Reprinted from

ENDOCRINOLOGY

THE BULLETIN OF
THE ASSOCIATION FOR THE STUDY
OF INTERNAL SECRETIONS

VOLUME 21 JULY, 1937 NUMBER 4

NEURAL AND ENDOCRINE FACTORS IN BODILY DEFENSE[1]

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It was in 1874 that Sir William Gull first described myxedema and connected it definitely with thyroid insufficiency. Ord confirmed this in 1878 and suggested the name. Murray successfully treated the first patient suffering from myxedema in 1891. He used a glycerine extract of the thyroid gland which he made himself.

Five years later, in the fall of 1896, there walked into my office a young woman whose face and hands were swollen; her eye-lids were almost closed, her voice was thick and her speech slow. She gave a history of progressive gain in weight and a gradually increasing apathy. I was impressed with the danger of approaching dissolution unless she could be quickly relieved, for I assumed the disorder to be of cardio-renal origin. I told her of the necessity of drastic action and prescribed the old-time remedies of purging and sweating. She replied that every doctor whom she had consulted had given the same treatment and that none of them had done her any good; and so she refused to be purged and sweated any more.

I then gave the matter a little more thought and recalled having seen such a case during my recent study in Europe, and remembered that it was said to be due to a failure of function on the part of the thyroid. I then knew that the case was not so urgent as I had assumed, and instead of purging and sweating I ordered desiccated thyroid. She started to improve at once and was soon able to resume her work as a teacher in the public schools. Shortly thereafter I lost contact with her. However, I had impressed upon her the importance of continuing the thyroid for a long time—probably during the remainder of her life. I neither saw her nor heard directly from her until 2 years ago, although indirectly I had heard that she was well and able to carry on her work. At the end of a public lecture given at Riverside, California, in 1934, she sought me out and told me how well she had become after starting thyroid medication. She said that she had continued its use for a few years and then found that she no longer needed to employ it.

This case is interesting from several standpoints. In the first place it was one of the early cases of myxedema successfully treated. Although the myx-

[1] President's Address read at the Twentieth Annual Meeting of The Association for the Study of Internal Secretions, Kansas City, Missouri, May 11, 1936.

edema was of a high grade it yielded readily to treatment, and the thyroid gland after a time was able to function sufficiently to maintain a physiologic balance and keep the patient in normal health for a period of 36 years, and possibly many more.

This was my introduction to endocrinology 20 years before our Organization was formed. The transformation of this patient from serious illness to health was so prompt that the picture frequently came into my mind during those early years of practice, although I did not know that this was to be my introduction to an important phase of physiologic medicine, which within a quarter of a century was to engage the minds of many of the ablest men of science.

My interest in endocrinology was next stimulated in 1908-9, soon after discovering the motor and trophic reflexes which are produced in skeletal structures by inflammation (tuberculosis) of the lung. I was forced to seek the explanation of these reflexes in the realm of visceral neurology, a subject which at that time had all but escaped the notice of investigators. I was finally able to establish the fact that the mediation of these reflexes takes place in the cervical portion of the spinal cord, particularly the 3rd, 4th and 5th segments. But this discovery demanded the investigation of the entire field not only of reflex action but of general reaction in visceral nerves; which again led to a study of the broad subject of physiologic control of body activity.

From study chiefly of the contributions of Langley and his associates, Gaskell, Cannon, Higier, and Müller, it was learned that the visceral nerves not only afford a system of control of activity in vegetative structures but that the afferent system of nerves from the viscera form a network through which activities in one viscus are correlated with activity in other viscera and with skeletal structures through efferent nerves belonging respectively to the visceral and somatic system; and that no individual viscus is independent in action. These studies had not progressed far when I learned of a second integrating and correlating mechanism, chemical in nature, which consists of the products of the endocrine glands.

It was further found that a stimulus going over a nerve to a viscus might produce its expected effect, no effect, or an effect opposite to the one usually assigned to it. To account for this we learned that nerve response may differ with different states of activity of an organ at the time of stimulation. Since organs are made up of aggregations of cells their activity is thrown back on the state of the cells, which in turn are dependent for their action upon substances which reach them through the body fluids which bathe them. This forced consideration of the facts which maintain physiologic equilibrium, the condition of homeostasis so beautifully described by Cannon, the *milieu intérieur* of Brown-Séquard, recently elaborated by Barcroft, with its hormones, electrolytes, vitamins, enzymes, lipoid substances such as lecithin and cholesterol, the products of normal metabolism, and the abnormal products which result from disease.

It became evident that the humors of the body were again returning to a place of primary importance in medicine, and that their investigation was

necessary to an understanding of physiologic function which, after all, is the basis of clinical medicine. The approach which seemed essential to the understanding of the body fluids and which seemed richest in promise was through investigation of the products of secretion of the endocrine glands, for these were assumed to influence and control so many functions.

This approach has now been justified because it has already shown that hormones not only exert an effect on cellular activity in various organs, but also, circulating in the fluid systems of the body, correlate and integrate visceral activity, supplementing the action of visceral nerves. We now know that hormones exert an influence upon fecundation, the maturation of the embryo and sexual development; that they are determining factors in the somatic and psychic spheres; that they influence metabolic activity, exert a control over the electrolytes and pH of the blood, and provide a chemical regulating and correlating mechanism for the body. Endocrine glands are activated by visceral nerves and are influenced by many products circulating in the body fluids other than hormones from other glands. So in the development of endocrinology scientists are forging one of the important links of physiologic medicine—the medicine which will in all probability dominate research and practice during the next quarter of a century.

While the relationship of endocrinology to the chemistry of the body is gradually unfolding, a study of its relationship to visceral neurology is lagging far more than it should. When our organization was founded, some of us who were interested in both subjects hoped that visceral neurology and endocrinology, the two correlating and integrating systems of the body, would be developed together; but like structural and functional pathology, it seems that they first had to be divorced so that they might have a happy reunion later; but reunion they will have.

To make endocrinological research of greatest importance to the clinician and to translate it into the most useful service to the patient, it must be intimately connected with all of the mechanism which have to do with physiologic control of the body. The many interrelationships between the various glands which are now being investigated, and the results of hypofunction and hyperfunction are of tremendous importance but fall far short of the full meaning of endocrinology to medicine.

The conception that the symptom-complex which we designate as a disease represents primarily the condition which is necessary for the organism to assume in order to protect itself against the morbific elements which play the etiologic rôle appeals to me as being most reasonable. With this conception, both inflammation which marks local reaction, and the general reaction of the body to toxic substances, become protective phenomena.

Substances which call forth reaction enter the body in two ways: *1)*, through the gastrointestinal tract, being subjected to natural digestion, in which case the readily diffusible products are absorbed and assimilated for the benefit of the organism and the useless ones rejected from the body; *2)*, through the walls of the gastrointestinal tract, having escaped natural digestion therein; and through other mucous membranes and through the skin. In case

of bacteria and protein substances in group *2)*, a different process of digestion and elaboration is necessary. If the substances are readily diffusible, they enter the cells directly, and are dealt with by a process similar to that used by unicellular organisms. Bacterial antigens are composed of a nucleoprotein and a carbohydrate-containing fraction. Sensitization of body cells, which is an exaggeration of their normal defense function, is produced only by the two fractions combined. The nucleoprotein is the fraction which is associated with the tuberculin reaction, while the carbohydrate-protein is the specific fraction that reacts with antibodies. Though both combined are necessary to produce sensitization, the nucleoprotein will call forth reaction after sensitization has been established. The soluble carbohydrate product is specific in nature and has a special action in dilating capillaries and acting upon smooth muscles. This substance differs with different diseases.

We conceive that every entrance of a foreign substance into the tissues calls forth a defensive mechanism on the part of the organism to deal with it. The mode of attack varies with the nature of the entrant and the tissues in which it finds itself. However, no matter what the nature of the foreign material and no matter where the reaction takes place, the defense phenomena represent normal, or an exaggeration of normal, cellular functions. In other words, defense is an exaggerated physiologic function in which there takes place a correlation and integration of the activities of the body which are useful in maintaining efficient body action while opposing the injurious substances which have found their way into the tissues. In spite of this assumed protective nature of the body's reaction it is not inconceivable that the reaction caused by morbific elements might cause such a concentration of physiologic effort for defense purposes that the normal physiologic equilibrium should fail to be maintained. This failure may be local or general; it may be transitory or continuous; it may be mild or serious. It may even prove to be so serious as to threaten or actually cause a stoppage of physiologic function and death.

That hormones have a part in aiding the organism in some way in carrying out parenteral digestion and in protecting the body from an injury that might result therefrom is suggested by clinical experience. We see evidence of this in the parenteral digestion of bacterial antigens and even more plainly in case of antigens responsible for the so-called allergic group of diseases in which the deleterious effects are often prevented and quickly relieved by adrenal hormones.

If we attempt to apply this idea to the solution of the riddle of specific defense or immunity to infectious diseases, assuming that protection is quickened and heightened physiologic action, then complete immunity is not only a rapid response of heightened reaction but a permanent ability of body cells to function quickly with heightened physiologic action; an ability so efficient at times as to make it impossible for certain microörganisms to grow and develop within the body, as is shown in case of such diseases as smallpox, typhoid fever, scarlet fever and diphtheria.

In diseases such as tuberculosis, pneumonia, steptococcal and staphylococcal infections, a heightened physiologic response is evident but not completely

protective. In some instances, of which tuberculosis is the best known example, protection appears both as a quickening and a heightening of the body's reaction whenever causative microörganisms come in intimate contact with the animal body after a primary infection has once been established.

The relationship of hormones to resistance to infections offers a fruitful field for study. The thyroid, adrenal and pituitary glands, particularly, have been suggested as being closely associated with resistance, and it is common clinical interpretation that hypergonadal and hypogonadal subjects resist infection with different degrees of efficiency. We have long used thyroid in the treatment of our tuberculous patients, seemingly with advantage to the patients. The observation that first caused us to use it was the dry skin which had been thought to be due to fever. We found, however, that it is present at times when fever cannot possibly be the cause, so we assumed that it was due to a deficiency in the action of the mechanism which controls the nutrition of the skin, and we administered thyroid as being the substance which seemed most apt to relieve this condition and were gratified not only in the effects on the skin but on the general stimulus which it seemed at times to give to nutrition and to the patient in fighting his infection.

More recently we have had experience with the products of the adrenal gland in treating certain infections. We have found that the duration and severity of colds have been lessened. We have had an unusual opportunity to observe this in certain children whom we have been treating for asthma. Whereas prior to treatment colds were frequent and usually followed by bronchitis and asthma, after treatment was established the colds lessened in number and severity, and the bronchitis and asthma gradually disappeared.

In tuberculosis we thought that there might be some relationship between the condition of the adrenals and the persistent tiredness which often accompanies but which more particularly follows the toxic stage of the disease. Francis M. Pottenger, Jr., made this a study and found that he was able not only to relieve the tiredness but also to produce unmistakable general improvement in patients by feeding raw adrenal glands or potent extracts of the cortical portion of the gland. He was also able by the cortical hormone to protect about 30 per cent of three different series of guinea pigs against infection with the tubercle bacillus, and to cause a more favorable course in the disease of those infected. Another observation that is worthy of consideration is that he has seen the reaction of hypersensitivity to tuberculin, also the sensitivity to antigens in asthma disappear in children whom he has treated with adrenal products.

Of the many patients so far treated for asthma, improvement in the general physical state was practically invariable. We can hardly suppose that these effects are produced because of any specific action that the hormones might possess but rather by the general restoration and maintenance of the physiologic equilibrium. However, the fact that by the use of adrenal hormones we have been able to prevent in animals infection with tubercle bacilli, to cause children who reacted positively to the tuberculin test to cease to react, and to eliminate the hypersensitivity of asthmatics to certain proteins would indicate

that they confer upon the animal an unusual degree of competency in opposing proteins which require parenteral digestion for their destruction. May we not interpret this disappearance of the tuberculin reaction and this loss of sensitiveness to allergens during the treatment of asthmatic children with adrenal hormones as evidence that a refractoriness to antigens has been produced, such as would be found in a more complete immunity. The time which has elapsed so far is not sufficient to warrant a too close interpretation, nor has it been sufficient to permit of more complete investigation. Nevertheless, this experience suggests that a better understanding of the protection of the body against bacteria and other sensitizing substances which require parental digestion for their destruction may come through the study of endocrinology.

Our development of endocrinology has followed much the same course as the development of other phases of medicine. First the disintegrating method of studying individual glands and their products had to be pursued; but this must now give way to a process of integration, of fitting our knowledge into the whole picture of physiology.

In the development of the endocrine system we are furthering knowledge of both normal and pathologic physiology, and adding to the understanding of man in health and disease.