Translations

THE INTERNAL SECRETIONS AND THE NERVOUS SYSTEM

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CHAPTER I

The young girl, who complains of palpitations and precordial pains with slight tachycardia, burning pains in the stomach, diarrheas and sweating attacks, in spite of being chilly and having cold feet; who has profuse lachrymation, who is often nauseated, and who has tendencies to be sick especially before her periods, who is easily seasick, who dislikes to ride backwards in a carriage or railroad car; who with a large palpebral fissure has a slight exophthalmos; who has a clear von Graefe's sign without the sign of Möbius; who has an abnormally low arterial tension, with perhaps an eosinophilia; whose overcontracted pupils are not dilated by adrenalin, and which contract with expiration (Samogyi's sign); who has an alimentary glycosuria with adrenalin; who has secretory crises with pilocarpine; and finally who is benefited marvellously by atropine as regards dyspeptic troubles, and whose constipation disappears at once—she is a vagotonic.

The woman with a well-marked tachycardia and few subjective symptoms; with exophthalmos and no von Graefe's sign, but with a clear sign of Möbius; with a large pupil and scanty lachrymal secretion; who has no sweats or diarrheas; with very marked loss of hair, with a tendency towards fever; who is always too warm; whose pupil dilates with adrenalin, who also has an alimentary adrenalin glycosuria; who does not react to pilocarpine, and stands atropine badly—she is a sympathicotonic.

This differentiation, true in general, has aroused many criticisms from the very first, especially from Fleischmann,⁸ Potzl, Eppinger

⁸ Fleischmann, *Med. Klinik*, 4 fev., 1910.

and Hess themselves,⁹ Falta, Newburgh and Nobel,¹⁰ Falta and Kahn,¹¹ Petren and Thorling,¹² Burstein¹³ and Bauer,¹⁴ etc., the justice of which has been admitted by myself and my interne Mlle. Romme at Beaujon Hospital.

It is thus that we have seen intense reactions to pilocarpine at the same time that adrenalin shows an exaggerated excitability of the vegetative system, the same individual presenting at intervals of some days different reactions, and adrenalin glycosuria has no value until the hepatic element is eliminated.

Finally I wish to state that the term tonic or tone does not seem to me well chosen, because it deals more with an exaggeration of the excitability of the nerve rather than an increase of its tonicity, and these two states are far from being always parallel.

Be that as it may, I differentiate in nervous disorders in addition to sensory-motor troubles and psychoses, the disorders of the vegetative system, and these sympathetic and autonomic abnormalities. We shall see later on that these disorders do not separate themselves into parallel series as simply as the theory would have them do. Then again many trophic disorders observed in endocrine syndromes are not actually trophoneuroses. It seems quite often that endocrine commotions reëcho on the morphology through a humoral intermediary and not through a nervous one. Nevertheless, as I can not dissociate in the actual enumeration of the trophic disorders those that have a nervous intermediary from those that have none, I will discuss them all, later on indicating how they may be distinguished.

Commotions of the internal secretions should include the disturbances of all the internal secretions, that is to say, all humoral pathology not to say all the pathology, because every cell from a cytological standpoint is a gland of internal secretion, and following Renault, who showed the secretory value of the cells of the conjunctivæ, Nageotte, just recently by mitochondrial methods, has demonstrated the secretion of the neuroglia, which was thought formerly to be a simple tissue of support.

In order to be brief, and admitting the three distinctive conditions, histological, chemical and physiological, of the glands of in-

⁹ O. Pözl, H. Eppinger et L. Hess, *Wien. klin. Woch.*, 22 dec., 1910.

¹⁰ W. Falta, L.-H. Newburgh et E. Nobel, *Zeitschr. f. klin. Med.*, 1914, LXXII, 1-2.

¹¹ W. Falta et F. Kahn, *Zeitschr. f. klin. Med.*, 1912, LXXIV.

¹² K. Petren et I. Thorling, *Zeitschr. f. klin. Med.*, 1912, LXXIII, 1-2.

¹³ M. Burstein, *Med. Obozr.*, 1912, LXXII, 10.

¹⁴ J. Bauer, *Deutsch. Arch. f. klin. Med.*, 1912, CVII, 1.

ternal secretion, claimed by Gley¹⁵ at the recent Congress of London, I will only picture among the internal secretions those that depend upon definite glands, in the front ranks of which I will place the classical hemato-vascular glands: thyroid, parathyroids, pituitary, suprarenals, ovaries and testicles.

I will add to this group the pineal, which in the infant, histologically as well as physiologically, is an endocrine gland; the choroid plexus, of which the secretion diffused in the cerebro-spinal fluid has been demonstrated by Pettit and Girard; the prostate, whose elective action on the genital organs has been brought in evidence by Hallion, Papin and Morel¹⁶ and the paraganglia of the sympathetic, which are chromaffin organs apart from the suprarenals.

In addition among the glands of external secretion, certain ones have at the same time an internal secretion of such importance that I must at least mention them; such are the liver, the kidney, the pancreas, the salivary glands, the mammary glands and the intestinal glands of which the endocrine action has been grasped histologically by P. Masson.¹⁷ Among these I will retain only the pancreas on account of its participation in the mechanism of glycosurias.

Finally among the lymphoid glands, ganglia, thymus and spleen, the thymus at least plays a secretory rôle.

I will consider then the nervous disorders linked with disturbances of the thyroid and parathyroids, the thymus, the suprarenals and paraganglia of the sympathetic, the pancreas, the pituitary, the pineal and the choroid plexus, the ovary, the testicles and the prostate.

In this clinical analysis I shall recapitulate at first in a critical review as briefly as possible the nervous disorders existing in the syndromes, that one as a rule places among the disturbances of the endocrine glands, that I have just mentioned, and reciprocally the endocrine disorders observed in the nervous syndromes.

In this critical review I will bring out the elements of an endocrino-neurological scheme, in which by the choice of certain nervous symptoms, certain endocrino-vegetative syndromes, certain traditional nervous syndromes, certain temperaments, certain characters, I will attempt to show by the method of double weighing, that some

¹⁵ E. Gley, *Relat. entre les organes à sécrétion int. et les troubles de ces sécrét.*, Rapport, sect. de Physiol., Congrès internat., Londres, 1913.

¹⁶ Hallion, Morel et Papin, *Act. vaso-dilatatrice péniesme de l'extr. prostateq.*, Soc. de biol., 28 fev., 1913, p. 401.

¹⁷ Masson, P., *La gl. endocrine de l'intestin chez l'homme*, Acad. des Sc., 5 janv., 1914.

among them are determined by an endocrine commotion in certain cases, and that in others they are the expression of a nervous upheaval of different origin reacting secondarily on the internal secretions.

And I will gather from this rather suggestive study of a subject so complex and so obscure some conclusions which I will advance for your discussion.

A. CRITICAL REVIEW

The endocrino-neurological clinical relationships form, a priori, two big groups:

1. Nervous disorders in the endocrine syndromes.
2. Endocrine disorders in the nervous syndromes.

Before discussing these I must explain the value of the methods of investigation which are permissible for proof. I will be very brief as regards the neurological methods and a little more explicit as regards the endocrinological procedures.

(a) *Methods of Neurological Investigation*

I skim over the current clinical methods employed for unravelling the motor, sensory, lisso-motor, secretory, trophic and psychic disorders of the nervous system to pause at the more complex experimental tests in clinical use to establish the so-called states of vago- and sympathicotonia. These tests are at the starting point chemical or mechanical. The first are the injections of adrenalin, of atropine, of pilocarpine, of eserine; the second are the ocular, auricular or solar ganglion tests permitting the consideration of the oculo-cardiac,¹⁸ auriculo-cardiac and coeliac hypotensory reflexes.¹⁹

Now each of these tests determines a series of reactions already quoted.

In order to judge of their diagnostic bearing on the neurological status one makes three hypotheses.

The first, that the antagonism between the sympathetic and the autonomic is complete.

The second, that just one of the results of each of the tests, which one regards as characteristic, is representative of the general orientation of all the results of that test.

The third, that the orientation of the test so determined is of use for deciding not only the state of the function thus investigated,

¹⁸ For the recent French bibliography, see: Vernet et Petzetakis, *Le réflexe oculo-cardiaque*, *Gaz. des hôp.*, 2 mai, 1914.

¹⁹ André, Thomas, et J., *Ch. Roux. Soc. de biol.*, 23 mai, 1914, p. 857.

but the state of the whole sympathetic or autonomic nervous system.

Now as regards the first hypothesis one can reply that if pharmacodynamics bring the innervation of the sweat glands under the control of the autonomic, there is nothing in anatomy or physiology to permit it to be separated from the sympathetic.

To the second one can answer that the results so often dissociated of adrenalin or atropine, raised blood pressure without glycosuria or vice versa, dilatation of the pupil without acceleration of the heart or vice versa, show clearly that one can not draw conclusions from the character of the physiological reaction, considering from the same standpoint the character of all the other possible reactions that one has neglected.

In a stronger way one should respond to the third hypothesis that the frequent confirmation of reactions in an inverse sense, of the vagotonic and sympathicotonic classification shows that one can not judge of such states from one single reaction, but further that the frequent confirmation of reactions in an inverse sense, sympathicotonic or vagotonic, that I have often observed as a result of different tests and even of the same test, shows at least the association or the succession of these two states of the vegetative system, and in consequence diminishes, if not the importance of the doctrine, at least the practical interest of this classification, of which the clear-cut outlines and the antagonism seem to have been exaggerated.

(b) Methods of Endocrinological Investigation

These methods are clinical, anatomical, organotherapeutic, physiological and chemical. In my report of 1908 I have shown the inherent causes of error in the first three.

Clinically one must not in an endocrino-neurological complex, of which the groupings may be more or less defaced, pick out as an element of causality that which perhaps is nothing more than a co-result of the same cause or which has nothing but a contingent relationship with the nervous or endocrine disorder.

In anatomo-morphological pathology one gathers facts of incontestable value, and that is why I have continued²⁰ to examine

²⁰ Laignel-Lavastine, Hyperplasies glandulaires de l'hypophyse. Congrès de Neurol., Amiens, 1911.

Laignel-Lavastine et Duchm, Les parathyroïdes chez les aliénés, Soc. de biol., 20 janv., 1912; 30 mars, 1912; Annales de Méd. (sous presse); Les parathyroïdes chez les déments séniles, Soc. de psychiatrie, avril, 1912; M.

systematically the endocrine glands of my nervous and mental cases, but as I said in 1908 one must always know how to read, and how to interpret these data; to read them, that is to say, observe the physiological, ethnic or geographical²¹ variations, the errors of technique, the post-mortem lesions, in order to distinguish the normal from the pathological; to interpret, that is to say, to distinguish in the pathological lesions those which are contingent, and are recent alterations due to terminal accidents, or which are but a co-effect resulting from the same cause as the nervous disorders, or results of a previous infection or intoxication, in order to be able with these lesions to establish beyond criticism a causal relationship between endocrine disorders and nervous symptoms.

Besides a last difficulty which is considerable renders these researches sufficiently rare under ideal conditions. The glandular disorders, which for the sake of argument one supposes to have reacted on the mental condition, are seldom severe enough to result in death.

A long time elapses between the onset of the trouble and the autopsy. Thus on the one hand additional lesions due to the pathological overcharge can render old glandular lesions unrecognizable, and on the other hand nervous and psychic symptoms born of a glandular disorder, which is often transitory, may outlast this disorder indefinitely.

These examples of nervous and above all mental sequelæ of a functional upset, which has ceased for a long time, are relatively very frequent illustrations of the great law of habit.

In organotherapy²² when it is a question of establishing a relationship of causality between a nervous disturbance and an endocrine disorder, because the administration of the extract of an incriminated gland has been followed by the disappearance or at least the attenuation of the nervous syndrome under consideration, it behooves one to be even more careful than in any other therapeutic induction, being aware already of the many fallacies of such

Labbé, Laignel-Lavastine et Vitry, *Diabète et lésions du pancréas*, Soc. anatomique, 8 mars, 1912.

Laignel-Lavastine et V. Jonnesco, *L'hypophyse des psychopathes*, Soc. anatomique, 30 nov., 1912; *Encéphale*, janv., 1913, pp. 25-45. Trois planches couleurs.

Laignel-Lavastine, *Anat. pathol. de la pinéale*, Mém. couronné par l'Acad. de Méd., 1913, *Arch. de Méd. exp.* (sous presse).

²¹ Il en est aussi pour la thyroïde. V. Parhon, Mlle. Mateesco, Tupa, *Nouv. recherches sur la thyr. des aliénés*, *Encéph.*, août-sept., 1913, pp. 139 et 235-55.

²² Hallion, L., *La pratique de l'opothérapie*, 1911.

because here the causes of error are particularly numerous: coincidence; general action on the organism and its metabolism by simple pharmaco-dynamic effect; suggestion; variability of the organotherapeutic extracts according to the method of acquisition, of preparation, of conservation, their age, the mutation of effect according to dosage, the avenue of introduction, the frequency of dosage, the difference between their action and that of the normal gland, the uncertainty indeed of the nervous syndrome being in line with the endocrine disorder, which in other respects may not have induced the nervous syndrome except through the agency of glandular commotions in one or many other of the endocrines, observing as well other intermediaries such as mechanical, physical, chemical, humoral, nervous or psychic causes.

In his report of 1913, Gley reiterated the causes of error in insisting upon the general toxicity of organic extracts and their variations, depending upon the method of preparation, autolysis, the production, the manner in which they are used, the heating and the quickness of injection. In addition he has drawn attention to a new cause of error: tachyphylaxis,²³ rapid immunization characterized by the fact that successive injections of organic extracts in small doses gives rise to an immunization that is produced in a few minutes. This phenomenon of tachyphylaxis for one organic extract can be aroused by the extract of another organ and vice versa. This crossed tachyphylaxis of Gley and Champy should be taken into consideration in the interpretation of such complex results as the effects of treatments by simultaneous or successive associations of glandular extracts. From this standpoint the theory of treatment by hormones²⁴ is guarded from such causes of error because the hormones entail neither anaphylaxis nor tolerance. In the above we have an instance of one of the differences between the action of adrenalin and that of extracts of the suprarenal gland.

Finally the new physiological methods, methods of Abderhalden, methods followed by Gley and Claude, etc., are themselves no longer shielded from causes of error.

The Abderhalden method has already been applied by numerous authors, Urechia,²⁵ Pesker,²⁶ Parhon,²⁷ Obregia and Pilulesco,²⁸

²³ Gley et Champy, *Soc. de biologie*, 1911, 22 juillet, p. 159; Gley, *Livres jubilaire du Pr. Richet*, 1912, pp. 111-29.

²⁴ Hallion, L., *Sur la part attribuable aux hormones dans les effets de l'opothérapie*, *Soc. de thérapeutique*, 26 nov., 1913, pp. 472-77.

²⁵ Urechia et Popeia, *Soc. de biol.*, Bucarest, 20 dec., 1913, p. 591.

²⁶ Pesker, *Ass. scient. des med. de l'Ass. psychiatrique Saint Nicholas a Saint Petersburg*, 10 janv., 1914.

²⁷ Parhon, et Parhon, M., *Soc. de biol.*, 25 avril, 1914.

²⁸ Obregia et Pitulesco, *Soc. de biol.*, Bucarest, 31 janv., 1914, p. 316.

Marinesco and Papazolu,²⁹ Mutermilch,³⁰ etc., to induce from their results an endocrinological origin for numerous nervous and mental syndromes.

Only recently, following his researches on the relations of the internal secretions and the psychoses, Parhon, with Odobesco,³¹ started to trace a psycho-endocrine syndrome characterized from the psychic viewpoint by great irascibility and ideas of persecution poorly systematized, and from a somatic viewpoint by ovarian disturbances, irregular menstruation or amenorrhea and especially thyroidal disturbances, congestion of the face, hot flashes, mononucleosis and a positive Abderhalden reaction for the thyroid.

Now Plaut has shown that in Abderhalden's reaction, kaolin talc, sulphate of barium produce dialyzable substances which react with ninhydrin just as the protein does which has served in the preparation of the animal,³² and H. de Waele concluded after a series of experiments that this ferment is unique: it is antithrombin. It is not the fragments of organs or proteins that undergo proteolysis but really the globulins of the serum. The specificity will simply arise from the preparatory injection which has created conditions favorable to the action of the protein on the globulins of the serum, and it appears probable that this bears a close relationship to the phenomena of agglutination and precipitation.

Even more recently Flatow³³ happened to show that it consists of simple variations of the proteolytic ferments of the serum. This study of antiferments for the diagnosis of endocrino-nerve relationships is, therefore, to my mind, extremely dangerous: it effects the recent criticisms of the Abderhalden reaction, in the recognition of the gross chemical interest, put one on guard against its pretended specificity towards the extracranial organs employed.

I will then consider that the new investigations are non-conclusive relative to the existence of an endocrine factor solely on the Abderhalden reaction.

The physiological method advocated by Gley in his report for judging of the functional capacity of the affected organ consists

²⁹ Marinesco et Papazolu, Soc. de biol., Bucarest, 29 mai, 1914, p. 1419.

³⁰ Mutermilch, S., L'application de la réaction d'Abderhalden au diagnostic et à l'état des mal. nerv. et mentales, Arch. de Neurol., avril, 1914, pp. 205-219. Bibliographie.

³¹ C. J. Parhon et Gr. Odobesco, Encéphale, 10 juin, 1914, pp. 489-582.

³² H. de Waele, Soc. de biol., 25 avril, 1914, p. 627, et Zeitschr. f. Immunitätsf.

³³ Flatow, A propos de la spécificité des soi-disant ferments protecteurs, XXXI Cong., allemand de med. int., Wiesbaden, mai, 1914.

of injecting into animals the altered tissue in order to see if it still manifests the physiological properties of normal tissue.

A priori, this method seems of value, and, as Gley says, "this type of study seems to recommend itself in a general way to pathologists. The anatomo-pathological research which allows certain lesions to be authenticated should be amplified." And as an example he has cited his experiences with the cardio-vascular action of adrenal extract from thyroidectomized dogs compared with that obtained from normal canine glands. He did not note any difference. Porak, who has followed this route, has arrived at unexpected results. Suprarenal extracts obtained under conditions of activity clearly greater than normal have given cardio-vascular reactions of less intensity than those that were obtained under normal conditions. As the cardio-vascular effect is proportionate to the richness in adrenalin one must conclude that not only is the richness in adrenalin of the suprarenals not in proportion to their activity, but that taken at a given moment they are less charged with adrenalin than less active suprarenal glands.

It is because function wears itself out with persistence, and by neglecting the time factor, one has been exposed to erroneous deductions, in conclusions drawn from the physiological method, which a priori is valuable in itself.

It is good because, contrary to precedent, it is capable of furnishing answers during the life of the individual. Better yet because it seems to be the method followed by Claude and his pupils.

It consists of injecting divers glandular extracts into patients, and observing their reactions systematically, and deducing from these reactions the probable endocrine disorders. Thus it permits the acquisition of individual indicators of physiological endocrine reactions, which, counting on the complexity of the cases, by the comparison of a large number of facts, may allow the formation of hypotheses if not of conclusions. Claude with his pupils, Baudouin and Porak, has already used this method with success in the study of acromegalics, Addisonians and just recently of Basedowians.³⁴

The many criticisms summed up by Biedl and Falta and Porak³⁵ have done full justice to the serological methods, such as that of Meltzer-Ehrmann, based upon the supposed fact that dilatation of

³⁴ Claude, H. Baudouin, R. Porak, L'épreuve des extr. hypophysaires chez les basedowiens, Soc. méd. des hôp., 19 juin, 1914, 1112.

³⁵ Porak, L'épreuve de l'hypophyse dans les maladies des glandes à sécrétion interne., Thèse, 1914.

the enucleated eye of the frog, in the presence of any serum indicates the existence of adrenalin in that serum. Mydriasis can be brought about by other causes than the presence of adrenalin. It is useless to argue further.

There remains the need of knowing how to interpret the results of the clinical, organotherapeutic, anatomo-pathological and physiological methods (Claude type).

I will now sum up the nervous disturbances in the endocrine syndromes and the endocrine disturbances in the nervous syndromes as rapidly as possible, because one finds them to-day explained at length everywhere.

1. Nervous Disturbances in the Endocrine Syndromes

Endocrine syndromes are increasing every day, perhaps because one finds definite endocrinal lesions in a syndrome till now confounded with an analogue, perhaps because one now erects at pleasure endocrine theories for divers affections of unknown origin. The first way is legitimate, although of a rather delicate interpretation—in fact we are all familiar with the frequency of lesions in the endocrine glands in all sorts of autopsies. The second is singularly fallacious when it depends only on experimental or clinical analogies or on debatable anatomical, humoral or therapeutic authentications. The syndrome of dystrophia adiposo-genitalis due to a pituitary lesion and precocious macrogenito-somatosis due to a pineal lesion are examples of the first. The endocrine theories as to the origin of seasickness, hysteria, Paget's disease, cholera are, in their turn, examples of the second.

In the beginning, in the period which might be called the uni-endocrine, each syndrome was connected with a lesion of one single gland, Basedow's with the thyroid, Addison's with the suprarenals, acromegaly with the pituitary, and in each gland only disorders of increase or decrease of secretion were seen (quantitative period).

In the meantime, after many others, I had shown with Thaon in 1905 a case of Basedow's disease in a woman with myxedema, which the simple quantitative theory could not explain.

(To be continued)