood of the suprarenal vein, adrenalin.

Numerous chemical investigations of the products of internal secretion are in progress at the present time. This research must ultimately lead to the determination of what these substances are, what is their nature and therapeutic value. In fact, with the exception of the products which serve as nutritive materials (glycose, fats, specific albumins), the products intended for excretion (as urea) and finally adrenalin, our knowledge of the chemical properties of these bodies is very limited. The most interesting from this point of view, as well as from the physiological standpoint, appear to be the bodies of synthetic intracellular origin, as adrenalin. But, for the present moment, this is the only one known; in spite of the efforts of A. Ostwald, of Zurich, we are not yet sure if his iodothyroglobulin is the active principle of the thyroid gland. Likewise, the chemical nature of secretin is as yet unknown.

(3) Physiological Condition. — That the physiological condition be fulfilled, we must find a specific substance in the efferent blood of a gland, as demonstrated by the physiological properties of this blood, collected and injected in variable quantities into another animal. Furthermore, this specific substance must remain for a sufficient period of time in the general circulation, since, to reach a more or less distant organ on which it acts, it is necessary, at least in the majority of cases, that the active product secreted passes with the efferent blood of the gland into the blood of the general circulation. It is all the more necessary that its presence

be speedily demonstrated, inasmuch as these glandular products, diffused throughout the blood stream, may very quickly lose their activity, either through excessive dilution, or as a result of a process of destruction as is the case, for example, with adrenalin (see p. 215). Their existence in the general circulation may therefore be so short, or they may be so minute in quantity, as to appear without any physiological significance. To this it could be objected, of course, that this substance, soon after entering the arterial blood, does not remain there, but fixes itself onto the organs on which it acts, this fixation being the condition for its action. Hence the difficulty of finding these substances in sufficient quantity at a given moment in the arterial blood. One could, in any case—provided he was assured of their physiological destination—detect them in the blood of the left heart. Only the physiological destination of the secreted product gives the true significance of a secretion (see p. 149). Now, in so far as the internal secretions are concerned, this destination is marked by the passage of a specific substance from the venous blood of the gland into the general circulation, and it is only the physiological properties of this venous blood, temporarily acquired by the blood in general, that attest it.

To recapitulate, the essential proof of an internal secretion—in addition to the clinical proof, when this is available (see below)—is the physiological proof, that is to say, the demonstration of the physiological properties of a specific glandular product transferred in a more or less durable form to the blood. This is, together with the chemical proof, whenever the latter can be given, the essential proof of an internal secretion; and it is perhaps the most important for physiologists and pathologists. Far from having been furnished for all the endocrine glands, its investigation, on the contrary, has been very much neglected.

1. The physiological demonstration has been given for the glands which elaborate the substances that modify chemical processes and act in the manner of diastases. One of these substances, that derived from the spleen, serves to activate a ferment,[14] although the mechanism by which this is accomplished is not known; another, that derived from the pancreas, favors a process of assimilation, and we are still discussing by what mechanism this takes

[14] This interpretation is the result of the experiments of Pachon (of Bordeaux) and his pupil Gachet (1897). These experiments consisted essentially in watching the speed of digestion, which permitted the observers to note the differences between the activity of pancreatic extracts from animals whose spleen had been removed, and normal animals. This also enables them to state with certainty the *activating* property of splenic extract from an animal while digesting on pancreatic digestion. And these authors have also shown that the splenic substance endowed with such properties is a ferment. This was, therefore, the first example of one ferment having an activating influence on another.

place; and a third, from the liver, plays the part of an antibody.

Thus the experiments of Herzen and of Lafayette Mendel and Rettger have proven the influence of the blood of the splenic vein on the proteolytic activity of the pancreas.

The rôle played by the pancreas as a gland of internal secretion was only appreciated as a consequence of experiments on extirpation of that organ; the only direct proof was furnished by experiments which I published in 1891 showing that the ligature of all the pancreatic veins was followed by glycosuria. But these experiments might be criticized because the dogs operated upon survived only for a limited term. The experimental grafting of the pancreas (O. Minkowski, Hédon, J. Thiroloix, Gley and Thiroloix) supplied better demonstrations. We know, however, that Pflüger contested its significance in the last years of his life. Finally, there came the experiments of uniting two animals, as jointed twins—parabiosis—made by J. Forschback (1908-09). Two dogs were connected to one another, the pancreas being removed from one of them. It was found that the glycosuria which was induced in this animal remained very feeble as long as it was in symbiosis with the other. This was evidently because the substance secreted by the pancreas of the normal dog, and which acted on the assimilation of sugar, passed into the blood of the dog without a pancreas. However, it had first passed through the blood of the normal animal and was thus diluted; hence the slight glycosuria. The same interpretation applies to the laborious experiments that Hédon has carried out with much perseverance during several years. Hédon saw, in fact (1909-1912), in experiments in which the circulations of diabetic and normal dogs were joined, a decided diminution of glycosuria taking place within several hours following the mixture of the blood of the two animals. Furthermore, he has stated [15] that the transfusion of pancreatic venous blood into the general circulation of a diabetic dog, by anastomosis of a pancreatic vein with the jugular vein, considerably reduces the excretion of sugar in the depancreatized animal; and he has found (1911) that when venous pancreatic blood is injected into the mesenteric vein of a diabetic dog, the glycosuria of that animal diminishes greatly for several hours. It is thus clear that the metabolic action of the pancreas on the sugar results from an internal secretion.

The proof of the anticoagulative function of the liver which was given by Gley and Pachon [16] has been completed and for-

[15] *C. R. de la Soc. biol.*, Feb. 1, 1913, LXXIV, 238.

[16] E. Gley and V. Pachon, "Du rôle du foie dans l'action anticoagulante de la peptone" (*C. R. de l'Acad. des sc.*, Aug. 26, 1895, CXXI, 383); "Influence de l'extirpation du foie sur l'action anticoagulante de la peptone" (*C. R. de la Soc. de biol.*, Nov. 23, 1895, XLVII, 741); *cf.* also *Arch. de physiol.*, 1895, 5th series, VII, 711-717, and 1896, VIII, 715-723.

tified by the experiments of Delezenne.[17] They have demonstrated the presence in the venous hepatic blood of the anticoagulative substance which one can force the liver to produce in large quantities by the administration of various substances, such as albumoses, extracts of various organs, some serums and venens, etc.

2. In the case of the two hormones which we know best—secretin and adrenalin—proof has likewise been given of the passage of these excitants into the venous blood of the organs that produce them.

The experiments, as far as secretin is concerned, are not numerous, but we may safely consider them as sufficient. The

[17] C. Delezenne, "Formation d'une substance anticoagulante par circulation artificielle de peptone à travers le foie" (*Arch. de physiol.*, 1895, 5th series, VIII, 655-668); "Recherches sur le mécanisme de l'action anticoagulante des injections intravasculaires de peptone, de sérum d'anguille et d'extraits d'organes" (in *Travaux de physiol. du laboratoire du professeur Hédon*, Montpellier and Paris, 1898, pp. 212-262; see page 241).

presence of this excitant in the venous blood of a segment of the jejunum (Wertheimer, 1903;[18] Fleig, 1903[19]) and even in the general circulation (carotid blood, Enriques and Hallion, 1903) has been demonstrated.

In the case of adrenalin the demonstration is as perfect as is possible. Small doses of venous suprarenal blood manifest all the properties of suprarenal extract by their action on the sympathetic system and, furthermore, their action is indeed that of adrenalin itself.[20] According to my experiments, it is sufficient to inject 1 cc. in a kilogram weight of the animal, or even less—0.7 cc. in some cases—into a dog to

[18] It should be remarked, however, that Wertheimer's experiments were not carried out with the normal excitant of the duodenojejunal mucous membrane—hydrochloric acid—which liberates the secretin of this mucosa, but with essence of mustard and with ether.

[19] Fleig's experiments were made with the use of hydrochloric acid as the excitant of the mucous membrane.

[20] I do not think, however, that any one has as yet endeavored to produce adrenalinic glycosuria by the injection of suprarenal venous blood.

provoke a very pronounced cardiovascular reaction.

As for the mammary hormone, the presence in the blood of a substance exciting the secretion of milk has only been proven indirectly. First, by the experiments of Mironoff,[21] which showed that after the section of all the nerves of the mammary gland in the she-goat, the breasts were nevertheless hypertrophied after the young had been brought forth; they secreted like those of a normal animal. This fact was confirmed by the experiments of Ribbert (1897-98), which consisted in the transplantation of mammary gland tissue under the skin of the auricle of a female guinea-pig. The transplant took, developed and even secreted when the guinea-pigs were impregnated.[22] And it is also confirmed

[21] M. Mironoff, "De l'influence du système nerveux sur le fonctionnement des glandes mammaires" (*Arch. des sc. biol.*, 1895, III, 353-380).

[22] These experiments have been successfully repeated on the bitch by K. Basch (*Deutsche med. Woch.*, May 26, 1910).

by observations on the Czech pygopagus monster,—the two connected sisters, Rosa and Josepha Blazek. When, three years ago, one of them, Rosa, became pregnant, twelve days after she had been confined the breasts of her sister Josepha were enlarged like hers and secreted milk at least as well as those of Rosa.[23]

The origin of this substance that excites the secretion of milk—the galactogogue hormone—has not as yet been absolutely determined. It may come from the placenta (K. Basch, 1909; B. Aschner and Ch. Grigoriu, 1911), or from the myometrial glands of the uterus (Ancel and Bouin, 1911), or from the suppression of an inhibitory stimulus of fetal origin, since although the development of the gland takes place during pregnancy, its secretion is not established till after the close of the gravid period, when the fetus is expelled.

[23] C. Trunecek, "L'accouchement du pygopage Rosa-Josepha Blazek" (*Semaine méd.*, May 18, 1910, p. 229).

This is the theory of Lane-Claypon and Starling.[24] In this uncertainty it would evidently be desirable that some one should discover in the venous blood of some organ the hormone which acts on the mammary gland.[25]

That the waste products should play the part of excitants, they must be found in the venous blood of the organ which produces them. This appears to be the case

[24] The experiments of Lane-Claypon and Starling have not been confirmed in all points by C. FOA (*Arch. di fisiologia*, 1908, V, 520-532). The latter, moreover, sets the important question, Does the mammary gland, once it is developed, have need of a functional stimulant and does not the supply of materials necessary for the formation of milk which is brought by the blood suffice to establish and maintain the secretion?

[25] E. A. SCHÄFER has recently announced (*XVIIth Intern. Congress of Medicine*, London, 1913, section II, Physiology, Part II, p. 81) that the serum of normal animals—e.g., guinea-pigs—may at times have a galactagogue action on the cat in lactation; but he was not able to determine the conditions which make this property appear. Some, however, he adds, may be disposed to think that this ''galactagogue hormone'' comes from the posterior lobe of the hypophysis. For the moment, however, this is only an hypothesis.

with urea at least (experiments of E. de Cyon, 1870; W. von Schröder, 1882, etc.). But does the urea of the blood, upon arriving at the kidneys where it is eliminated, become an excitant of the renal cells? We know nothing which permits us to affirm this, although the diuretic action of urea, when injected in quite strong doses, is well established.

Carbon dioxid, as is well known, is found not only in the blood of any particular organ, but in the blood of all organs. This is (see below) one of the reasons why we (Gley, Meltzer) do not consider this substance as a true hormone.

It is now to be remarked that none of the *internal secretory products with a morphogenic action*—this term will be defined later on—has been found in the venous blood of the glands in which we have, on some other grounds, reasons for admitting their existence. The physiological attempts made with thyroid blood, as I have already observed, have up to now been fruitless. No one has ever, for anatomical reasons, attempted to collect the blood which comes from the hypophysis, ovaries or thymus. It should be possible to make this attempt with the testicle; and it is much to be desired that this be done.

Definitely speaking, the sum total of our knowledge of the properties of the various sorts of glandular venous blood is very modest. While the doctrine of internal secretions has been expanding more and more, the solid foundation on which it rests has remained narrow, for the substances whose presence in the venous blood has been physiologically demonstrated in an indisputable manner number only four: the pancreatic substance which serves to regulate the normal glycemia, the hepatic antithrombine, secretin and adrenalin.

Action of Organic Extracts.—Besides the methods of study of the products of internal secretion mentioned above, there is another and more simple one; in fact so simple that it has turned experimenters from the rational path, which is the investigation of the physiological properties of venous blood from various sources. The other method consists in the administration of organic extracts.

It is but just to recognize that there was, besides its ease, a scientific excuse for the use of this method which has spread so widely and rapidly. The first extracts to be thus studied successfully were from the thyroid and suprarenal bodies. Thyroid extract manifested, even in the first experiments (G. Vassale, Gley) and the first applications to the treatment of myxedema (G. R. Murray), its specific action against disorders arising from the suppression of the thyroid secretion. From this it was to be seen that the injection of an organic extract replaces immediately and for the time being the function of that organ. This led to attempts to generalize and to use extracts from other organs in the same manner. The unfortunate experiences, for example, in the treatment of Addison's disease by suprarenal medication, or in the employment of pancreatic extracts against diabetes, did not stop these therapeutic attempts. Besides, the important discovery by Oliver and Schäfer of the cardiovascular action of suprarenal extract, confirmed a year later by the discovery of the similar action of the suprarenal blood, appeared to show the excellence of this method and it paved the way for the discovery of the specific properties of internal secretions. The result is that nearly all the investigations made in the past fifteen years on this question have followed a method which, while not absolutely defective, is incomplete and therefore inadequate.

Not that several warnings have not been given. "It is necessary," I said in 1899,[26]

[26] In CH. BOUCHARD's "Traité de pathologie gén.," t. III, p. 169.

"to ask oneself if all the glands in question . . . normally produce substances identical with those whose actions are manifested by their extracts. In fact, the substances contained in the extracts may not exist in the living glandular tissue; furthermore, nothing proves *a priori* that, if they are formed in the living gland, they regularly leave it by the blood vessels in order to exercise their influence on the different arterial regions of the organism. . . . It is necessary that the demonstration given for the suprarenal bodies be also supplied for the other glands. . . . This demonstration is particularly necessary, for example, in the case of the thyroid gland."

In the same year Lewandowsky[27] remarked in connection with the suprarenal extract, that we cannot conclude anything about the action of an organ in the body from the results of injecting an extract of

[27] *Ztschr. für klin. Med.*, XXXVII, 535-46.

that organ into the blood. M. Lambert,[28] in giving his first warning of the toxicity of extracts of the corpora lutea, adds: "I will take good care not to formulate an hypothesis on the mechanism of internal secretion of the corpus luteum because of these observations. The activity or the toxicity of any organ whatsoever does not authorize such deductions. The isolation of substances, elsewhere so interesting, extracted from those glands of internal secretion which have been most studied, has not yet led to any sure conclusions as to the rôle they play in the economy." Later, Biedl expressed himself as of the same opinion:[29] "To prove conclusively that in an organic extract we have a hormone, the product of internal secretory activity of the particular organ we deal with, we must first establish two postulates, in effecting which, at the present state of our

[28] *C. R. de la Soc. de biol.*, Jan. 12, 1907, p. 18.
[29] "Innere Sekretion," 2nd Ed., vol. i, p. 30.

knowledge, we encounter great difficulties. First, it is absolutely necessary that we have a thorough knowledge of the chemistry of the active substance. In this direction there is, as yet, a vast field for research before us. . . . A second, just as important, postulate lies in the proof that the active substance shown to be present in the organic extract is produced in the gland *intra vitam* and is discharged into the circulating blood.'' And Biedl shows that the only hormone which responds to these two desiderata is adrenalin.

No attention has been paid to these warnings. It is therefore of importance to recall that from the action of an organic extract we have no right to draw conclusions as to its internal secretion without further investigation, as has been done only too often. In order to admit that an organ has such a function, we must, at least in the absence of the above mentioned chemical and physiological requirements—

discovery of a specific product in the venous blood—have a mass of concordant facts, of physiological, pathological and therapeutic nature. It is necessary that the extirpation of the organ to which we attribute an internal secretion give rise to a series of functional disorders, to a syndrome (which may attain actual disease in man) the attenuation or eradication of which is obtained through the administration of an extract of the organ, or through grafting whenever the latter is possible. The success of this substitution therapy is the counterproof of experiments consisting in the destruction of organs. It is because this concordant mass of facts has been obtained in the study of the function of the thyroid and in that of the interstitial glands of the germinal organs that the thyroid, the interstitial testicular gland and the corpus luteum are justly considered as organs of internal secretion.

The determination of the action of organic extracts, taken by itself, is powerless to reveal such a function.

Not that I fail to realize the importance of some of the results that have been attained through investigations of organic extracts. And when I think of the information on the physiological action of various extracts that has been furnished us through such studies, from which interesting therapeutic applications have resulted; when I think of the contributions supplied to the question of the coagulation of the blood, of theories of immunity, etc., I am almost tempted to regret my criticisms. For I would not like to appear ungrateful towards so many assiduous investigators. But the physiologist, seeing matters from his own particular point of view, must maintain his criticisms. We will soon see how important these are, especially at present. Besides, it is less a question of combating this method of investigation itself than of stopping its almost exclusive use and the abuses which it has suffered in the investigation of internal secretions. It has held back work on the physiological properties of venous blood coming from the various organs. To be sure, the latter method is much more laborious, infinitely more difficult and less fertile in immediate results, but it is surer and more precise.

The study of internal secretions by the method of administration of organic extracts raises objections of principle, or theoretical objections, and objections of fact.

1. *Theoretical Objections:*

A. There is no available *a priori* proof that the substances present in the extract existed in the living glandular tissue.

B. There is no proof that the substances present in the living gland are regularly excreted into the venous blood of the gland.

C. Every extract of an organ is a conglomeration of substances, and this conglomeration is evidently not discharged at random, or continuously, into the venous blood of the organ. On the contrary, according to what we know, it would seem that when required for special physiological purposes at a given moment, a certain substance passes in the venous blood, a sole product of secretion.

D. Likewise, the physiological action of an organic extract, which contains various substances, can only be complex; nothing proves that the venous blood of the organ has this action.

To sum up, organic extracts, no matter what is their origin and mode of preparation, surely contain substances other than the products which the living organ delivers to the venous blood. What are the physiological and toxicological actions of these substances, and how are we to recognize those of the specific products? May not the properties of the one mask or exaggerate those of the other, and to what degree is this a fact? These questions cannot be answered at the present state of our knowledge.

2. *Objections of Fact.*—Then come the objections of fact, of which there are many. First, there is to be considered the well-known toxicity of organic extracts, *per se,* which may mask the action of the specific products.

Furthermore, as this toxicity is very variable—changing according to the origin,[30] the mode of preparation, the time

[30] Numerous examples of this fact could be mentioned. I will only cite PEARCE'S experiments with kidney extracts (quoted by J. L. and E. M. MILLER, "The Effect on Blood Pressure of Organ Extracts," *J. of Physiol.,* 1911, XLIII, pp. 242-246) and those of CHAMPY and GLEY with extracts of corpus luteum (*Soc. de biol.,* July 22, 1911, p. 159). It is of interest to note here that the action of organic extracts may vary according to conditions of the animal from which they were derived (sex, age, inanition, fatigue, sexual activity, etc.); *cf.* ALDO PATTA, "Contributo critico e sperimentale allo studio dell'azione degli estratti di organi sulla funzione circolatoria" (*Archivio fi farmacologia sperimentale e scienze affini,* 1906, V, pp. 188-215 and 576-605, and 1907, VI, 80-119).

that has elapsed between the extirpation of the organ and the preparation of the extracts, the degree of autolysis that could have taken place in the interval, the site of administration, the method of use (dilution, heat, speed of absorption), the manner in which the organ was preserved,[31] etc.—we may ask ourselves if, in the midst of such variations—depending on so many complex and variable factors, some of which are difficult and others impossible to control—the action of a specific principle is assured and constant. At least it would be necessary that proof of this identity and constancy be given. And it is certain that experimenters do not always guard

[31] I have shown that organic extracts, even though preserved in aseptically prepared powders and carefully dried, quickly lose their toxicity (E. GLEY, "Toxicité des extraits d'organes, tachyphylaxie, anaphylaxie," in *Mélanges biologiques*, Jubilee volume of Prof. Ch. Richet, Paris, 1912, pp. 111-129). This simple observation explains both the uncertainty of the method of organic extracts and why they may prove themselves untrustworthy in many therapeutic attempts.

against all these difficulties. Undoubtedly, a considerable part of the contradictions that may be noted in the reports of experimental investigations is due to this cause.

The multiplicity of organic extracts which provoke an identical physiological reaction is proof of the non-specificity of these extracts and shows that we have to do here with a more or less general pharmacodynamic effect. It is for this reason that a galactagogue action has been attributed by Schäfer and Mackenzie [32] to extracts of the hypophysis, corpora lutea, uterus (in evolution), mammary glands (during lactation) and by Isaac Ott and J. C. Scott [33] to the same pituitary and cor-

[32] E. A. Schäfer and K. Mackenzie, ''The Action of Animal Extracts on Milk Secretion'' (*Proceedings of the Royal Soc.*, 1911, LXXXIV, Series B, p. 16); K. Mackenzie, ''An Experimental Investigation of the Mechanism of Milk Secretion, with Special Reference to the Action of Animal Extracts'' (*Quarterly Jour. of Experimental Physiol.*, 1911, IV, 305-336).

[33] I. Ott and J. C. Scott, ''The Action of Animal Extracts upon the Secretion of the Mammary Gland'' (*Therapeutic Gaz.*, Oct., 1911); ''Action of Different

pora lutea extracts, and besides to extracts of the thymus and the pineal gland.[34] It is thus that extracts of the thymus, the thyroid, testicles, prostate, and pancreas provoke contraction of the bladder.[35] From these two examples alone we can see that extracts of the most divers organs, organs which play no part in the system to which the stimulated organ belongs, as well as organs dependent on the same apparatus, start either a secretion or a contraction of a smooth muscle. Is it not plausible that this action depends on the presence of a substance which occurs in all these extracts, consequently a substance that is quite widely distributed, and therefore

Agents upon the Secretion of Milk'' (*Ibid.*, May, 1912, p. 310); ''The Action of the Internal Secretions upon the Milk Secretion'' (*Ibid.*, November, 1912, p. 761).

[34] Pituitary extract and that of corpora lutea have been shown to be inactive in a therapeutic attempt on a woman and in several experiments on milch cows.

[35] I. OTT and J. C. SCOTT, ''The Action of Animal Extracts upon the Bladder'' (*Monthly Cyclopedia and Medical Bull.*, July, 1911).

rather general than specific? And would it not be opportune to investigate whether the venous blood of some one of these organs does not manifest, either on the bladder or on the female breasts, the action stated to occur when organic extracts are used?

It may be, moreover, that the administration of organic extracts is followed by anaphylactic reactions, since these extracts contain foreign albumins. This observation applies, above all, to the therapeutic use of many of them, inasmuch as attention has been called elsewhere in this book to the consecutive anaphylactic phenomena following the injection of protein substances.

The phenomena of *tachyphylaxia,* or very rapid immunization against the toxic action of an organic extract, upon which light was shed by the researches of Cesa-Bianchi in Italy, H. Dold in Germany, Ancel, Bouin and Lambert, and Champy and Gley [36] in France, shows how very imprudent it is to consider an extract against which the organism protects itself in several minutes as a product of internal secretion. The phenomenon of tachyphylaxia for a given extract may be provoked by another extract, and *vice versa,* as was shown by Cesa-Bianchi, Ancel, Bouin and Lambert, and Champy and Gley. It is what the latter have termed *crossed tachyphylaxia,* and herein lies an important fact, which, in the face of actual therapeutic attempts at simultaneous or successive administration of several extracts, should not be forgotten.

Most certainly, the question is, above all,

[36] The bibliography of this question is to be found in CESA-BIANCHI's memoir: "Contributo alla consoscenza de mecanismo di azioni degli estratti polmonari" (*Archivio di farmacol. sperimentale e scienzi affini*, 1912, XIII, pp. 407-453, 481-514, and 529-546), and in a work by GLEY: "Les phénomènes de tachyphylaxie et leur signification présente" (*Arxivs de l'Institut de ciencies,* I, No. 2, Barcelona, 1912).

to learn if there is tachyphylaxia against the specific action as well as against the general toxic action of organic extracts. In fact, the phenomenon may be a means of defense against this toxic action and not be produced in the presence of specific actions. "The work to be undertaken at present is therefore the careful investigation of the individual actions which the various organic extracts may have, independent of their general toxic action, which we now know to be accompanied by this tachyphylactic reaction. . . . Many physicians and several physiologists tend to accord to organic extracts, considered as substitutes for internal secretions, great importance in the regulation of arterial pressure. Does it not appear that all studies made in this direction must be reversed in the light of the new notion of tachyphylaxia? And, likewise, other effects hitherto attributed to the action of various organic extracts must be traced back to this phenomenon.''[37]

Now, Howell[38] has already noticed that a second injection of pituitary extract, administered soon after the first, has not the same effect on the arterial pressure as the first, which fact was verified by Schäfer and Swale Vincent.[39] Later, Étienne and J. Parisot[40] found that repeated injections of the same extract no longer provoked the augmentation of the force of the car-

[37] E. GLEY, *loc. cit.; Arxivs de l'Institut de ciencies*, I, p. 21.

[38] W. H. HOWELL, ''The Physiol. Effect of Extracts of Pituitary Body'' (*Jour. of Exper. Med.*, 1898, III, 215, 245).

[39] E. A. SCHÄFER and SWALE VINCENT, ''On the Action of Extract of Pituitary Injected Intravenously'' (*Jour. of Physiol.*, 1899, XXIV, p. xix); ''The Physiol. Effects of Extracts of Pituitary,'' *Ibid.*, 1899, XXV, p. 87-97). The authors even take care to remark that this particular differentiates the action of pituitary extract from that of suprarenal extract.

[40] G. ÉTIENNE and J. PARISOT, ''Action sur l'appareil cardio-vasculaire des injections répétées d'extrait d'hypophyse. Comparison avec l'action de l'adrénaline'' (*Arch. de méd. expér. et d'anat. pathol.*, 1908, XV, pp. 423-437).

diac pulsations which was caused by the first injection; and J. Salvioli and A. Carraro [41] have affirmed the same fact. Have we here to deal with another action of the same extract? We again find the same particular circumstances: v. Frankl-Hochwart and A. Fröhlich [42] have observed that the action of successive injections of pituitary extract on the bladder is less and less marked; and E. A. Schäfer and P. T. Herring [43] remarked that a second injection is less sure than the first to cause dilatation of the renal vessels and diuresis. Furthermore, Roger and Josué [44] found

[41] J. SALVIOLI and A. CARRARO, "Sur la physiologie de l'hypophyse" (*Arch. italiennes de biologie*, 1908, LXIX, pp. 1-38).

[42] V. FRANKL-HOCHWART and FRÖHLICH, "Über die Wirkung des Pituitrins" (*Wiener klin. Wschr.*, 1909).

[43] E. A. SCHÄFER and P. T. HERRING, "The Action of Pituitary Extracts upon the Kidney" (*Proceedings of the Royal Soc.*, 1906, LXXI, p. 571). The diuretic action of pituitary extract was discovered by E. A. Schäfer and R. Magnus (*Proc. of the Royal Soc.*, July 20, 1901; *J. of Physiol.*, XXVII).

[44] H. ROGER and O. JOSUÉ, "Action de l'extrait d'in-

that the fall of arterial pressure caused by the injection of intestinal extract (aqueous extract of frozen, macerated rabbit's intestine) was not reproduced by a second injection. Together with Champy, I have demonstrated the same fact in the case of extract of corpora lutea. From this we concluded that it is difficult to admit the assumption of a normal vaso-dilatatory action exercised by the secretory products of the corpora lutea.

Such experiments should be methodically pursued with the extracts of organs ordinarily used. These researches are all the more imperative now that we have learned to recognize the difference, with regard to the tachyphylactic reaction, between suprarenal extract, which determines this reaction (Cesa-Bianchi), and the active principle of this extract, adrenalin, which does not provoke it (see p. 158).

testin sur la pression artérielle'' (*C. R. de la Soc. de biol.*, Feb. 24, 1906, LVIII, p. 371).

We know, for example, that several successive injections of adrenalin may be given without missing the hypertensive effects after any of them. Does the organism have the same tolerance for other actions of adrenalin? Does not the question confront us since the experiments of N. Waterman (1911), which tend to show that a sort of immunization may be produced against glycosuria resulting from the administration of adrenalin? Moreover, we must not be at all surprised at this, for we know that the hypertensive action of adrenalin and its property of accumulating sugar go on *pari passu*, according to the researches of P. Hari.[45] We can see how complex may be at times the investigation of the phenomenon of tachyphylaxia, the question of learning if a certain active principle of an organic extract

[45] PAUL HARI, "Über den Einflus des Adrenalins auf den Gaswechsel" (*Biochem. Ztschr.*, 1912, XXXVIII, 23-45).

gives rise to a tachyphylactic reaction, as does the entire extract.

The facts of tachyphylaxia, taken all in all, form a very strong argument against the significance, too easily accorded, of the pharmacodynamic action of organic extracts. For it is one of the characteristics of an internal secretion that its effects can be repeated quasi-indefinitely. Adrenalin and secretin behave thus. Can we, on the contrary, see a product of internal secretion in an extract against the effects of which a protective reaction—tachyphylaxia—is established so rapidly—no matter what else might be the mechanism of this reaction? Or, if there is really an internal secretion in the extract, should we not think that its specific action may be masked by the toxic action of the complex substances composing the extract as soon as a stage is reached when a defensive reaction of the organism manifests itself?

Finally, there is another objection which is no less important. It arises from a fact to which, it would seem, little attention has been accorded. There are extracts with which a characteristic physiological effect can be obtained only by injections of large doses, and these doses are often so excessive that they represent in weight the total mass of the organs from which these extracts were obtained, and even several of these organs. A. Patta,[46] for example, has stated this to be the case when extracts of thyroid, thymus, hypophysis, ovaries or testicles act on the circulation: "per otteneri fenomeni apprezzabili," he says, "spesso occorsero dosi de estratto corrispondenti a parecchi organi." This is a fact which I have often had occasion to observe with thyroid extract and which was also noticed by Quinquaud and myself in our researches on the

[46] ALDO PATTA, "Contributo critico e sperimentali allo studio dell'azione degli estratti di organi nella funzioni circulatoria" (*loc. cit.*, VI, 1907; see above p. 115).

influence of organic extracts on the suprarenal secretion.[47]

Taken by themselves, these two facts—tachyphylaxia and the activity of extracts in extra-physiological doses—suffice to throw suspicion on the therapeutic method of organic extracts, in the manner that it has been and still is commonly applied.

It is not, therefore, astonishing that the exclusive use of this method has led to many unjustified conclusions; too many risky theories have been propounded; too many hazardous applications have been made. Not that there is a question of scientific physiological explanation like that of dividing the endocrine glands into "hypertensive" and "hypotensive," or of a pathological explanation like that which attributes the hypertrophied heart in the *status lymphaticus* with a large thymus to

[47] E. Gley and Alf. Quinquaud, "Action de l'extrait thyroidien sur la sécrétion surrénale," *C. R. de l'Ac. des sciences*, June 30, 1913, CLVI, p. 2013; see also *Arch. internationales de physiol.*, 1914, XIV, p. 152-174.

an excessive thymus secretion (?), or of the use of a new medicinal agent like that of "hormonal."

In reality, because many of these extracts have an action on the arterial pressure, one does not have the right to conclude, without further investigation, that these organs discharge hypertensive or hypotensive substances into the blood. It was not even noted that in order to obtain appreciable phenomena, it is often necessary to inject quantities of extract corresponding to several of the organs from which they were obtained.[48]

We thus see how many assumptions and hypotheses exist in the theory of the pathogenesis of disturbances in the functions of the endocrine organs cited above. We must admit the discharge into the venous blood from the thymus of a substance which lowers arterial pressure and accelerates the heart action, then the normal

[48] *Cf.* Aldo Patta, *loc. cit.*

antagonism of this substance to adrenalin, and finally that in the *status lymphaticus* there is suprarenal insufficiency. It is needless to add that the fact lying at the base of all this reasoning—the reality of an internal secretion of the thymus—is not as yet in the least proved.

Hormonal medication may be cited as a good example of the point we want to raise. As is well known, it is based solely on the fact that the extract of the duodenal mucous membrane has the property of exciting intestinal peristalsis.[49] The same is true of splenic extract. As a result of these facts, the supposition that a hormone is present in these extracts was immediately advanced. Even disregarding the fact that these extracts may contain albumoses, and all physiologists know that

[49] See ZÜLZER, DOHRN and MARXER, "Specifische Anregung der Darmperistaltik durch intravenöse Injektion des Peristaltikhormons" (*Berl. klin. Woch.*, 1908, No. 46); ZÜLZER, "Die Hormontherapie: I. Das Peristaltikhormon" (*Therapie der Gegenwart*, May, 1911, p. 197).

albumoses provoke more or less violent intestinal movements, how could one fail to think, before forming any theory, of collecting the blood from the intestinal or splenic veins of an animal in a sufficient quantity, and investigating if this blood, injected into another animal of the same species, manifests the same properties as the extract. Furthermore, grave accidents have already been mentioned following the use of hormonal: considerable lowering of arterial pressure, which is not astonishing to any one who knows the hypotensive action of intestinal extracts, with a tendency to collapse, dyspnea, feeble heart action, etc.[50] Two cases of death have even been observed.[51] It is quite possible that the intestinal venous blood has been found to

[50] DITTLER and MOHR, *Münch. med. Woch.*, Nov. 14, 1911, p. 2427; HESSE, *Deutsch. med. Woch.*, April 4, 1912, p. 525; ROSENKRANZ, *Münch. med. Woch.*, April 22, 1912, p. 931; WOLF, *Ibid.*, May 14, 1912, p. 1107, etc.

[51] A. T. JURASZ, *Deutsch. med. Woch.*, May 30, 1912, p. 1037; MOHR, *Wien. klin. Woch.*, May 16, 1912, p. 840 (case of death observed by Madlener).

have an excitatory action on the musculature of the intestine; yet, should this prove to be the case, we must assure ourselves that we are dealing with a specific action, as Zülzer claimed, and not with the general action of any of the smooth muscular fibers. The word "hormone" is being very much abused while this demonstration is being awaited. And how many other examples could we not give? We have already seen (p. 64) exactly what must be understood by this word, and I will return to it later on (pp. 135 and 143). This extension—abusive because it is made without experimental basis—of a perfectly clear and precise term would in itself suffice to show what dangers may follow the method of organic extracts when it is exclusively and recklessly applied.

What we must nevertheless retain from the results of researches carried out with organic extracts, is that among these substances some may be found which, thanks to their physiological properties, constitute therapeutic agents of value. It has been stated that various extracts of value —testicular, pancreatic, thyroid, thymus and prostate—augment the contractions of the bladder;[52] that extracts of the hypophysis (posterior lobe), the pineal gland, the thymus or the corpora lutea, injected intravenously, provoke the secretion of the mammary glands;[53] and it would be easy to mention other observations of the same sort on different organs. Perhaps herein lie reasons for the introduction of the extracts into pharmacology. But from the results of the pharmacodynamic study of organic extracts we have positively no right to draw conclusions as to the physiological activities of these organs. How

[52] ISAAC OTT and J. C. SCOTT, "The Action of Animal Extracts upon the Bladder" (*Monthly Cyclopedia and Med. Bull.*, July, 1911).

[53] ISAAC OTT and J. C. SCOTT, *Therapeutic Gaz.*, May and Nov., 1912, pp. 310 and 761; E. A. SCHÄFER and MACKENZIE, *Proc. of the Royal Soc.*, 1911.

could effects obtained through experimental violence confer this right? The true criterion of the function of internal secretion is the presence of a specific product in the venous blood of a gland.

II. PRINCIPAL DISTINCTIVE CHARACTERISTICS OF THE PRODUCTS OF INTERNAL SECRETION

The products of internal secretion differ very much from one another in their nature, but above all in their mode of action and their physiological destination. We may classify them in the following categories.

(1) Nutritive Substances.—A first category is that of substances which serve as *nutritive materials,* either for energy production (glycose of hepatic origin, fats) or for blood repair (specific proteins of the blood).

(2) Morphogenetic Substances (Harmozones).—Another category which naturally follows the one above, includes sub-

stances serving as tissue builders, in the course of ontogenetic development, or *morphogenetic substances.* Neither histological nor chemical facts have provided us with this notion; it is the result of a large number of physiological experiments (experiments on extirpation of organs) and numerous anatomo-clinical proofs. Thus was formed the group of glands of *morphogenic action* (interstitial gland of the testicle, corpora lutea, thyroid, hypophysis and thymus), or better, of *secretory products of morphogenic chemical action,* whose nature and mode of action are both unknown (by catalysis, by a process analogous to chemiotaxis, by fixation of mineral materials, etc.), and for which I have proposed the name harmozones (from Greek ἁρμόζω, I rule, I direct).

I think that these distinctions are indispensable. It is impossible to qualify as hormones, as is done only too often at present, all the products of internal secretion. How many physicians and even physiologists have permitted themselves to be carried away by this confusion! "A science is a well made language." Confusion of terms can only be followed by confusion of ideas. A hormone is nothing but an exciting agent, according to its etymology and, moreover, according to the meaning that the creator of the term, Starling, assigned it. The word is not suited to anything but what had previously been termed *specific functional excitants* (see pp. 62-65). In what respect is the hepatic glycose a hormone? Such a denomination is inapplicable to that substance, being of the type of those which constitute the first category of endocrine products; namely, nutritive materials.

It is no longer possible, at least in accordance with what we actually know of the physiological action of morphogenetic substances, to confound these with hormones. Can we, for example, class as a hormone that substance, of testicular origin, which regulates the development of the skeleton in such a manner that, subject to its influence, the bones grow in length? And how are we to explain that disease or extirpation of the hypophysis is followed by a disproportionate development, in length and in thickness, of the extremities, the skeleton, the soft parts and the face; that hypofunction of the thymus renders the bones shorter, thinner and more fragile. The fact that after castration the epiphyses persist explains nothing, and needs, on the contrary, to be explained itself. This persistence of the connecting cartilages also occurs in dethyroidated animals and in myxedematous children, in whom the development of the bones, particularly of the long bones, is arrested, and in whom the development of the osseous system is improved by thyroid treatment. We cannot admit that the action of the two substances, thyroid and diastema,[54] act in the same manner, since the results of the suppression of the two secretions are the reverse of one another. Besides, can we give a clear account of the process of the growth of bone? Several histological and chemical conditions are necessary: the proliferation of the marrow of the bone, the division of the cartilaginous cells, the processes of ossification and calcification. If we ascribe to the substance of the thyroid an excitatory action, on what part of this complex process is this action exerted? And in what, for example, does an excitation of the process of ossein formation consist? Like difficulties are encountered while trying to explain the osseous alterations in acromegaly. Are we to suppose that the growth of the skeleton in young sufferers from acromegaly—in whom, it has been

[54] From διάστημα, interstice, a word used by P. Ancel and P. Bouin to designate the interstitial gland of the testicle.

maintained, the development of the genital organs is arrested—depends not on an action of the hypophysis itself (hyperfunction of the pituitary?) but on a diastematic insufficiency? Without insisting on the hypothetical character of this explanation, the difficulty here would be that the growth in length of the bones of castrated animals and eunuchs does not in the least resemble the hypertrophy of the extremities of acromegalics. Is it not more prudent for the time being to avoid combining all these products of secretion, to refuse to identify the substances having a morphogenetic action with the functional excitants proper, or hormones? When we better understand the conditions and causes of ossification, as well as the influences which may be exerted on one or the other, we will perhaps be in a position to determine exactly the mode of action of the substances coming from the thyroid, testicle or hypophysis. Meanwhile, the name of harmozones expresses a fact, without anticipating anything as to its nature.

Not only the development of the skeleton is regulated by internal secretions. The development of the genital tract and its accessory glands is subject, in the male, to the action of the interstitial glands, and in the female, to that of the corpora lutea, which also regulate the development of the breasts. Finally, the development of the germinative gland depends, at least in part, on the action of the thyroid, as well as of the central nervous system. We have no idea of the nature of the phenomena which take place in any of these organs under the influence of the secretions mentioned. We may say that they are phenomena of assimilation, but that does not advance us at all.

Here we might set a new problem of a totally different order, and which, furthermore, should occupy biologists: if we now understand at least a part of the mechanism of development (i. e., the action of internal secretions), we do not explain better than by the above why this development stops at a given moment.[55] Let us suppose that the interstitial gland of the testicle, or another gland with similar functions, is reduced in functional activity. Is the quantity of active substance that it sends to the organ on which it acts consequently diminished? But there is no proof of such a functional diminution; and, furthermore, since these substances act in very small doses, we must under such circumstances assume the almost absolute

[55] Although we have no space to examine them here, it is not without interest to mention the relations that Rubner has established between the consumption of energy, the intensity of growth and the duration of life, his very penetrating ideas drawn from the laws of growth and the almost mathematical cessation of the latter. (*Cf.* RUBNER, "Das Problem der Lebensdauer," München, 1910.) Also of great value on this subject is a recent study by YVES DELAGE on the progressive decrease in physiological fecundity being proportional to the increase in height. (*Revue scientifique,* July 19, 1913, LI, 65-69.)

suppression of their functioning. The problem is not decided.

I therefore maintain that there are endocrine products which cannot be qualified as hormones; all that we know at present concerning morphogenetic substances is that they regulate development. Starling has called hormones "chemical messengers," but the two expressions are not synonymous. All hormones are endocrine products, *chemical messengers,* but all endocrine products, i. e., all chemical messengers, are not hormones. The remark which follows corroborates this distinction further.

The name of harmozones may, indeed, be applied to those substances which act as modifiers of chemical processes in which they appear to play a rôle analogous to that of diastases: the substances, secreted by the pancreas, which regulate the glycose-forming function of the liver, either by transforming the glycose into glycogen (diastatic action), or by diminishing the transformation of glycogen into glycose, or by destroying the glycose in the tissues, and particularly in the muscles (by a ferment adjuvant to the glycolytic diastase); and the hepatic antithrombin which opposes the process of intranuclear coagulation as in the coagulation of blood *in vitro*.

(3) THE HORMONES.—A third category is reserved for the substances which provoke functional activity and consequently play the rôle of excitants. These are the true hormones, or specific functional excitants. They may be divided into: (1) chemical hormones (excitants of chemical phenomena); and (2) physiological hormones (excitants of physiological phenomena, or functions).

The first class is represented by the substance produced in the spleen, which activates trypsin, and by the substance secreted by the thyroid in so far as it modifies general nutrition, augmenting the nitrogenous and respiratory exchanges,[56] and which therefore reveals itself as a powerful agent of disassimilation; or does the thyroid secrete several substances of opposed trophic rôles? We have no information on this subject.[57]

The physiological hormones are secretin, adrenalin and the substances (of as yet uncertain origin, see above, p. 101) which provoke the secretion of milk. Perhaps we must add the product of the secretion of the prostate, according to the experiments of A. Vichnevsky (1909). The latter, in the laboratory of Mislavsky, has

[56] It is known that it increases them much more in myxedematous than in normal individuals (Magnus-Levy).

[57] Other organic extracts, those of the testicles, ovaries, hypophysis, etc., appear to also modify the mineral, hydrocarbon and nitrogen exchanges. I have not touched upon this question. Both the literature of the subject and a discussion of it will be found in ''Probleme der physiol. und pathol. Chemie,'' by O. VON FÜRTH (Leipzig, 1912), and in the ''Handbuch der speziellen Pathol. des Harns,'' by F. BLUMENTHAL (Berlin, 1913); also in BIEDL's book and the article by MAGNUS-LEVY cited on p. 68.

shown that the secretion, and not the extract of the prostate, obtained by the excitation of the fibers of the prostatic plexus, provokes movements of the spermatozoa much more intense than those caused by various saline solutions or by the serum of the animal experimented on, etc. As for the "gastric secretion" studied by Edkins,[58] and the hypertensive substance of renal origin (R. Tigerstedt),[59] there is not

[58] E. A. EDKINS, "The Chemical Mechanism of Gastric Secretion" (*J. of Physiol.*, 1906, XXXIV, pp. 133-134).

[59] R. TIGERSTEDT and P. G. BERGMANN, "Niere und Kreislauf" (*Skand. Arch. für Physiol.*, 1898, VIII, 223-271). In the last edition of his "Lehrbuch der Physiologie des Menschen" (7th ed., Leipzig, 1913), Tigerstedt recognized that it has not been demonstrated that the hypertensive substance of the renal extract passes in the venous blood of the kidney. "Ob die Wirksame Substanz auch im Nierenvenenblute vorkommt, ist noch nicht bestimmt entschieden" (*loc. cit.*, vol. I, p. 523). On the subject of an internal secretion of the kidneys (Brown-Séquard), we may for the meantime recall the experiments of E. MEYER, of Nancy (*Arch. de physiol.*, 1893, pp. 760-765), which show that the injection of renal venous blood into a uremic dog (by double nephrectomy) suppresses the periodic respiration and reestablishes the normal respiratory rhythm. A. PI Y SUNER

sufficient experimental justification for considering them as products of internal secretion.

(4) The Parhormones.—Finally, there remains one more class of secretory products. In it are included excretory products, such as that which the liver elaborates in transforming toxic substances like ammonia and the amino-acids or like the phenols into urea and phenylsulphates, compounds which are almost harmless. It is known as the antitoxic function of the liver. Must we place urea among the hormones? This question confronts us all the more since there are other similar products that many physiologists, following Bayliss and Starling, have included in the class of hormones. A typical one is carbonic acid,

(1905) has maintained that the kidney is not a true internal secretory gland, but a gland having an antitoxic function, which is exercised principally on the blood of uremics; the latter offer an obstacle to the urinary secretion and the injection of renal extract from uremic animals provokes diuresis.

which excites the respiratory center in the bulb. This compound has even been considered as an example of those substances by which the neurochemical correlations are established. Carbonic acid is produced in large quantities by the work of the muscles and its accumulation in the blood would be noxious, but it augments the activity of the respiratory center, increasing the frequency of respiration with resulting increase in the pulmonary ventilation and consequently of the quantity of oxygen admitted into the blood, and, finally, regulating the oxygen content of the blood and of respiration. As for urea, we now know that this is only a very slightly toxic substance, the reverse of carbonic acid. It has, however, one property in common with the latter, namely, to excite the cells of the kidneys. Moreover, it does this not indirectly, through the medium of the nervous system, but the cells of that excretory organ by which it is eliminated are directly affected. The diuretic action of urea is in fact well known.

But there is no reason for considering these excretory products as true hormones. This is an opinion that I have already maintained and which is also held by S. J. Meltzer.[60] My reasons are: The conception of a gland, as I showed as far back as 1893, is clear and precise only in case it conveys a physiological notion. It must show a specialization of the secretory cellular elements and the destination of the products secreted. Otherwise, all cells might be termed glandular, for there is no cell which does not elaborate a substance that it uses or discharges into the blood, and we would thus come to confuse "secretion with the acts of cellular nutrition themselves."[61] What, then, is the

[60] S. J. MELTZER, "Animal Experimentation in Relation to our Knowledge of Secretions, Especially Internal Secretions" (*Proc. of the Pathol. Soc. of Phil.*, 1910, N.S., XIII, 170-196).

[61] E. GLEY, "Conception et Classification physi-

true physiological nature of products elaborated in real secretory elements? They are not substances arising from *nutritive transmutations,*[62] the resulting material does not become an integral part of the protoplasm. The secretory cells manufacture it for special purposes; not for themselves but for other organs and for the general functions of the organism, all parts of which form a solidarity. The destination of the secreted products is, in fact, no less characteristic than their nature. These products are utilized for other objects than those of the cells which have manufactured them and altogether in other parts of the organism. It is remarkable that histologists have arrived at an analogous conception of a gland.[63]

ologiques des glandes'' (*Revue scient.*, July 1, 1893, LII, p. 8).

[62] The terms *nutritive transmutations* and *functional transmutations* are due to Charles Bouchard.

[63] See A. NICHOLAS, ''Contribution à l'étude des cellules glandulaires'' (*Jour. intern. d'anat. et de physiol.*, 1891,

From this point of view, what is carbonic acid? It is the excretion of the nutritive transmutations of a large number of cellular elements, muscular cells and glandular cells;[64] it is in no wise a specialized product, it is a general substance resulting from the katabolism of the tissues. What is its destination? It is principally a product of excretion. And what is urea? Most assuredly it is mainly a substance formed in and by the hepatic cells, but it has been established that it is formed elsewhere in small quantities. It is also a waste product, an excretion. It is true that these substances, once in the blood, manifest physiological actions, or vital activities. But they have not been

VIII, 279); LAGUESSE, "Les glandes et leur définition histologique" (*Semaine méd.*, May 11, 1895, p. 213); A. PETTIT, "Sécrétion externe et sécrétion interne" (*La Presse méd.*, July 12, 1913).

[64] An excellent series of investigations on the production of carbon dioxid by glands has been published by the English physiologists Bancroft and Brody and their collaborators.

excreted especially in order that they might perform these actions. The reverse is true of true secretions. And, furthermore, could it not be that products of disintegration have no physiological action? Is this not so in the case of the phenylsulphates, which are also formed by the hepatic cells? And is this not also true, at least as far as our actual information goes, in the case of uric acid in birds, similarly elaborated in the liver, to be taken up by the blood and eliminated by the kidneys? A particular sensibility of the bulb for carbonic acid has been invoked, a sort of adaptation of the organ to its excitant, as one might invoke a particular sensibility of the renal cells to urea. But "what does this specific irritability mean?" Meltzer [65] asks justly, "only that the organism protects itself by rendering the respiratory center so sensitive to this dangerous excretory product that the surplus automati-

[65] *Loc. cit.*

cally activates an efficacious mechanism for its rapid elimination." And Meltzer adds, not without humor: "We know that the animal organism is provided with numerous defenses against the invasion of bacteria or of other harmful agents. Is the existence of these means of defense within the body a proof that these bacteria and deleterious substances form a part of the animal economy?" On my part,[66] I have written: "The excretions resulting from the activity of the cellular elements . . . may well, even in the course of their elimination, play a physiological rôle. . . . Thus, carbonic acid, which has been cited as the most simple of hormones, constitutes, in consequence of a special irritability of the bulb respiratory center towards this substance, a stimulant of the respiratory movements. But it is not in the least

[66] *Revue scientifique*, March 4, 1911, p. 257 (a lecture taken from my course of 1909-10 at the College of France).

a product of secretion of muscular cells; the production of carbon dioxid in greater or lesser quantity is positively not one of the functions of muscle. And it has been conceived that other products of disintegration may likewise, in an accessory manner, exercise a physiological action. On the other hand, only the protein iodid matter of the thyroid is secreted by the cells of that gland, only adrenalin is secreted by the adrenals, etc., and the only destination of substances of this category is to fulfil their specific functional rôles. In the course of fulfilling this rôle they are not otherwise eliminated; they are destroyed, as is the case with adrenalin and secretin. Hence we may consider the term hormone as being too universal (in the logical sense of the word) and not comprehensive enough. There exist at least two classes of functional excitants, different in origin, in the character of their action (secondary or essential), and in their destination. At most we might apply the term *parharmones* to the excretory products which play only an accessory rôle as excitants, reserving the name of hormones for the specific glandular products."

In the second edition of his "Innere Sekretion,"[67] Biedl does not believe that he can admit this distinction. "If through the medium of the ordinary end product of the material exchanges," he says, "chemical correlations are established in the organism, and if the exciting action, as this term is understood in the concept of hormone, is due to this product, then we must consider it as a hormone without consideration of its origin, composition and destination." It seems to me that this contains no adequate reply to the arguments of Meltzer and myself; he simply maintains that it is sufficient for an organic extract to have an excitatory action in order that it be included among the hor-

[67] Vol. I, p. 11.

mones, without taking account of its origin, nature and destination. But I insist that we cannot satisfactorily define products of secretion unless we take into account their origin and destination. On this point I am in accord with the most competent histologists as well as with numerous physiologists. Is it not sufficient to designate as *parharmones* those excretory products which have a physiological action?

How many products of excretion manifest, while being eliminated, their physiological properties and serve for the establishment, rapid and transitory, though capable of being renewed, of a chemical or neurochemical correlation, is another question which no one can cast into doubt. "The example of carbon dioxid," says Biedl,[68] "which is not unique but which is one of the best studied, shows in an obvious manner that the products of the material exchanges play an important part by

[68] "Innere Sekretion," 2nd Edit., vol. I, p. 12.

means of chemical correlations." I do not gainsay this. Undoubtedly, the conception of hormones is inseparable from that of functional correlations; but functional correlations may be effected by substances other than hormones; this term being reserved for the specific excitants, products of secretion.

(5) THE DISTINCTIVE CHARACTERISTICS OF THE ENDOCRINE PRODUCTS.—All these products present certain properties in common and some differences which are important and deserve elucidation.

1. Between the substances of the first category (nutritive substances) and those of the two following classes (harmozones and hormones) there exists an important difference: The nutritive substances intended for energy production or tissue repair (*Verbrauchssekrete,* following the nomenclature of Biedl), i. e., for transmutation of matter—are discharged into the blood stream in quite considerable quanti-

ties; this is a matter of course, for these are the substances which carry to the organs energy-producing and combustive material, and the organs always have need of one and the other in considerable quantities.

Morphogenetic substances and hormones, on the contrary, act in very minute doses; they are substances which appear to act after the fashion of a nervous excitation or of a diastatic action; they bring no energy to the tissues or organs which they influence, but they only liberate preexisting energy; they regulate anabolism and katabolism, construction and disintegration of the tissues.

2. In addition to this difference we have a resemblance: not only hormones proper, as Biedl has observed,[69] have the characteristic of not being antigens [70] and not giv-

[69] A. Biedl, "Innere Sekretion," 2nd Edit., Vol. I, p. 1.

[70] Bayliss and Starling were the first (1906), I think, to indicate this important characteristic of hormones.

ing rise, following their injection into the blood, to antibodies; this is also true of the substances having a morphogenic action, and the nutritive materials, such as glycose, specific albumins, etc. "The only characteristic which generally distinguishes hormones," says Biedl, "is at the present state of our knowledge a negative one." And this characteristic, undoubtedly negative, but important, applies to all true internal secretions; [71] it is like a signature, being essential to action; their penetration into the internal medium does not provoke a reaction which would annihilate their effects. The importance of this fact is a consequence of what has been said about tachyphylaxia.

3. One of the important characteristics

[71] However, the following curious fact has been observed (Abderhalden and Slavu, 1909; A. Fröhlich, 1909): Successive injections of artificial suprarenin (synthetic adrenalin) immunize against considerable doses of extractive adrenalin. Artificial suprarenin is a substance which does not exist in the organism.

of hormones (and also of harmozones) is their specificity of origin, of action and of function; that is to say, anatomically and physiologically, but not zoologically. The products which are secreted and endowed with an elective action come from a certain organ and only from that organ; but no matter from what species of animal they are derived, they exert their action on animals of other species.

Is this specificity absolute? We cannot here enter into a discussion of the doctrine of cellular specificity, or raise in opposition to the theory of *predetermination*, or *preformation* (Weismann, Bard, Hansemann, etc.), that of *epigenesis* (Hertwig, Wilhelm Roux, Wilson, Delage, etc.). Let us only examine the facts within the domain of internal secretions. As a result of castration the respiratory exchanges are diminished, both in the male and in the female; they may be enhanced again by the administration of ovarian or testicular extract (A. Loewy and P. F. Richter, 1899), but only those particular extracts have that action; thyroid extract does not have it according to the experiments of Loewy and Richter. Finally, this substance is also specific considering that it acts only on castrated animals. Evidently, the profound difference between the two substances is not as yet very well understood: both the one which comes from the genital glands and the one from the thyroid manifest the same physiologico-chemical properties and yet cannot substitute for one another. Furthermore, the action of the thymus on the growth of bone appears to be analogous to that of the thyroid (see in particular the figures published by M. Lucien and J. Parisot [72] on the arrest of the development of the skeleton observed in young dethymated animals).

[72] M. Lucien and J. Parisot, ''Contribution à l'étude des fonctions du thymus . . .'' (*Arch. de méd. expér.*, 1910, XXII, 98).

Let us examine two more examples. It now seems that secretin is not furnished exclusively by the duodenojejunal mucous membrane; it has been extracted from the gastric mucous membrane and from that of the ileum by other procedures than the use of acids [73] (by the method of extraction in boiling saline solution). Moreover, the tissue of the hypophysis presents, like that of the suprarenal bodies, the chromaffin reaction and its extracts have properties analogous to those of adrenalin—action on the heart, the vessels and the pupil. It is true that, according to H. H. Dale (1909), the mechanism of its action on the smooth muscles [74] is not the same as that of adrenalin. This analogy between

[73] L. CAMUS and E. GLEY succeeded in obtaining it in small quantities by the acid maceration of the mucous membrane of the stomach (*C. R. de la Soc. de biol.*, June 7, 1902, LIV, 648).

[74] Moreover, adrenalin does not exercise any influence on the coronary vessels or on the branches of the pulmonary artery (Dale, 1909), the contraction of which is determined by the extract of the hypophysis.

the principal physiological properties is constantly found and it is possible, moreover, that there is a relation between the constituents of certain bases having a hypertensive action, of the active principle of the hypophysis and of adrenalin.[75]

We are thus led to ask ourselves if the physiological differentiations have not been evolved like the cellular differentiations of a morphological nature (according to the ideas of the partisans of epigenesis). That is to say, if they have arisen, not by virtue of a fixed and preestablished plan, but as a function resulting from extrinsic conditions, as a result of the divers external influences exerted by elements to which they have been gradually adapted; consequently, if these differences are something really absolute, and if one could not find again, contradictory to the law of the division of labor, in another organ the pe-

[75] H. H. Dale and W. E. Dixon, 1909.

culiarities which characterize or dominate a given organ.

Unquestionably, these reflections do not conflict with anything we know about the specificity of the albumins which constitute species and individuals (specific albumins; see what is said above, p. 85, about absorption and the internal secretory rôle of the intestinal epithelium) which are formed in the course of assimilation. Assimilation, as is well known, is a form of differentiation *par excellence;* it is the formation of particles of living matter identical with those which formed them; identical with non-specific substances, provided they contain the necessary chemical groups to elaborate the specific substances, albumins of the blood and, in each variety of cells, the substances proper to that cell. The products derived from the cellular constituents also participate in this specificity. And it is this physiology that explains, besides the physiology of the species, that of the individual; this, the physiology of the future, will be added to general physiology, the physiology of the particular. This new field we are permitted to examine through the facts of anaphylaxis and also some of those that have been observed in cases of parabiosis, spontaneous or experimental.

4. The action of hormones is not durable. This is because they are unstable, or labile substances; they disappear rapidly from the blood, being either destroyed by oxidation or, being fixed in the tissues on which they act (*corpora non agunt, nisi fixata,* Ehrlich), they are rapidly destroyed there. Moreover, we have here a condition for their action (Starling), since, things being so, their effects do not persist long enough to fatigue the stimulated elements; the latter therefore remain able to receive new excitations.

5. The action of internal secretory products is either local or general. What

must we understand by this? It is of no importance that the products, having been poured into the blood stream, are transported to the entire organism. This is only what seems to be the case, but in reality they attach themselves, following the actual speed of the circulation, to the tissues with whose constituents they are in chemical correlation. Thus, the local action of these substances is better comprehended than their general action.

The correlations are close in the same system of organs. Nothing illustrates this fact better than the formation of secretin and the connections established through the intermediary agency of that substance, between the stomach secreting hydrochloric acid and the duodenum and jejunum on whose mucous membrane the hydrochloric acid acts, and the pancreas in which secretin excites secretion. This is one of the reasons, among others, for the great biological interest of Bayliss and

Starling's capital discovery. Likewise, the chromaffin substance is connected, physiologically as well as embryologically, with the sympathetic system. The connections between the liver and the pancreas, as we ascend in the animal scale, are such that nothing is more natural than this functional association between the two organs which cause, through the influence of a substance coming from the pancreas, the hydrocarbon material to be mobilized in the liver.

Let us now consider the phenomena of development. The diastematic substance (see p. 138) which regulates the development of the accessory genital glands, and that coming from the corpora lutea also act in the same organic system to which they belong; only when we reach the mammary gland, the development of which is also under the influence of the corpora lutea, have we an organ which cannot be considered a dependent of the female genital system, of the uterus, not only because of physiological reasons, but also for reasons of comparative anatomy, e. g., the external uterus of Marsupials.

There are, however, hormones having a general action, such as the thyroid substance which augments the intensity of the nutritive exchanges; a like effect—the increase of nitrogen eliminated and carbon dioxid excreted—is the result of a general action, carried out on all the tissues. And is not the influence exercised on the development of the skeleton by various internal secretions the same?

III. CLASSIFICATION OF THE INTERNAL SECRETORY GLANDS AND THE PRODUCTS WHICH THEY SECRETE

The determination of the peculiarities of the endocrine glands and of the distinctive characteristics presented by the products they secrete leads to a classification of these organs and products.

The latter, in fact, have certain characteristics in common and also present certain differences. They differ in nature, mode of action and physiological destination. Thanks to these similarities and differences, they can be classified. And thus from the analysis by which we have been enabled to determine the conditions for, and the characteristics of, internal secretions, we rise to synthesis. For all scientific classification is synthetic, since it presents its objects in an entirety, arranged in such a manner as to reveal the connections which unite them; synthesis has provisional truth, more or less durable according to the state of development of the particular science at the given moment.

A chemical classification of endocrine products is absolutely impossible; at present we know the chemical nature of only a few products, such as the glycose secreted by the liver and the adrenalin secreted by the suprarenal capsules.

However, a physiological classification may be attempted. That which I have drawn up, therefore, rests only on physiological facts. And the functional point of view dominates it throughout; a physiological classification can only be founded on the notion of function. This is the principle which has already aided me in establishing a general classification of glands, in 1893.[76]

There will be remarked in the double classification that I present (see pp. 172-174) quite numerous gaps; these are the blanks in our actual knowledge. Thus, as yet we know neither the active substance manufactured by the thyroid and parathyroids, nor that produced by the interstitial gland of the testicle, nor that which the corpora lutea produce; we do not know what is the principle formed in the thyroid which

[76] E. GLEY, "Conception et classification des glandes" (*Revue scientifique*, July 1, 1893, LII, p. 8). *Cf.* also "Essais de philosophie et d'histoire de la biologie," by E. GLEY, Paris, Masson and Co., 1900, p. 123-160.

manifests so powerful a morphogenetic action; we are likewise ignorant concerning the substances of pituitary and thymic origin, since no one has even attempted—which is partially explained by the difficulties in technic—to search for them in the venous blood of the hypophysis and thymus. And lacking as we do this fundamental proof, we do not possess either for one or the other of these organs, any evidence that the symptoms produced by extensive disease or complete extirpation of either organ may be greatly ameliorated or cured by the administration of the extract of the affected organ. In other words, there is no proof by "substitution therapy" (*Substitutionstherapie*).

The reader will also note the question marks in the table. Do we know, for example, the nature and mode of action of that product of the pancreas which plays so important a part in the regulation of glycemia? Are we sure that *iodothyro-*

globulin is the cause of the excitatory action of the thyroid secretion on the nitrogenous and respiratory exchanges? Likewise, it is not as yet certain that the parathyroids act by an antitoxic mechanism; and we do not know positively, in spite of the researches of Ancel and Bouin, Lane-Claypon, and Starling, the organ which supplies the blood with the substance whose action establishes the secretion of milk. Furthermore, we are not sure, in spite of all that has been written on the subject, that there is true suprarenal insufficiency of a functional nature.

Whatever these considerations may be, it has appeared to me to be possible, from the physiological point of view and by constant criticism made from this point of view of the knowledge really acquired, to establish a classification of the endocrine glands and the products in the two following tables.

I. Table of Internal Secretory Glands, Giving the Depending on Them, and the Diseases or Alteration of These Organs

		Organ	Products Secreted
I. Nutritive Glands (taking part in transformation of matter) and elaboration of—	1. Substances taking part in nutrition	Glands of the intestinal mucous membrane......	Fatty bodies.... Albumins of the blood (?).......
		Liver..........	Glycose........ Fibrinogen......
		Pancreas.......	Diastase (?) participating in glycogenesis or glycolysis
		Adrenals.......	Adrenalin......
	2. Excretory products	Liver..........	Urea; phenylsulphates.........
		Parathyroids....	....
	3. Substances taking part in morphogenesis	Interstitial gland of the testicle and corpus luteum...	....
		Thyroid........	....
		Hypophysis......	....
II. Glands serving to maintain the composition of the internal medium...........		Liver..........	Antithrombine..
		Choroid plexuses.	Cerebro-spinal fluid
III. Glands which regulate or stimulate functions.......		Glands of the duodeno-jejunal mucous membrane..	Secretin........
		Adrenals.......	Adrenalin......
		Myometrial gland, or placenta, or fetus (?)..	A galactogogue substance.......
		Thyroid........	A substance which excites katabolism (iodo-thyroglobulin?)..........
Organs participating in nutrition or morphogenesis...		NON-GLANDULAR	ORGANS BUT WHICH
		Fatty bodies....	Fat...........
		Spleen.........	Trypsinogenin ..
		Thymus........	....

PRODUCTS SECRETED, THE FUNCTIONAL CORRELATIONS
DISORDERS RESULTING FROM THE INHIBITION OR
AND THEIR SECRETIONS

Physiological Rôle of Products Secreted	Correlations Between	Diseases
Production of energy Plastic rôle........	Intestine and tissues	
Production of energy	Liver and muscles..	Diabetes through hepatic hypersecretion of sugar
Plastic rôle........	Liver and blood	
Formation of glycogen or destruction of sugar............	Pancreas and liver.	Diabetes through suppression of pancreatic action
Mobilization of sugar	Adrenals and liver.	Glycosuria through hyperadrenalinemia
Transformation of toxic products into non-toxic (antitoxic function of the liver)	Liver and kidneys	
Antitoxic function (?)	Thyroid and Parathyroids..........	Tetany through suppression of function
Development of the genital tract and of the accessory genital glands, development of the skeleton.....	Interstitial gland or corpus luteum and accessory genital glands, interstitial gland & osseous tissue	Infantilism of testicular origin
Development of the skeleton nervous system germinal gland	Thyroid and osseous tissue Thyroid and brain Thyroid and testicles or ovaries	Arrest of development, cretinism, myxedematous conditions
Development of the skeleton...........	Hypophysis and osseous tissue.......	Acromegaly
Coagulability of the blood............ Physical rôle known Eliminative rôle (?)	Liver and blood...	Hemophilia through an excess of antithrombine
Pancreatic secretion	Stomach, duodenum and pancreas	
Functions of the sympathetic nervous system...........	Adrenals and sympathetic nervous system.............	Addison's disease. Suprarenal insufficiency (?)
Secretion of milk...	Uterus, placenta or fetal organs, and breasts	
Nitrogenous and respiratory exchanges..	Thyroid and tissues in general........	Inhibition of nutrition because of lack of thyroid secretion
FUNCTION AS ENDOCRINE GLANDS		
Production of energy Activation of trypsin Development of the skeleton..........	Spleen and pancreas Thymus and osseous tissue	

II. Classification of the Products of Internal Secretion According to their Action

		Product Secreted	Secretory Organ
I. Nutritive Materials		Glycose	Liver
		Fat	Intestinal mucosa, adipose bodies
		Albumins of the blood	Intestinal mucosa (?), liver
II. Harmozones (substances regulating chemical processes or functions)	1. Substances taking part in the nutritive exchanges	The substance regulating the production of sugar	Pancreas
		Adrenalin in so far as it serves to mobilize sugar	Suprarenals
	2. Substances participating in the maintenance of the internal medium	Antithrombin	Liver
	3. Morphogenetic substances (having a chemical morphogenetic action)	"	Interstitial gland of the testicles and corpora lutea
		"	Thyroid
		"	Hypophysis
		"	Thymus
III. Hormones	Having a chemical rôle	The substance which activates trypsin	Spleen
		A catabolic substance which augments the nitrogenous and respiratory exchanges	Thyroid
	Having a physiological rôle	Secretin	Duodenojejuna mucous membrane
		Adrenalin	Suprarenals
		A galactogogue substance	Myometrial gland or placenta or fetus (?)
IV. Parhormones		Carbon dioxid	Muscles and glands
		Urea	Liver

III

THE FUNCTION OF THE INTERNAL SECRETORY GLANDS

The normal and the pathological activities may be considered separately. From this second point of view we are confronted by the pathological problems which are of the principal importance at present.

I. THE NORMAL ACTIVITIES

We are first called upon to answer two questions, the first of a chemical nature and the second physiological. The first is to learn out of which materials the glandular elements manufacture the specific substances which they secrete; or, in other words, where they obtain the substances which they use in the production of the specific secretions; and the second is to learn the causes which provoke cellular excretion, or the discharge of the gland. The influence of the nervous system on the internal secretions is then to be considered, and finally that of the reciprocal actions of these secretions and their products. On this last point rest important pathological problems.

1. The first question, that of the formation of specific products, has been well studied for the glands which elaborate and discharge into the blood nutritive materials. We are acquainted with a considerable number of influences which cause an increase in the quantity of hepatic glycogen, that is to say, of the substance from which comes the glycose of the blood. Similarly, the liver, which receives much of ammonia salts, produces much urea. It has been known for a long time that the excessive ingestion of fats causes an increase in the fat deposits which are seen in adipose subjects.

We have little evidence about the other categories of endocrine glands. In the case of the production of substances having a trophic function, the little that we know concerns the thyroid. It has been stated that the administration of foods rich in iodin, or of iodid preparations, causes an increase of the iodin present in the thyroid. Confirmation of the first experiments of Baumann is still awaited.

In the case of the suprarenal glands, it has been thought (Battelli, 1903) that the substances formed in muscle during activity or in the central nervous system engender a "proadrenalin."

2. No further progress has been made in studying the question of the glandular excitants. Quite a large number of substances are known which cause the passage of antithrombin in the blood of the hepatic vein. As an example we may take the influence of the albumoses, which has been thoroughly studied. It is known with the

highest degree of certainty that secretin is discharged into the blood after contact of acids or soaps with the duodenojejunal mucous membrane. But do these substances cause its formation from a "pro-secretin," which had previously existed in the mucous membrane, or do they merely liberate the secretin, already completely formed? In the case of the suprarenal secretion, Tscheboksaroff has observed in the laboratory of Mislavsky that an injection of physostigmin increases the amount of adrenalin which is discharged into the capsular vein (experiments on dogs, 1910); pilocarpin has not this effect. Finally, histological observations have shown that pilocarpin causes swelling of the thyroid, and the collection of colloid matter in the vesicles, this then spreading into the intervesicular lymphatic spaces; the same is true after ligature of the common duct (K. Hürthle, 1894). Hence we may suppose that the bile excites thyroid secretion.

Undoubtedly, other facts might be added to these. They are, however, too uncertain for us to be able to consider them as demonstrated without the most rigorous verification. Thus, it has been stated that when an organic extract is introduced into the body, it tends towards the homologous organ, hypertrophies and stimulates it. *Homostimulants* have even been spoken of. Contradiction notwithstanding, it has even been maintained that these extracts, when administered in small doses, moderate the function of the homologous organ. In such a manner is the practise of organotherapy justified by its supporters, in spite of the contradictions constantly being encountered.

3. The influence of the nervous system on the internal secretions has been demonstrated in the cases of the glycogenic function of the liver and the passage of adrenalin into the blood. The evidence in the case of the liver is found in all treatises on

physiology. The proofs for the second are given largely in Biedl's book and Swale Vincent's study, already mentioned, as well as in a remarkable study by G. Bayer [1] [and in more recent works of Crile, Cannon and others—Ed.]. Finally, it has been thought possible to prove directly the action of the nervous system on the thyroid by showing that stimulation of the laryngeal nerves (L. Ascher and M. Flack, 1910) increases the excitability of the depressor; it being admitted, following the researches of E. de Cyon, that the latter is dependent on the thyroid secretion.

4. The *reciprocal glandular actions,* or *humoral interrelations,* belong to the group of phenomena termed as functional humoral correlations. But all correlations of this sort, which are determined and characterized by the action of an internal secre-

[1] G. BAYER, "Die normale und pathol. Physiologie des chromaffinen Gewebes der Nebennieren" (*Ergebnisse der pathol. Anat.,* 1910, XIV, 132).

tory product on an organ of the same anatomical system or of a distinct and more or less distant system, are not interrelations. The latter are characterized by the reciprocal action of two products of internal secretion.

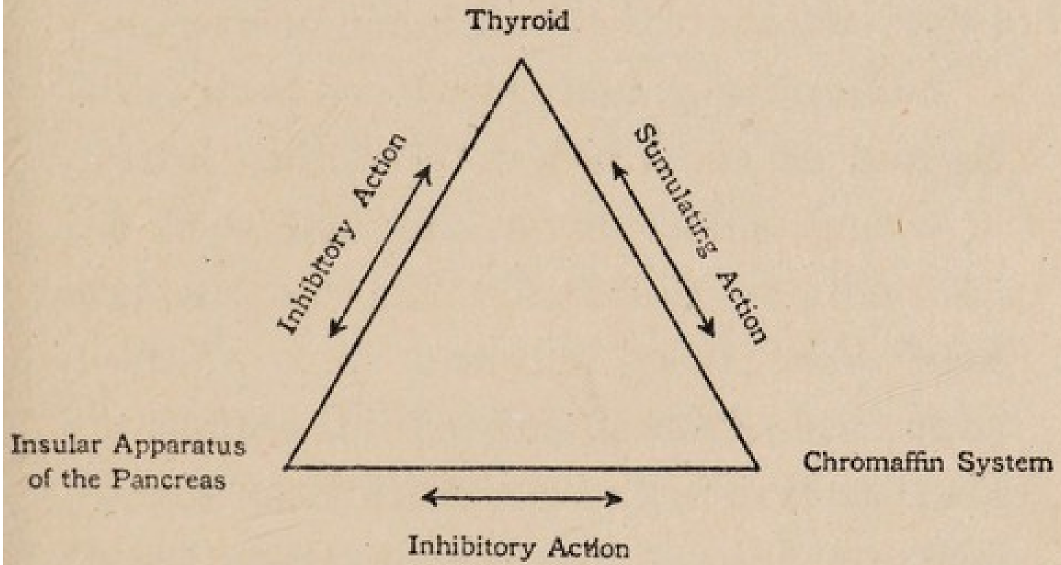
Undoubtedly, confusion between these two notions tends to exist. To avoid this, however, it would suffice to use a little criticism and consider some fundamental facts in the history of internal secretions. If secretin, for example, is the specific excitant of pancreatic secretion, does the pancreas furnish a product of internal secretion acting on the intestinal secretion? And where, therefore, is the reciprocal connection between the pancreatic substance which acts on the liver, the organ in which the metabolism of the carbohydrates occurs, and a substance of hepatic origin? The demonstration which follows shows how important it is to maintain the distinction between functional humoral correlations and humoral interrelations.

How has the latter theory become so widely accepted? It has been admitted that there is no endocrine gland which has no mutual connections with one or several others, either of excitation or of reciprocal antagonism. Let us now reproduce the diagram of the promoters of the theory, the Viennese pathologists, Eppinger, Falta and Rudinger (1908),[2] which sums up the principle of these actions.

From this diagram it is seen that the thyroid secretion is the excitant of the suprarenal apparatus, and adrenalin the excitant of the thyroid. Furthermore, adrenalin exercises an inhibitory influence on the

[2] H. Eppinger, W. Falta and C. Rudinger, "Über der Wechselwirkungen der Drüsen mit innerer Sekretion" (*Zeitschr. für klin. Med.*, 1908 and 1909, LXVI, 152, and LXVIII, 380); W. Falta, "Über der Korrelationen der Drüsen mit innerer Sekretion" (Lewin's *Ergebnissė der Wissenschaftliche Med.*, 1909, I, 108-118). *Cf.* also Caro, "Wechselwirkung der Organen mit innerer Sekretion" (*Mediz. Klinik*, January 23, 1910, VI, 136-139).

pancreas, and the secretion of the latter has the same influence on the adrenals. Also, the thyroid secretion moderates the activity of the pancreas and the internal pancreatic secretion holds the activity of the thyroid within bounds. Assuming, for



example, hypoactivity or suppression of the activity of the thyroid and there will result hyperfunction of the pancreas resulting from the disappearance of the normal restraining action of the former gland upon the latter; likewise a diminution in the function of the adrenals occurs. Let there be given, on the other hand, hyperactivity, from some morbid influence, of the thyroid. The restraining action of the pancreas will be exercised more energetically and there will result a more or less marked insufficiency of the functions of the latter gland, and at the same time hyperfunction of the chromaffin system.

Analogous connections have been investigated as regards the functional activity of other endocrine organs and their authenticity established. This is the case with the ovary, thyroid and pituitary body; the adrenals and genital glands, etc. Isaac Ott, for example, maintains that the anterior lobe of the pituitary body has an inhibitory action on the genital glands, the testicles and ovaries, and, reciprocally, that the latter have a like action on the hypophysis. He also says that the thyroid and pituitary are mutually compensatory.[3]

Such are the efforts that have been made

[3] Isaac Ott, "Internal Secretions from a Physiological and Therapeutical Standpoint," *Phil.*, 1910; see p. 125.

to generalize the conception of humoral interrelations.

Both parts of the *vegetative nervous system* share in these reciprocal actions. They are the autonomous and the sympathetic systems. It is known, for example, that the product of the adrenal secretion is the excitant of the sympathetic nervous system. We might therefore say that adrenalin is *sympathicotropic,* and the product of the thyroid secretion, which acts on the tone of the vagus (F. Kraus, 1908), is *vagotropic,* or, better, *autonomotropic.* Thus adrenalin produces the same effects as a stimulant of the sympathetic system; whenever it encounters a motor fiber of this system, it produces a motor effect; if it strikes an inhibitory fiber of the same system, the effect is of an inhibitory character. But there are some organs which possess a double enervation, autonomous and sympathetic. In this case, as has been well said by G. Fano,[4] these organs ''possono reagire a sostanze iniettate dall'esterno o elaborate dall' organismo raggiungondo effetti molto notevoli perché a quelle stimolazioni tossiche possono risponderi non solo liberando le determinanti d'una funzione ma pure contemporaneamente inibendo quelle condizioni antagonistiche che si opporrebbero alla sua facile e completa attuazione.'' The first question to be discussed is if all the actions started by endocrine products are the results of the stimulation or inhibition of sympathetic or autonomic nerve fibers. It is evident that we may say, for example, that the action by which glycogen is collected in the liver is regulated by the sympathetic, and that the internal secretion of the pancreas is regulated by the vagus. But there is no proof that these secretions cannot take place under purely humoral influences, and there are proofs that the

[4] *Loc. cit.*

mobilization of sugar in the liver in the form of glycogen and the accumulation of the latter are diastatic phenomena. Likewise, the formation of fibrinogen in the liver, and of antithrombin in the same gland, take place independently of the nervous system. And it would be easy to cite other instances of the same nature.

It is no less important to discuss another question which concerns the connections between the vegetative nervous system and reciprocal glandular activities. We have been led to admit (Eppinger and Hess, 1909-1910) that a certain rise in the normal tone of the pneumogastric (*constitutional vagotonia*) or of the sympathetic (*sympathicotonia*) may be observed in various subjects. Hypertonia of the vagus nerves, i. e., vagotonia, is caused by the excessive secretion of autonomotropic hormones accompanied by a deficient secretion of sympathicotropic hormones. This is a constitutional anomaly and quite a variety of disorders may arise from it. The victims of this anomaly show a particular sensibility to autonomotropic poisons, like atropin and pilocarpin, and a lesser sensibility to sympathicotropic poisons, as adrenalin. The reverse is true in sympathicotonia, which furnishes us with a complete series of diagnostic signs.

But the proofs of the existence, and *a fortiori* of the action, of autonomotropic (thymicolymphatic and pancreatic) hormones are altogether insufficient. Is there a physiologist who has actually recognized a hormone in a thymus extract, in the sense that the word hormone should be used (see p. 136)? The theory is therefore based on an unstable foundation. Furthermore, the facts on which it rests are either uncertain or altogether inexact and the pharmacodynamic criterion to which has been attributed so high a diagnostic value is far from being infallible. Some most useful points on these various questions will be found in several recent studies.[5] In any case, the question if nervous actions participate in reciprocal glandular activities, and to what degree this occurs, is as yet far from solved.

However, it is of importance to examine the theory of humoral interrelations in itself, and we shall do this immediately.

What are the facts on which it is based? They are anatomo-pathological data, clinical observations and some animal experiments. At the bedside we analyze a syndrome in which disorders depending on the alteration of an endocrine gland appear to predominate. At the autopsy we actually

[5] K. PETREN und I. THORLING, ''Unters. über das Vorkommen von 'Vagotonus und Sympathicotonus' '' (*Zeitschrift für klin. Med.*, 1911, LXXIII, 27-46); J. BAUER, ''Zur Funktionsprüfung des vegetativen Nervensystems'' (*Deutsches Arch. für klin. Med.*, 1912, CVII, 39); P. FLEISCHMANN, ''Über die Wechselbeziehungen der Drüsen mit innerer Sekretion'' (*Med. Klinik*, Feb. 4, 1912, p. 177); N. PENDE, ''Sulla vagotonia constituzionale e morbosa di Eppinger ed Hess e su alcuni recenti metodi d'indagine semiologica del sistema nervoso simpatico'' (*Il Tommasi*, April 30, 1912, VII, 265).

find this change, but, besides, there are discovered lesions of other endocrine glands by which it is believed possible to explain disorders which were not accounted for by the lesion of the organ primarily attacked. By combining clinical facts and post mortem observations, a connection between the various organs studied is finally arrived at. The question is, What is the nature of this connection? Are we dealing with a synergic, reciprocal relation, like that maintained by Eppinger, Falta and Rudinger? Or have we simply concomitant phenomena, provoked by the same cause acting on divers organs?

The second notion, which results solely from the consideration of clinical facts, has given rise to the establishment of *syndromes of pluriglandular insufficiency,* due to several French pathologists (H. Claude, 1907-1908; L. Rénon, 1908; L. Rénon and Arthur Delille, 1908, etc.). The conception of these syndromes has led to *associative opotherapy,* the simultaneous administration of several organic extracts (L. Rénon, 1908), which has been much vaunted. However, the anatomo-pathological method is subject to errors of interpretation. The statement concerning lesions in various organs does not prove that there normally exists any association whatsoever between these organs. There have been found lesions of the testicles in individuals affected with cirrhosis of the liver, and likewise following resection of the liver or ligature of the bile duct. Has any one, therefore, drawn the conclusion that there is a relation between the bile duct and the testicles? Is it probable that the retention of toxic substances, following lesions of the liver, causes parenchymatous alterations here and there, but more markedly in the testicles? Similarly, are we justified in maintaining that the lesions found in a number of organs of thyroidectomized animals are directly due to the loss of the thyroid function? Are they not rather one of the effects of the intoxication and metabolic disorders which occur in these animals?

The tendency at present to consider the study of hormones as being nothing else than the investigation of reciprocal actions, or humoral interrelations is therefore little justified. If, as I have already said,[6] interrelations enter into the group of functional humoral correlations, it is necessary that all the latter be interrelations. This is what is shown by the actual facts.

Reciprocal Relations between the Pancreas and the Adrenals.—Let us consider the reciprocally antagonistic relations admitted to exist between the pancreas and the adrenals. In favor of the

[6] E. Gley, ''Corrélations fonctionelles et inter-rélations humorales'' (*Rev. générale des sciences,* July 30, 1913, p. 537).

idea of an inhibitory action of the pancreas upon the adrenals, it has been maintained that following the suppression of the former organ the action of adrenalin is more marked. The following was observed by O. Loewi:[7] He removed the pancreas and then noticed that the administration of adrenalin was followed by dilatation of the pupil, which does not occur in a normal animal. Loewi observed in ten out of eighteen diabetics a marked dilatation of the pupil following the administration of adrenalin, while in thirty healthy subjects this phenomenon was noted but twice. To explain this effect it is suggested that the pancreas secretes a substance antagonistic to adrenalin. The latter acts on the pupil through the intermediary of the sympathetic. The antagonistic substance inhibits the sympa-

[7] O. Loewi, "Eine neue Funktion des Pankreas und ihre Beziehung zum diabetes mellitus" (*Wiener klin. Woch.*, 1907, p. 747).

thetic or stimulates the constrictor, so that when the pancreas is destroyed this action can no longer be exercised and the adrenalin is free to produce its full effects.

These observations of Loewi are certainly exact. Is the interpretation correct? In this connection we should mention that Bittorf[8] (1911) carried out Meltzer's reaction with the blood serum of ten diabetics and in no case did he find an augmentation in the quantity of adrenalin in the blood. Furthermore, in diabetic animals and in man, permanent dilatation of the pupil has never been observed. But why not decide the question on a surer and more solid basis—that of direct experience? Has any one found an increase in the proportion of adrenalin in the suprarenal blood of depancreatized animals? The experiment has not even been at-

[8] A. Bittorf, "Ist beim Diabetes Mellitus eine Ueberfonktion der Nebennieren nachweisbar?" (*Münchener med. Woch.*, 1911, No. 42).

tempted as yet. Researches on this point have been begun in my laboratory.

It has been maintained that the suprarenal capsules have a reciprocally inhibitory action on the function of the pancreas. The following is the experiment performed by R. Pemberton and J. E. Sweet (1908, 1910), according to whom this action is even manifested on the external pancreatic secretions: A preliminary injection of adrenalin prevented the action of secretin. This antagonism of the two substances was not found by Gley (1911).[9] Zülzer[10] observed glycosuria following the extirpation of the pancreas cease after ablation of the two suprarenals. Also, Frouin[11]

[9] When an antagonism is stated to occur, it is due to the temporary anemia of the pancreas, resulting from the vasoconstriction produced by the adrenalin (Willis Edmunds, 1910; Wertheimer, 1911; Gley, 1911).

[10] G. Zülzer, M. Dohrn, and A. Marxer, "Neuere Unters. über den experimentellen Diabetes" (*Deutsch. med. Woch.*, 1908, p. 1380).

[11] A. Frouin, "Ablation des capsules surrénales et diabète pancréatique" (*C. R. de la Soc. de biol.*, Feb. 8, 1908, LXIV, p. 216).

has published the results of two analogous experiments in which pancreatic diabetes in a dog was diminished after the ablation of one suprarenal capsule and two-thirds of the other. But Zülzer's dogs only survived twenty-four to thirty-six hours. Under these conditions, what does a diminution in the elimination of sugar signify? Is it not a well known fact that in animals suffering from malnutrition, cachectic animals or those near death, diabetes is attenuated or may even disappear? We should not forget the somewhat paradoxical but just expression of Claude Bernard that "in order to be diabetic, one must look well." Now, decapsulated animals are in a state of organic decay. The recent experiments of Athanasiu and his pupil Gradinesco [12] have, moreover, shown that

[12] *Cf.* J. ATHANASIU and GRADINESCO, "Les capsules surrénales et les échanges entre le sang et les tissus" (*C. R.*, August 9, 1909), and A. V. GRADINESCO, "Der Einfluss der Nebennieren auf den Blutkreislauf und den Stoffwechsel" (*Arch. f. die ges. Physiol.*, 1913, CLII, pp. 187-253).

adrenalin, by the tonic influence that it exerts on the endothelium of the blood capillaries, regulates the material exchanges between the blood and the interstitial plasma of the tissues, so that if the secretion of this product is abolished these exchanges are put in a state of profound disorder and their reduction appears to be the cause of death following ablation of the adrenals. It would therefore seem that one passes by the facts too boldly when he maintains that there exists—alongside of a "positive adrenal diabetes," due to a hyperactivity of the suprarenal glands which produce more adrenalin, leading, under the influence of this substance, to hyperglycemia and glycosuria—a "negative diabetes," from the suppression of the permanently moderating influence exercised by the pancreas on the suprarenal capsules, and that in the classic pancreatic diabetic (J. von Mering and Minkowski, Lancereaux), this last factor plays its rôle. Following the destruction of the pancreas, adrenalin would be secreted in excess and thus the pancreatic diabetic would in reality be an adrenalin diabetic (Zülzer). As G. Bayer[13] justly remarks, the physiological antagonism between the two glands and the fact of the hyperactivity of the chromaffin system after extirpation of the pancreas could only be accepted if there were found: (a) Histological signs of increased function in the suprarenal glands of depancreatized animals; (b) abnormal quantities of adrenalin in the blood of depancreatized animals and diabetic human beings; (c) in the same animals signs of hyperactivity of the chromaffin system, as elevation in the arterial pressure. Such a demonstration has not as yet been furnished. The facts amassed by Viennese pathologists only show that the loss of the pancreas has, under certain conditions, the same effect

[13] *Loc. cit.*

as excitation of the adrenals, that is, increased secretion of adrenalin. Thus the result is the same as after section of the inhibitory nerves of the heart or stimulation of the accelerating nerves. Section of the vagus does not provoke acceleration of the heart beat because increased activity of the sympathetic follows, but because the normal inhibitory influence is suppressed. Likewise, the pancreas and the suprarenals act opposingly on the accumulation of sugar. That does not prove that the action of one is determined by the suppression of the action of the other, and conversely.

Reciprocal Relations between the Thyroid and the Adrenals.—Is it very well established that the thyroid and adrenals exert reciprocal stimulation on one another? According to the experiments of Eppinger, Falta and Rudinger,[14] adrenalin no longer causes glycosuria in

[14] *Loc. cit.*, 1908.

thyroidectomized animals;[15] if these animals be administered thyroid preparations the action of adrenalin is reestablished.[16] From this there follows immediately the explanation of the glycosuria observed very frequently in exophthalmic goiter; in fact, nothing in the theory is more simple, if it is true that exophthalmic goiter depends on hyperfunction of the thyroid, which hyperactivity is followed by an increased secretion of adrenalin, one of the effects of which will be

[15] The same would not be true after thyroparathyroidectomy. Eppinger, Falta and Rudinger admit in fact that there is an antagonism between the thyroid and the parathyroids and that their actions on the sympathetic nervous system are the reverse of one another, the thyroid secretion exciting and the other inhibiting the nerves of this system. The proofs brought to the support of this conception are insufficient and it is far from being established. Moreover, F. Kraus and R. Hirsch have noted (1909) that thyroparathyroidectomized dogs and rabbits become exquisitely glycosuric under the influence of adrenalin.

[16] According to F. Kraus and Rahel Hirsch, on the contrary, adrenalin does not produce glycosuria in the dog if thyroid extract is administered at the same time.

glycosuria. Now, contrary to the experiences of the Viennese pathologists, the experiments of Underhill and Hilditch,[17] and of Underhill[18] have shown that glycosuria is exquisitely produced after thyroidectomy under the influence of adrenalin. Moreover, E. P. Pick and F. Pineles[19] (1908) observed that the same is true in the rabbit; in the young she-goat, on the contrary, glycosuria was prevented by the operation. It is, in fact, possible that among thyroidectomized animals there are some that are incapable of reacting to adrenalin. We know how much the metabolism is disordered in these animals and the

[17] FRANK P. UNDERHILL and W. W. HILDITCH, ''Certain Aspects of Carbohydrate Metabolism in Relation to the Complete Removal of the Thyroids and Partial Parathyroidectomy'' (*Amer. Jour. of Physiol.*, 1909, XXV, p. 67).

[18] FRANK P. UNDERHILL, ''The Production of Glycosuria by Adrenalin in Thyroidectomized Dogs'' (*Ibid.*, 1911, XXVII, pp. 331-339).

[19] E. P. PICK and F. PINECLES, ''Über die Beziehungen der Schilddrüse zur physiol. Wirkung des Adrenalins'' (*Biochem. Zeit.*, 1908, XII, p. 473).

disorders are variable in intensity; if they are profound it is not astonishing that the animal thus attacked cannot become hyperglycemic or glycosuric, which has already been mentioned above. This interpretation finds support in a series of experiments made by H. Ritzman [20] (1909) which show that, in athyroid cats, when the phenomena of intoxication are acute, adrenalin does not provoke glycosuria; if the disorder is ameliorated it reappears. The cause of the absence of glycosuria does not, therefore, lie in the lack of thyroid secretion, but in a change of the general condition.[21]

Let us suppose the case to be the reverse of that just examined. Hyperthyroidism brings after it a stimulation of the chromaffin system followed by emaciation and

[20] "Über den Mechanismus der Adrenalinglycosurie" (*Arch. f. Exper. Path. und Pharmak.*, 1909, LXI, p. 231).

[21] It is interesting to state in this connection that A. Bonanni (*Arch. italiennes de biologie,* 1912, LVIII, pp. 157-172) has noted that the glycosuria which is provoked by carbon dioxid is not produced in debilitated animals.

glycosuria, which are so frequently found in these conditions of thyroid hyperfunction. But is the reality of these conditions firmly established? It is a point that we will investigate immediately.

I would like to go immediately to the pith of the question. We might, to judge by the reciprocal connections between the chromaffin system and the thyroid, institute direct experiments. It is not always possible to carry out such experiments; the investigator is often obliged to attack the problem by indirect methods and he can only arrive at the solution sought for by successive and gradual approximations. In the case in question, on the contrary, the direct study is easy; the experiments of Cybulski, J. P. Langlois, J. P. Langlois and L. Camus, Biedl, Dreyer and above all, those of Tscheboksaroff [22] have taught us

[22] N. Cybulski, "Über die Funktion der Nebenniere" (*Wiener med. Woch.*, 1896, pp. 215 and 255); J. P. Langlois, "Sur les fonctions des capsules surrénales," Thèse de doctorat ès sciences, Paris, 1897; L. Camus

that the suprarenal blood can be collected in quantities large enough to discover in it the action of adrenalin through the process of injecting this blood into another animal. With a view to studying this question, we can call to mind many other experiments. But there are two series which, it appears, should be mentioned first: (a) Is the thyroid secretion really an excitant of the suprarenal? And does the suprarenal blood therefore contain more adrenalin after the injection of thyroid extract? (b) Do extracts of suprarenal glands of thyroidectomized animals which have succumbed to the operation contain less adrenalin? On these two points I have col-

and J. P. LANGLOIS, "Sécrétion surrénale et pression sanguine" (*C. R. de la Soc. de biol.*, March 3, 1900, p. 210); A. BIEDL, "Beiträge zur physiol. der Nebennieren. Die Innervation der Nebennieren" (*Arch. für die ges. Physiol.*, 1897, LXVII, p. 443); GEORGE P. DREYER, "On Secretory Nerves to the Suprarenal Capsule" (*Am. Jour. of Physiol.*, 1899, II, pp. 203-219); M. TSCHEBOKSAROFF, "Über sekretorische Nerven der Nebennieren" (*Arch. für die ges. Physiol.*, 1910, CXXXVII, pp. 59-122).

lected a large number of facts.[23] These facts prove that the adrenals of thyroidectomized animals do not contain less active adrenalin than those of normal animals and, furthermore, that the suprarenal blood does not become richer in adrenalin after the injection of thyroid extract in physiological doses than after that of any other organic extract, at least of those which have been tested in the experiments of Gley and Quinquaud, viz., hepatic, pancreatic, testicular and renal.

Hence the experiments so far carried out do not appear to favor either the theory of the reenforcing reciprocal action of the thyroid and the adrenals, or the theory

[23] See E. GLEY and ALF. QUINQUAUD, ''Contribution à l'étude des interrelations humorales, I.—Action de l'extrait thyroïdien et en général des extraits d'organs sur la sécrétion surrénáles'' (*Archives internationales de physiologie,* January 31, 1914, XIV, pp. 152-174); ''Contribution à l'étude des interrelations humorales. II.—Valeur physiologique de la glande surrénale des animaux éthyroïdés'' (*Ibid.,* pp. 175-194). *See also* E. GLEY and ALF. QUINQUAUD, *C. R.,* June 30, 1913, CLVI, p. 2013.

of the inhibitory reciprocal action of the pancreas and the adrenals. Would it not be the same with the other interrelations that have been so easily admitted?

Reciprocal Relations between the Thyroid and the Pancreas.—The third case is the interrelation between the thyroid and the pancreas. According to Lorand,[24] extirpation of the thyroid suppresses glycosuria in depancreatized animals. Why, by what mechanism? The answer given is that following the loss of the inhibitory influence exercised by the pancreas on the thyroid gland, the thyroid secretion is increased in these depancreatized animals, which is followed by a secondary augmentation in the quantity of adrenalin.[25] Hence if the thyroid is re-

[24] A. Lorand, "Les rapports du pancréas (îlots de Langerhans) avec la thyroïde" (*C. R. de la Soc. de biol.*, March 19, 1904, LVI, p. 488).

[25] We have already seen that it does not matter if the injection of thyroid extract in physiological doses does not augment at all the adrenalin content of the

moved, the secretion of adrenalin diminishes and at the same time the hyperglycemia and the glycosuria disappear.

This explanation does not take into account several important facts. The first is that in thyroidectomized animals glycosuria has several times been found; the above theory does not explain this—in any case it is seen that the question is complex. Similarly, cases of myxedema with diabetes have been found. Besides, let us suppose that the facts are always so. It is to be recalled that thyroidectomized animals suffer from disordered metabolic exchanges, which are profoundly diminished, and that consequently glycosuria,[26] no matter by what cause it is provoked, may very well be diminished for this reason alone. This is the observation which has already

suprarenal blood. The reasoning is therefore fundamentally wrong.

[26] No one has even attempted to investigate how the various sorts of glycosuria run their course following thyroidectomy.

been made with regard to the connection between the pancreas and the adrenals. Another argument has also been invoked, *viz.*, the increase in volume of the thyroid in depancreatized dogs, combined with augmentation of the colloid substance.[27] Taken by itself, this statement does not mean very much. Licini, more prudent than others, has asked himself whether this is a compensatory phenomenon or is it due to the suppression of a specific secretory product of the pancreas; or perhaps, we may add, is it a more general phenomenon resulting from reactions against the intoxications which may result from disorders in the nitrogenous metabolism which are presented by depancreatized dogs.

Reciprocal Relations between the Thyroid and the Gonads.—The same uncertainty exists in connection with the rela-

[27] C. Licini (a pupil of Kocher), "Der Einfluss der Extirpation des Pankreas auf die Schilddrüse" (*Zeitschr. für Chirurgie*, 1909, CI, p. 522).

tions between the thyroid and the ovaries. The ovaries exercise an inhibitory action on the thyroid; in fact, the latter becomes hyperactive after castration, and there is an increase of colloid matter. This is the cause, it is said, of the large number of cases of exophthalmic goiter after the menopause. Is it necessary to point out how very injudiciously statistical methods are applied here? The loss of the thyroid function should be followed, reciprocally, by hyperfunction of the ovary. The latter has not been proven at all. It is true that Champy and myself noted that thyroidectomy in the rabbit is followed by hypertrophy of the insterstitial gland of the ovary. But von Eiselsberg[28] showed long ago that thyroidectomy causes atrophy of the genital organs. The truth is that these

[28] FR. VON EISELSBERG, "Über vegatative Störungen im Wachstume von Thieren nach frühzeitiger Schilddrüsenexstirpation" (*Arch. für klin. Chirurgie,* 1895, XLIX, pp. 207-234). *Cf.* also a preliminary note in *Berliner klin. Woch.,* 1892, No. 46, p. 1178.

statements of a morphological nature do not permit of drawing any conclusions as to the direct connections between the organs involved.

Other interrelations are no better established. It is commonly thought that when an increase in volume is observed, one may conclude a concomitant augmentation of function. But it is necessary to prove first that a hypertrophy really corresponds to functional hyperactivity. It is high time that a physiological study be made of the organs thus stated to be altered, as well as of the properties of the blood in diseases attributed to disorders of internal secretion. Without this physiological study hypotheses are being too liberally formulated.

That there are connections between the various glands is one of the fundamental facts maintained by the doctrine of internal secretions, and to deny them would be to deny a part of the doctrine of internal secretions itself. But what I criticize is the insufficiently demonstrated theory of reciprocal relations.

II. THE DISEASED FUNCTION

From the physiological point of view, the diseases of the endocrine organs may be divided into two large classes,—those attributed to hyperfunction, and those to hypofunction. Moreover, this is the distinction most naturally made by pathologists. The notion of insufficiency has been realized by physicians, one might say, from time immemorial. But it has now been developed to such a point that pathologists like Chauffard have been led to think that this notion dominates pathology. The notion of excessive functioning is more recent and has not as large a range as before the discoveries relative to the internal secretions and their disorders.

Some reflections of a physiological nature on the value of these two notions may not be out of place here. As for the clinical questions which confront us at this point in large number, I have neither the means nor the intention to examine them.

(1) Hypersecretion.—I have mentioned above that the substances having a trophic rôle, and hormones, act in minimal doses. It is therefore sufficient for the glands to discharge very small quantities of them into the blood. This is one of the reasons why it is so difficult to discover their presence in the blood of efferent veins of the glands, at least when we are not dealing with extremely active products, like secretin and, above all, adrenalin. Furthermore, these substances disappear very rapidly in the blood.

For this reason, is it possible for an excess to remain in the blood? A gland may indeed show exaggerated function. In order that a morbid syndrome be established in connection with this hyperfunction, still another condition is necessary; namely, that the product liberated in excess should not be liable to destruction in the blood or tissues. In the conditions described as resulting from glandular hyperactivity, no one has ever investigated if this second condition, necessary though it is, is fulfilled. In view of properties continuously manifested, it is most assuredly true that there are hormones which are constantly being produced. The best example appears to be that of adrenalin. But these hormones are formed and secreted only in very small amounts. In order to admit that a permanent state of hypersecretion exists, it would first be necessary to demonstrate that these destructive mechanisms have ceased to act. Just as the excess of digestive ferments is absorbed or eliminated, so the endocrine products disappear rapidly in the blood—secretin in several minutes, adrenalin almost immediately after it has been injected.[29]

Besides, have the states of hypersecretion just described indeed been proven to exist?

Hyperthyroidism, of which so much has been spoken, has never really been reproduced experimentally, neither by Cunningham, nor by Gley, nor, in the last few years, in the researches methodically pursued by Carlson and by Coronedi.[30]

No one has, by repeated injections of pituitary extract, caused symptoms of acromegaly to appear, no more than symp-

[29] Experiments of J. de Vos and M. Kochmann on the rabbit. One-third and even two-thirds of the minimal fatal dose of adrenalin disappeared almost immediately after the injection (*Arch. intern. de pharmacodynamie*, 1905, XIV, pp. 81-91).

[30] R. H. Cunningham, "Experimental Thyroidism" (*Jour. of Exper. Med.*, 1898, III, pp. 147-243); A. J. Carlson, J. R. Rooks, and J. F. MacKie, "Attempts to Produce Experimental Hyperthyroidism in Mammals and Birds" (*Am. Jour. of Physiol.*, 1912, XXX, pp. 129-159); G. Coronedi, "Un coup d'œil d'ensemble sur mes expériences actuelles relatives à la glande thyroide" (*Arch. italiennes de Biologie*, 1912, LVII, pp. 252-262).

toms of exophthalmic goiter have been provoked by injections of thyroid extract. It will be remarked that the experiments of Bircher on the reproduction of Graves' disease by intraperitoneal implantation of hypertrophied thymus are of an entirely different nature.[31]

Does hypersecretion of epinephrin itself, of which so much has been spoken during the last few years, surely exist? Its reality in exophthalmic goiter is well contestable. While Meltzer's reaction has been obtained in the blood of many patients suffering from exophthalmic goiter, yet the serum of the blood has not the cardiovascular properties of adrenalin (M. Cléret and E. Gley,[32] 1911); on the contrary its

[31] E. BIRCHER, "Zur experimentellen Erzeugung des Morbus Basedoweii" (*Zentralbl. für Chirurgie,* Feb. 3, 1912, XXXIX, pp. 138-140).

[32] E. GLEY and M. CLÉRET, "Recherches sur la pathogénie du goitre exophtalmique. I. Action cardiovasculaire du sérum sanguin des malades atteints de goitre exophtalmique" (*Jour. de physiol. et de pathol. générale,* 1911, XIII, pp. 928-944). *Cf.* also M. CLÉRET'S

action is clearly hypotensory. The hypertension observed in many renal affections has also been considered as a sign of adrenalinemia. But Meltzer-Ehrmann's reaction is not given by the serum of these sufferers and, furthermore, Janeway has been unable to discover any vaso-constrictive substance in the blood of six patients with hypertension. In this investigation, neither defibrinated blood nor serum should be used, for these are liquids in which substances having a vaso-constrictive action are formed.[33] Also the facts governing the alleged increase of adrenalin in various pathological conditions can no longer be accepted without reserve.

thesis ("Etude sur la pathogénie du goitre exophtalmique," Paris, 1911), in which can be found the criticism of what I have called the thyroido-suprarenal theory of exophthalmic goiter.

[33] J. M. O'Connor, "Über den Adrenalingehalt des Blutes" (*Arch. f. exper. Pathol. und Pharmak.*, 1912, LXVII, pp. 195-232).—Th. Janeway and E. A. Park, "The Question of Epinephrin in the Circulation and its Relation to Blood Pressure" (*Jour. of Exper. Med.*, 1912, XVI, p. 541).

Moreover, in Lucien and Parisot's [34] recent work will be found the reasons why we have no right to surmise a relation of cause and effect from the simple anatomo-pathological fact of suprarenal hypertrophy, and the clinical phenomenon of arterial hypertension.

(2) Hyposecretion.—There are also reasons for asking if it is possible that a state of hypofunction of the endocrine glands is ever produced. This question is connected with that of profuse or excessive functioning, so widespread throughout the organism. Just as machines, says Meltzer, are constructed in such a manner as to possess a resisting force superior to that required of them, so must the animal [35] organism have on hand a superabundance of tissues and energy. There is an ex-

[34] M. Lucien and J. Parisot, "Glandes surrénales et organes chromaffines" (Paris, F. Gittler, 1913).

[35] Meltzer (*loc. cit.*) wrote *human.* Is it not preferable to say *animal?* The reader will permit me to take this liberty.

cess of digestive secretions, excessive action of the heart and respiratory movements. Similarly, we have surplus endocrine secretions. Let us recall the fact that minimal doses of products secreted by the ductless glands suffice to fulfil the rôle assigned them.

Facts pertaining to this point are available in abundance. A small fragment of the pancreas, adrenals or thyroid, insignificant in weight when compared to the total mass of the organ—it has been estimated that a twelfth of the pancreas is sufficient to prevent glycosuria—preserves animals from the fatal consequences of the extirpation of these glands. Undoubtedly, in the case of the pancreas it has several times been observed by Hédon, Sandmeyer, Thiroloix and others, that animals in whom a small fragment of the gland has been left, either intentionally or inadvertently, finally became diabetic. One is tempted to believe that the fragment became insufficient. Is it not surprising that a portion of an organ that, although very small, has sufficed for a long time to maintain the function of the organ, should suddenly lose its ability to fulfil its office, although one would think that the increased demand calling for hypertrophy would increase its functional capacity? Sooner than accept this hypothesis, could we not suppose the intervention of purely mechanical causes —adhesions and sclerosis, for example—gradually rendering the circulation in the remaining fragment of the organ difficult, which, furthermore, has perhaps preserved but a few small blood vessels.

Another pertinent fact in this connection is the following: The suprarenal glands are more or less severely attacked by various microbic toxins, and the extract of glands coming from infected animals appears much less active than that from normal glands. However, the arterial pressure of these animals is not always very low. This was recognized in the case of rabies in my laboratory by R. Porak.[36] Thus the small quantity of adrenalin still secreted by these altered glands almost suffices to maintain the vascular tone. It is more difficult than is generally appreciated to render the liver insufficient; the blood continues to contain sugar and urea. At autopsies, cirrhotic livers have been found in subjects in whom the organ had appeared to function normally.[37]

While we thoroughly understand insufficiencies of organs furnishing mechanical labor, as the heart, or organs having quantitative chemical functions, as the liver and

[36] R. Porak, "Des altérations fonctionelles des glandes surrénales dans la rage" (*C. R. de la Soc. de biol.*, Dec. 7, 1912, LXXIII, p. 601).

[37] Almost the same is true in the case of the kidney. Greatly altered kidneys are found in very many cadavers, although the urine of the subjects had always been normal and they had never presented any serious sign of renal insufficiency. It is likewise with the blood which certain pathologists (Widal and his pupils, for example) are investigating for signs of renal or hepatic insufficiency.

the kidneys, it is difficult, for reasons which have just been indicated, to understand insufficiencies of endocrine glands, since the latter furnish but minute quantities of extraordinarily active substances and we must suppose them almost entirely destroyed in order that they should not have the ability to furnish the small quantity of secretion absolutely necessary for the vital functions. This does not mean, however, that we must deny *a priori* the reality of these insufficiencies, but that we should be more stringent than heretofore in accepting demonstrations of this reality. Explanation has been much abused in attempting to account for disorders of hyposecretion and also, generally speaking, for the disorders of all the internal secretions. This has reached such a point that when a syndrome cannot be explained by assuming either hypersecretion or hyposecretion of an endocrine gland, the two factors are brought in. Has it not been said—in acromegaly, for example—that there is at the same time partial "hyperpituitarism" and "hypopituitarism"? Would it not be right to apply to this sort of considerations and to these pathological explanations of glandular disorders what Vulpian wrote concerning pathological explanations by vaso-motor disturbances, at a time when it seemed to physicians that the discoveries of physiologists about the action of the vascular nerves could explain all morbid phenomena? "It was soon admitted that the greater part of the morbid disorders of the organism had for their origin or mechanism a functional modification of the vaso-motor nerves. Fever, inflammation, hemorrhages, dyspepsias, the chief neuroses, . . . tetanus, various forms of paralysis, diabetes, albuminuria, etc., all these pathological states, or at least their principal symptoms, were due to a perturbation of the vaso-motor apparatus. . . .

"For my part, I have always fought

against this deplorable tendency to apply prematurely facts from experimental physiology, as yet uncertain, to pathology. The greater part of the assertions thus made, without any critical spirit, are, besides, absolutely lacking in proof. They are purely theoretical conceptions, the results of the sort of speculations that can be made as one desires.''[38]

(3) Trophic Deviations.—It appears certain, however, that there are certain diseases depending on alterations of the endocrine glands. I have posed the question, Can toxic products not be formed in the endocrine glands, the more or less active absorption of which causes morbid syndromes? This question confronts at once experimental pathology, pathological chemistry and the clinician. The notion is undoubtedly hypothetical, but there are some facts which render it interesting.

[38] Vulpian, ''Leçons sur l'appareil vaso-moteur,'' vol. i, preface, x, Paris, Germer Baillière, 1875.

Among the theories proposed to explain exophthalmic goiter, there is one, dysthyroidism, which furnishes an example of trophic deviations with concomitant functional disorders. I do not mean by this that the theory of dysthyroidism should from now on be considered as proved; what I do mean is that if it were definitely established, it would show the pathological importance of functional deviations. It appears to be demonstrated that the thyroid tissue also can be altered by various influences; it has been observed that in many infectious diseases the thyroid secretes an abnormal colloid matter which does not possess its normal staining reactions (M. Garnier, 1899); this is dysthyroidism. It would be interesting to investigate if this altered tissue still manifests the physiological properties of normal thyroid substance. Unfortunately, we have as yet no absolutely characteristic test for proving the activity of the substance of the thyroid.

Speaking generally, this sort of studies appears to me to be very useful to pathologists. Anatomo-pathological investigation, by which the presence of lesions may be ascertained, must be surpassed. What should really interest the physician and the therapeutist is a knowledge of the functional capacity of the diseased organ; the lesion is of little importance as long as the organ fulfils its function. But, in order to make sure of this last point, physiological research is necessary. There are many affections considered as glandular or pluriglandular in which physiological research has been completely neglected and which are only known through post mortem findings. And is not the interpretation of these findings uncertain? Let us take for an example the reaction of hyperplasia, often found in the endocrine glands; at the time when connections between these glands were first beginning to be perceived, this reaction was attributed to a specific vicarious function (hypertrophy of the hypophysis after thyroidectomy, for example). At present the tendency is to connect it with the suppression of a normally antagonistic action. Would it not be possible that the suppression of an endocrine gland should be followed by a special intoxication, which would provoke in other glands a reaction bordering on hyperplasia? In order to judge, we must have recourse to investigative procedures other than the anatomo-pathological. Pathologists are now engaged in the field of physiological exploration, thanks, above all, to the progress made in our knowledge of the chemistry of the blood; but they should also make use of the other methods of physiology.

Is not the same true of the adrenals? Is it not generally admitted that the effects of extirpation of these organs do not reproduce exactly the symptoms of Addison's disease? Are there not cases of Addison's disease in which the arterial pressure is not particularly low? And does not the pigmentation of the skin, so characteristic in this syndrome, prove that the metabolism of the adrenals has undergone alterations because of the influence of the morbid cause? [39] And has not Pende [40] recently attempted to explain the disorders of acromegaly by positing a vitiated pituitary secretion, "qualitatively different from the physiological secretion"? Insufficiency or even loss of function may therefore not constitute the entire disease; the symptoms may depend on the disordered metabolism of the organ.

Hence we see that various toxic substances—exogenous as well as endogenous poisons—may act on the glandular cells.

[39] See O. von Fürth, "Probleme der physiol. und der pathol. Chemie," Leipzig, 1912, Bd. 1, pp. 418-419.

[40] N. Pende, "Studio di morfologia e di fisiopatologia dell'apparato ipofisario, con speciale riguardo allo neuroipofisi ed alla patogenesi dell'acromegalia" (*Il Tommasi,* June 10, 1911, pp. 364-369).

There are some that fix the cell, then it may degenerate and atrophy. Does not atrophy of the cells cause passage into the blood of toxic substances that have been received by them and more or less modified, and at the same time of cellular proteins, products of autolysis or degeneration, themselves toxic? Let us but recall what occurs in cancerous cachexia, resulting from the liberation of endocellular ferments (F. Blumenthal).[41] These liberated poisons are different according to the organ in which this process occurs. Hence the different syndromes. In some of these syndromes it may be that there is nothing depending on an actual insufficiency of the gland attacked, the parts which remain unaffected still assuring enough of the specific function; but the metabolism of the gland itself is changed and this is perhaps

[41] F. BLUMENTHAL, "Die chemischen Vorgänge bei der Krebskrankheit" (*Ergebnisse der Physiol.*, 1910, X, pp. 363-428).

enough to cause trouble. At least, we may indicate this opportunity for investigation.

The problem is complex. Physiology has furnished the foundations and traces its limits; the solution will be the result of extensive analysis, in which physiology will play its part, but which will no less result from the convergent efforts of clinical science, experimental pathology and chemistry.

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