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## RESULTS OF RECENT STUDIES ON DUCTLESS GLANDS\*

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During the past four or five years many of the researches of the Harvard Physiological Laboratory have been concerned with the bodily changes which accompany strong emotions, such as fear and rage. These are fundamental experiences in man and the lower animals, so much so that their expression constitutes a sort of common language. The studies which have been carried on have revealed interesting relations between these emotions and certain glands of internal secretion, and have suggested also a way in which emotional excitement may occasion pathologic states.

When a cat becomes infuriated, the pupils are dilated and the hair is erect from the neck to the end of the tail. But besides these surface manifestations there are internal changes; for example, the heart beats rapidly and the activities of the stomach and intestines are stopped. Both the internal and the external changes are due to the passage of nerve impulses to viscera along the neurons of the sympathetic division of the autonomic system. The relation of the fibers connecting the central nervous system with these neurons is such as to provide for diffuse action on all the viscera that are innervated by this division.

The suprarenal glands are supplied with nerves from the sympathetic division; and also the secretion of the suprarenal medulla affects all structures innervated by the sympathetic division precisely as if they were being stimulated by its impulses. We have found that the suprarenal glands secrete epinephrin in times of great excitement, that there is an increased liberation of sugar from the liver so that glycosuria may result, that there is an abolition or prompt lessening of muscular fatigue, and that there is a very much more rapid clotting of blood. It is known also that epinephrin causes a redistribution of blood in the body so that it is sent away from the alimentary canal, whose activities are inhibited, to the heart, the lungs, the central nervous system and active skeletal muscles. It is known, also, that epinephrin causes dilation of the bronchioles, and it is known that it increases the number of red blood corpuscles per cubic millimeter—an increase which Jamson has shown occurs also to a marked degree in case of emotional excitement.

These changes, as true of man as of the lower animals in times of great emotional stress, are significant when the conditions which would give rise to the emotions are considered. Fear is associated with the instinct to flee; rage with the instinct to fight. These are the emotions and instincts underlying the struggle for existence. They are also the emotions and instincts into which all other instincts may be readily turned when they are thwarted. The internal changes are all directed toward increasing the efficacy of the organism for physical struggle. The increased blood sugar provides a source of muscular energy. The altered distribution of blood and the increased number of red blood corpuscles arrange for carrying an abundance of oxygen to the active structures. The dilated bronchioles allow ready ventilation of the lungs when oxygen is greatly needed and carbon dioxide is being produced in large amounts. The provision for lessening muscular fatigue is directly useful in muscles likely to be employed in continued action. The rapid coagulation of blood tends to preserve that precious fluid in case of injury to blood vessels. The organism in which these changes most promptly occur has the greatest reinforcement of its abilities and is most likely to be favored in physical struggle. These arrangements for reinforcement account for the great power and endurance which are exhibited in times of intense excitement.

Other glands than the suprarenal are not so readily studied because of the difficulty of recognizing their secretions. It has long been known, however, that physiologic activity is accompanied by the presence of an electrical difference which may be observed by connecting an active part with an inactive part of the body through a sensitive galvanometer. Justification of this method of studying glands can be obtained by applying it to the submaxillary gland. It has been found that the electrical change begins before the external secretion appears, disappears as secretion stops, and is not related either to flow of fluid in the ducts or a change of blood flow in the capillaries. Since the only feature that cannot be abolished without abolishing the electrical change is secretion, the electrical effect is a true indicator of a secretory process. When this method, therefore is applied to the thyroid gland, the positive testimony of the galvanometer is evidence of thyroid secretion.

The electrical method shows that the thyroid gland is subject to impulses from a part of the sympathetic division of the autonomic system, that is, the cervical sympathetic. The secretion comes promptly—after a latent period of from five to seven seconds. The vagus nerve is without control, and pilocarpin, as a stimulator of vagus endings, is likewise without control. The influence of the sympathetic is not due to anemia, for

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shutting off the blood supply has no such effect as is produced by sympathetic stimulation.

Control by the sympathetic implies that epinephrin may be effective in stimulating the thyroid. This, in fact, is the case, for a marked electrical change is produced when epinephrin (0.1 c.c. of 1:100,000) is injected intravenously into a cat. Furthermore, the action current of the thyroid appears if the nerves to the suprarenal gland are stimulated, an effect which does not occur if the suprarenal glands have been previously removed and which is delayed if the return of blood from the abdominal cavity is delayed, until the blood is again allowed to flow.

Thus a hormone relation between the suprarenal and the thyroid is clearly demonstrated. This electrical evidence, which was obtained in cooperation with Mr. McKeen Cattell, has been confirmed by the observations of Dr. Robert L. Levy. He has found that both stimulation of the cervical sympathetic trunk and injection of stimulating doses of epinephrin greatly augment the effects of small doses of epinephrin in raising blood pressure. This increase of efficacy of epinephrin is not produced if the thyroid glands have previously been removed.

The proof that the thyroid responds rapidly to sympathetic stimulation and that it is effective in combination with suprarenal secretion shows that there is another bodily change to be added to those already mentioned as occurring in times of great emotional excitement.

In the course of this work two questions have arisen: First, why are organs which are disturbed in times of emotional stress not disturbed at other times? It seemed probable that they were protected from interference by a high neuron threshold interposed between the central nervous system and the visceral cells. Consequently only when great excitation is present in the central nervous system is this threshold crossed and the changes in the viscera brought to pass. The second question is, Why, in certain pathologic cases, is there apparently frequent or continuous disturbance of the same viscera? It seemed possible that this might be due to a wearing down of the high threshold here or there from frequent or great emotional experiences. Thus the situation would be like a break in a dike, and only a slight disturbance in the central nervous system might then be needed to result in a pouring through of impulses at the low point and consequently a fairly frequent or continuous disturbance in the viscus innervated by this region. Thus dyspepsia, tachycardia and possibly persistent glycosuria, reported as having an emotional origin, might be accounted for.

To test the effect of continuous stimulation, the phrenic nerve was fused with a peripheral portion of the cut cervical sympathetic. This operation, done with the aid of Dr. C. A. L. Binger, resulted in some animals in tachycardia, increased excitability, loose movements of the bowels, exophthalmos on the operated side (in one case) and, as Dr. Reginald Fitz showed, in great increase of metabolism (in one case an increase of 130 per cent.). These phenomena have disappeared on removal of the thyroid gland on the operated side. The suprarenal glands in two animals that have died of the disease have been greatly enlarged.

The changes thus produced resemble in many respects the symptoms of exophthalmic goiter and support the view that this disease may be primarily due to

overactivity of that part of the nervous system disturbed in emotional excitement—possibly, as suggested above, a local stimulation in the cervical region. Two vicious circles may be operative: one through the nervous system due to increased excitability from increased thyroid secretion and resulting thus in increased nervous stimulation of the gland; the other through the blood stream, due to increased suprarenal activity from overaction of the thyroid and stimulating the thyroid in turn in the manner indicated above.

The evidence previously presented shows that besides any routine function, the suprarenal gland has an emergency function brought out in times of great excitement. It is not unreasonable to suppose that the thyroid gland likewise has an emergency function evoked in critical times, which would serve to increase the speed of metabolism when the rapidity of bodily processes might be of the utmost importance, and besides that, augmenting the efficiency of the epinephrin which would be secreted simultaneously.

#### ABSTRACT OF DISCUSSION

DR. A. J. CARLSON, Chicago: I have been very greatly interested in this line of thyroid work. I should like to ask whether these records of the electric response of the thyroid were in animals under anesthesia. I should like to know if, on continued stimulation of the cervical sympathetic for half an hour, whether the secretion and the electrical response continued for that half hour or possibly longer. Does the electric response continue, in the case of the salivary glands, as long as the secretion? In other words, I am not certain that the electric response is the true measure of the duration or extent of the secretory activity. I do not know, possibly Dr. Cannon can tell us, whether parallel experiments have been made on the kidneys, an organ undoubtedly controlled through chemical stimuli. On the introduction of a diuretic which acts for an hour or an hour and a half, do we get a continued proportional electric response from the kidney? I asked the question regarding the continued anesthesia because as I recall Dr. Elliott's work on the suprarenals, he makes the statement that by repeated injections of the same strength and amount of epinephrin one gets absolutely identical vasomotor responses. There seems to be a contradiction here between Elliott and Cannon. I am not certain that the changes in the suprarenals after the thyroid nerve anastomosis are in any way related to hyperactivity of the thyroid. After complete thyroidectomy (young rabbits), we invariably get a hypertrophy of the suprarenals to two or three times their normal size. My colleague, Dr. Bensley, who has had the privilege of examining some of the thyroids of Dr. Cannon's cats, tells me that the histologic picture of those thyroids is not that of hyperplasia. On the contrary they appear to be atrophic.

DR. EMIL GOETSCH, Baltimore: During the past year I have been in the habit of testing out the sensitiveness to epinephrin of patients suffering with thyroid trouble, not only those suffering from hyperthyroidism but also from hypothyroidism, colloid goiter, and adenomatosis, and acute toxic hyperplasia. It has been uniform in my experience that in the hyperthyroid cases, especially in the early stage, in which we think that there is a very marked hypersecretion of the gland, and hence a hyperthyroid condition of the blood, in all these cases the reaction to a very small dose of epinephrin when given hypodermically is extremely acute.

The clinical picture is also markedly exaggerated. All the symptoms which we regard as typical of marked hyperthyroidism become very much exaggerated. An equivalent dose of epinephrin given to a patient with colloid goiter is almost without effect whatever. Similarly the effect on a normal person is slight.

Then, too, as indicating the degree of hyperthyroidism present, it is interesting to note the effect of the epinephrin after operation. When one does a lobectomy (on one side

or both sides), the greater the amount of the gland removed the less the reaction to the epinephrin afterward. This, I think, is an additional fact to corroborate Dr. Cannon's experimental work. In other words, the greater the degree of hyperthyroidism present, the greater we find the reaction to hypodermic administration of epinephrin.

With reference to the sensitiveness of the sympathetic in hyperthyroid conditions, it is interesting to note the effect of epinephrin on the eye. When 2 drops of a 1:1,000 solution are instilled into the conjunctival sac, there is almost complete blanching of the vessels of the conjunctiva, whereas in a normal person there is none of this even after repeated amounts have been put into the eye. In hyperthyroidism, there is a marked dermatographia, a sympathetic reaction on the part of the skin to a scratch, or any other mechanical irritation. If one injects intradermally from 1 to 2 minims of a 1:1,000 solution of epinephrin there is a marked blanching in an area of considerable size, which is almost like a necrosis, surrounded by a very large areola of a bright reddish blush. This central vasoconstriction with the peripheral dilatation lasts from an hour to an hour and a half, and it is interesting to watch the reaction between the central white and the peripheral reddening. In a normal person this same reaction shows a very slight central blanching, and a very slight peripheral dilatation, and in about twenty minutes to half an hour the reaction is entirely gone. We see then that there is a very marked reaction locally to an intradermic injection of a minute dose of epinephrin in cases of hyperthyroidism, whereas in colloid goiter or even in normal cases this reaction is very slight.

DR. WALTER B. CANNON, Boston: One of the first difficulties we had was with anesthesia. Urethane gave an admirably quiet preparation, but we could not get responses from the thyroid if we gave the usual dose of urethane for anesthesia. We could not get the characteristic response if we used very deep ether anesthesia. So we used only so much ether as would result in a quiet preparation. We tried to get rid of an anesthetic altogether by destroying the central nervous system to a very large degree, but that lowered the blood pressure to such an extent that we thought probably we were making the animal more abnormal by that procedure than by light ether anesthesia. The question was also raised as to whether the electric change is really concomitant with activity, i. e., whether it is not a brief momentary appearance at the beginning of the activity, disappearing though activity continues. No very exact studies have been made of that matter, but I may say that a dose of pilocarpin, which has the effect of producing a prolonged secretion of the submaxillary gland, causes a concomitant electric difference that persists during the entire period, and promptly disappears when atropin is given.

The histologic appearance of the overstimulated thyroid gland has been mentioned. We have not obtained the characteristic hyperplasia of the thyroid that is observed in most cases of exophthalmic goiter in man. Dr. Homans, however, who worked with the Bensley technic, has studied these preparations, and says that the cells look like those of the islands of Langerhans, after partial extirpation of the pancreas, when apparently there has been an overdemand made on them, that is, there is "hydropic degeneration." It seems possible that what has occurred in these cases is a very much more acute condition than is usual in exophthalmic goiter—a stimulation of the thyroid which has not allowed any sort of hypertrophy or compensation, an activity of the cells so great that they have poured out their secretion so vigorously that they have actually been used up in the process. Certainly, the animals go to pieces with extraordinary thoroughness. They show no signs of infection. They have no characteristic rise in temperature, they eat enormously, and yet they continue losing weight until they become so wasted away that they are mere skin and bones. The eye, which may be prominent at first, becomes actually sunken into the head because of the disappearance of the fat about the eyeball.

I was unaware of enlargement of the suprarenals in cases of removal of the thyroid. Certainly, in these cases there has

been no removal of the thyroid, and we have much evidence of increase in the activity of the gland. There is other evidence than that I have presented, which indicates that thyroid material causes hypertrophy of the suprarenal. It seems reasonable to expect, therefore, that overactivity of the thyroid or increase of thyroid material in the blood will result in an increase of the suprarenal size.

## SOME CLINICAL STUDIES OF THE PROBLEMS OF CEREBRAL TONE\*

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During the last five or six years some important additions to our knowledge of muscle tonicity and the more generally inclusive topic of cerebral tone have been made by clinicians and pathologists. The clinical bearings of cerebral tone, which have usually been left for the discussion of psychologists, are becoming more and more recognized by neurologists, who are finding in their study some matters of practical value in diagnosis and treatment, especially the former.

In many forms of cerebral and spinal disease, as, for instance, in hemiplegias, diplegias, jacksonian spasms, perseveration, catalepsy, catatonia, atonic and spastic paraplegias, disseminated sclerosis, tabes, amyotonia, dystonia and Thomsen's disease, the presence and pathogenesis of muscle tonicity are of especial interest.

In a large majority of the cases of permanent hemiplegia—hemiplegia persisting as a marked loss of power for more than six months—the general picture as to contracture or spasticity is that well known to neurologists, and such as has been described in numerous treatises on nervous diseases.

Under the designations "early and late contractures," certain interesting phenomena of tonicity have been discussed by nearly all writers of neurologic textbooks and by many contributors to current neurologic literature. The so-called early contractures in hemiplegic cases are usually observed in apoplexy of marked severity, as, for instance, that in which a hemorrhage breaks through the cerebral substance into the lateral ventricles. These early contractures, as indicated by Oppenheim, are usually attributed to irritation of the pyramidal fibers. Developing within a few hours, if death does not supervene, as not infrequently happens, these may disappear after a short period, that is, in the course of a few days. The musculature of the paralyzed side of the body in these early contractures is affected generally, the spasticity not assuming the usual forms observed in the so-called late contractures.

Late contractures which have received much attention since almost the earliest days of the study of hemiplegia usually come on after a period ranging from two weeks to as many months. Sometimes they do not begin to be noticeable until three months after the apoplectic attack, but development as late as this is comparatively rare. The condition as to tonicity may be fairly regarded as permanent after the lapse of six months. It is generally held that permanent contracture increases with degeneration of the motor centers and tracts. While this is correct, it is now believed that it is not a sufficient explanation of such contractures, to say that they are due to secondary degen-

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