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[Reprint from Medicine and Surgery, January, 1918.]

TETANY AND THE PARATHYROID GLANDS

By W. F. Koch, Ph.D., of Detroit Professor of Physiology, Detroit College of Medicine and Surgery

From a perusal of the literature, one must recognize that a few facts of value have been contributed on this subject, but that the findings have not been discussed from a physicochemical basis; and therefore the physiology of the parathyroids shares the same obscurity as the other glands of internal secretion. However, in the light of certain confirmed observations and with a working hypothesis regarding their phylogeny, we can make some rational but uncertain surmises as to their function, recognize the syndrome of parathyroid insufficiency, and draw conclusions as to therapy.

We have long been possessed of the view that the various glands of internal secretion were among themselves very antagonistic structures. But I fear that such a view has inhibited rather than promoted progress; and when more observations, such as those of Stewart and Rogoff,1 have been made, we find that the co-workings of these glands are one of harmony. In line with our accepted theories of differentiation and specialization of function of the various tissues, it is easy to build a simple hypothesis of the phylogeny of the glands. I will give one here because it explains the observations which follow below according to a principle more acceptable to our evolutionary scheme than does the theory involving antagonism and because it suggests what direction future work on the parathyroids should take.

In the unicellular organism all functions are carried on by the same protoplasmic aggregate, but with. the development and differentiation into a multicellular organism certain spacial relations are interposed, and according to the environments of the component cells certain functions are stimulated and others are retarded. But all the vital protoplasmic needs are present in all the cells, and as environmental relations prohibit the carrying on of certain activities in certain cells these become parasitic upon those cells which have better environmental opportunity for pursuing this activity and thus a differentiation in function is attained. To illustrate: Take a three-layer-stage as Amphyoxus, the ectodermal layer becomes protective, the entodermal is quite protected and still in close relation to the external food supply, so it becomes a digestive tissue; and the mesoderm removed from external harm and food supply, need not develop a resistant structure nor differentiate into a digestive structure, but can differentiate along other lines, thus becoming contractile or what not. In order to obtain food supply it can remove from its immediate environment those diffusible nutritional substances which the entoderm has manufactured from the external food supply. Likewise the ectodermal layer can absorb and use those substances from its environment which the middle layer elaborates. The possibility for such changes lies in the permeability of the cell membranes to diffusible substances as well as to homologous non-diffusible substances. Internal secretions then come into existence by virtue of the fact that cells selfishly manufacture diffusible substances for their own metabolic needs; but being diffusible they get out of the cell and can be removed from the exterior of the cell by diffusing into another cell in which the partial pressure of the substance is less, and this partial pressure will have a value depending upon how rapidly the substance is metabolized therein.

Now with a higher differentiation of the organism, up to where the vascular system is in operation, the same phenomena hold good and the exchange takes place through the lymph spaces and blood-stream. The fact is the glands of internal secretion have the greatest blood supply of all the tissues of the body. According to this scheme, the blood carries diffusible substances which have escaped from all body cells. These substances diffuse into all body cells as fast as their partial pressure in the cells is lowered by their metabolism. And since the early environmental differential relations have determined a certain facility for carrying on a certain process, a differentiation of function has arisen. Thus we observe certain glands of internal secretion thymus, parathyroids, thyroid, anterior lobe of the hypophysis, liver and the islets of the pancreas developing from the primitive digestive canal, and hence their disturbances of function are accompanied by well-defined dystrophies. The occasion may arise, however, where a tissue, very active for the time being, must obtain more substance from some internally secreting gland than the blood supply to the needy tissue ordinarily carries. So this tissue may develop an agent which it sends out into the blood and which when carried through the certain gland of internal secretion by chemical combination hooks onto the special product of this gland. Thus the partial pressure of the secretion about the cells of this gland is lowered and a diffusion of more substance to the outside of the cell occurs. The gland cell must then elaborate more of this substance to maintain its usual content.

In this way the output of any gland of internal secretion is regulated by the demand for its special products. The above hypothesis explains the following well-confirmed facts, the presence in the highly developed organism of glands secreting diffusible substances necessary to the normal metabolism of the rest of the organism, and that the special products are immediately used up as fast as formed, that is, their reaction being quantitative. It is also introductory to the discussion of certain findings enumerated below. Yet since the hypothesis has been proposed it is necessary that it should answer all known facts; and I beg to digress for a moment to explain the position of the nerve supply to some of these internally secreting glands. Before the development of a nervous system, the chemical mechanism of coordination of all cell activities was naturally the only one, but as nerve control became potential, reflex trophic arcs with their afferent and efferent neurones, synapses, and modifying neurones had the same chance to develop as any other reflex arc. Although it remains for investigation to prove their existence, we find affirmative evidence in the phenomena of exophthalmic goitre, where indeed a psychoneurosis can be proved the cause of the hyperactivity of the gland.

## **SYMPTOMATOLOGY**

The symptoms of parathyroid insufficiency may be described as depression with muscular twitchings and tremors, refusal to take food or vomiting after doing so, jerkings, tonic and clonic convulsions, spasticities with ataxia, exophthalmos, tachycardia, and hyperpnea. The central nervous system is hyper-irritable with a resulting increased stimulation of the voluntary muscles producing characteristic postural spasms, and convulsions. After section of the motor nerves to a part, these changes are abolished, but tremors and jerkings are observable, due to increased irritability of the myoneural junction, as was shown by Paton 2 and his co-workers. The hyper-irritability of the myoneural junction of the visceral nerves is also demonstrated by their abnormally high susceptibility to adrenalin. Because of the similarity in the postural changes in parathyroidectomized monkeys to that of children in idiopathic tetany and in man in post-operative hypoparathyroidism, and since the mechanical and electrical reaction of the myoneural junction, the tremors, depressive convulsions and spasms are exactly similar in these conditions, it is concluded that they are identical syndromes. As will be shown below, the same etiological factor is present in these conditions, a fact which justifies the conclusion. The tetany and convulsions occurring during pregnancy and lactation, 3 other than uremic and hysterical, are also regarded as belonging to the same syndrome because of the similarity in symptomatology. With the termination of pregnancy or lactation the symptoms rapidly disappear, and so it would seem that they resulted from excessive strain upon the parathyroid function. Seitz and Thierry 3 find 10 percent. of all women during the last months of pregnancy in a subtetanic state. I have recently seen an infant six hours old, delivered from a mother in non-nephritic eclampsia, that showed the carpal spasm, exophthalmos with Graefe's sign and Stellwag's sign and Chvostek's

symptom. Evidently mother and child were under the influence of the same etiological factor, which in the mother resulted from a greater metabolic demand than could be satisfied, as is evidenced in the fact that removal of the child restored her normal metabolic balance. A study of her catheterized urine is now in progress. It differs from the normal in containing an exceedingly large quantity of lipoidal material and some of the guanidin bases which will be reported upon later. As will be seen below these bases are the etiological factor in the tetanies under discussion.

## **PATHOLOGICAL CHANGES**

The pathology as I have reported previously <sup>4</sup> is in part an encephalitis with chromatolysis and edema of the cerebral cells, parenchymatous hepatitis and nephritis, changes in the endothelial cells of the blood-vessels, and ante-mortem coagulation of the blood. No doubt many other changes also occur. The findings of Wilson, Steams and Janney <sup>5</sup> show an increased alkalinity in the blood preceding the tetany and a temporary acidosis resulting from the tetany. MacCallum and Voegtlin <sup>6</sup> claim a decreased calcium content in the blood and brain. Cook's <sup>7</sup> analysis of such brains shows no such calcium changes.

Many investigations have been undertaken to clear up the real mechanism of hypoparathyroidism. Two schools now hold very different views regarding its essential pathology. The older view of MacCallum, Voegtlin, Lambert, and Vogel is that the condition is essentially a condition of calcium insufficiency, since they find an increased urinary output of calcium and a diminution in the soluble calcium salts of the blood. This latter claim is open to argument, for it is difficult to understand how a blood low in diffusible calcium content can carry to the kidneys, so large a quantity of diffusible calcium that the urine should continuously have excessive calcium content. They base their conclusions besides on perfusion experiments, finding that by perfusing a normal animal's limb with calcium-free blood, and perfusing the limb with blood from a tetany dog, produces tetany therein, and that injections of oxalates cause tetany in normal animals because of precipitation of their blood calcium. <sup>8</sup> As will be seen from the following discussion, the findings of these later experiments show that calcium insufficiency has little to do with the essential etiology of parathyroid tetany.

The other view regarding the pathology of this condition is based upon the findings reported by the writer <sup>4</sup> several years ago, of the presence of guanidin bases in the urines of parathyroidectomized dogs in toxic quantities. The largest quantity of guanidin isolated was 9.8 mgrm. per kilo body weight. The toxic dose is variably 20 mgrm. per, kilo body weight. Besides guanidin the alkylated compounds, methyl guanidin, di-methyl guanidin, and a substance which upon analysis appeared to be amino-butyl guanidin were also isolated. The alkylation of guanidin in this way is no doubt an effort at its detoxication. Now since the total quantity of guanidins in the urines exceeded that which was isolated, and since some must have been destroyed and some retained in the body, and since the quantity isolated exceeded the toxic dose, the quantity active at death was no doubt lethal. Furthermore, the symptoms of guanidin poisoning are exactly those of parathyroid tetany. These findings of the author have been amply confirmed by the work of Paton, Findlay, Watson, Burns, Sharp, and Wishart <sup>2</sup> in their studies on parathyroidectomy in dogs, monkeys and other animals, the idiopathic tetany in children, and the tetany in post-operative hypoparathyroidism. These observers studied the urine and blood content of the guanidin bases, and following my methods of isolation found in the urine an increase of them of from 100 to 500 percent., and in the blood after parathyroidectomy an increase of from 400 to 1,200 percent. They also showed that the excised muscle of the frog showed similar tremors whether bathed in guanidin solution or in blood obtained from parathyroidectomized animals, and that the point of action was the myoneural junction. Their studies on the nitrogen distribution in guanidin poisoning, after parathyroidectomy in animals and in idiopathic tetany and post-operative tetany in man, show it to be the same in these conditions. The rate at which the guanidin bases are produced and the intensity of the symptoms also indicate that this substance is the etiological factor. My supporters find the average urinary output of 1.08 mgrm. of guanidin per kilo body weight in dogs with an average life of over ten days as compared to my findings of 9.8 mgrm. in a dog which died in three days. They consider this quantity excessive, but a more rapid intoxication is to be expected to be followed by an early death, pointing to this poison as the etiological factor. We may therefore conclude in concurrence with my first report

on this subject that the cause of the tetany is the guanidin intoxication of the central nervous system and the myoneural junction.

In order to reach a therapeutic basis for discussion it is necessary to inquire into the source of the guanidin bases, the relation of acid and calcium injections to the production and action of this poison, and the relation of the guanidin intoxication to the nutritional changes. All these questions are answered by one fact-namely, the occurrence in the urines of parathyroidectomized dogs of methyl cyanamide. 9 This substance was isolated from the urines of 47 dogs after parathyroidectomy, though in exceedingly small quantity-namely, 1.2 grm. of the picrolonate of the cyanamide and 2 grm. of the picrolonate of its polymer trimethyl-melamine. I take this substance to be the mother substance to the guanidins, that it was excreted in a methylated form simply again refers to the methylation facilities of the organism for detoxication purposes, as occurred in the case of the guanidins. The methyl cyanamide then represents cyanamide. Both these substances add ammonia very readily and are thus converted to guanidine. Several factors in this connection are to be recalled: First, that a meat diet increases the severity of the tetany; secondly, that as Wilson, Stearns and Janney 5 have shown, the alkalinity of the blood increases up to the tetany point, when convulsions occur. Now during the metabolization of amino acids, whether from a protein diet or from the tissues of the starving animal, ammonia groups are produced. They generally unite with carbon dioxide to form urea, an innocuous substance, or with other acids, forming salts, but in this condition they have the cyanamides to unite with, and as a result the alkaline guanidins are formed, only small quantities of the cyanamide escaping into the urine as such. When the threshold dose of the guanidins is reached, convulsions develop, and, through the attendant lactic-acid production of the tetany, the acidity of the blood is raised and the ammonia can now join acid radicals, the cyanamides thus being prevented from forming guanidins. This is fortunate since the cyanamides, though very poisonous, can be easily hydrated, thus forming the nonpoisonous urea, or be disposed of in other ways. These observations also explain the findings of Wilson, Stearns and Janney, that before tetany appears the ammonia excretion is lowered, and after tetany the ammonia and lactic acid excretion is raised. The tetany then serves as a detoxication mechanism.

The relation of the calcium blood-content to the tetany of parathyroid insufficiency is very simple. However, Voegtling 8 of the Calcium School finds it difficult to understand why calcium administration does not continuously control the tetany. This question can be reasonably answered on a physico-chemical basis. In the perfusion experiments referred to above, calcium was withdrawn from the limb in one case; in the other, the toxic guanidins were perfused through it. The oxalate injections removed soluble calcium from the blood by precipitation. Now where the protoplasmic complex, with its normal content of bivalent and monovalent cations, has the bivalent cations removed, the permeability of the cell is increased, a lipid in water phase being produced. Swelling of the cell then occurs, the diffusion of substances (substrate for ferment activity) into the cell and the diffusion of waste products out of the cell are facilitated, and as a result intracellular ferment activities are enhanced and the metabolism rate correspondingly quickened. The same conditions occur in acidosis. Thus the cells of the respiratory centre, influenced by increased carbon-dioxide blood-content, send out more powerful impulses to the respiratory muscles. Likewise the cells of the spinal cord, under the influence of asphyxia, cause through stronger impulses a great vasoconstriction. With a slight acidosis, muscle cells likewise carry on greater metabolic exchanges, and in this way calcium withdrawal must produce tetany.

Administration of calcium on the other hand, conditions a water in lipid phase of the protoplasmic complex decreasing the permeability of the cell, and thus its physiological activities are depressed. The only limit of this depression is the death of the cell through inanition. Incidentally, calcium administration thus diminishes the entrance of guanidin into the cell and lessens its activity. But with time the guanidin bodies enter the cell with sufficient accumulation to effect an intoxication, unless, of course, so much calcium is administered that cellular exchanges are practically prohibited and death results from cellular inanition. Such a state of affairs the Calcium School has realized as a result of the calcium administration to control the tetany.

There is one more factor which the literature has so far neglected-namely, the rapid excretion of lipoids. This indeed is fundamental both because of their large

output and their properties. Their interest in this connection lies in their relation to cell permeability. The greater their loss from the body, the greater the cell permeability and therefore the greater the intoxication by the guanidin bases.

Certain findings regarding the effects of injections of methyl cyanamide necessitate a return to this phase of the subject. A first intravenous injection of a few milligrams per kilo body weight produces a fall of about 30 mm. Hg in blood-pressure. A second injection following the return of the blood-pressure to normal by 25 seconds produces no effect; only after waiting about 40 seconds can a further drop in pressure be produced and this drop is greater the longer the interval between the injections. Thus the organism is for a time refractory in its reaction to second injections of this substance, a fact which means that the substance reacting with the cyanamide to produce this effect is slowly elaborated and that the reaction between the two substances is quantitative and therefore, hormone-like. It is interesting to note here that, experimentally produced, hyperparathyroidism is accompanied by a low blood-pressure. The excretion after parathyroidectomy of this substance signifies that it is produced in other tissues of the body than the parathyroids and that in the absence of their secretion it is not used. Hence we may conclude that the cyanamide is the agent which the body cells elaborate to react with the parathyroid secretion, and in the light, of the introductory hypothesis it is the "hook" they send out to obtain parathyroid secretion for their metabolic needs. The findings of Halsted 10 and others, that parathyroid transplants only grow where a parathyroid insufficiency is present may be referred to the stimulating action of this substance upon the transplant. Such findings are confirmatory to our conclusion. The behavior of this substance also gives strength to our hypothesis in that it suggests an explanation of the apparent antagonism between certain glands of internal secretion. Thus it is possible that the agent ("hook") sent out by a cell may bring to it more than one glandular product, and if this can be proved true, that is, if it can be shown that more than one set of glands is stimulated by it, injection into the body of the secretion of one of these sets of glands ought so to monopolize the agent ("hook") that stimulation of the other set of glands is suspended temporarily. The introduction of the above hypothesis regarding the mechanism of activity of the glands of internal secretion has brought up a number of problems for investigation. Thus administration of cyanamides and guanidin production after parathyroidectomy must be studied, as well as the effect of administration of the cyanamides upon parathyroid and other glandular activity.

## **TREATMENT**

From the foregoing evidence, it appears that the only sufficient repair for parathyroid insufficiency is removing the need of increased parathyroid function, such as the emptying of the pregnant uterus, or the implantation of sufficient parathyroid material from the same species to make good any deficiency. The latter course, however, carries the difficulty of obtaining the planting material. The use of extracts of the parathyroid gland have been very serviceable in the experience of Beebe 11 and others. Yet their content of active material must be small, and because of its instability and difficulty in preparation it does not promise a ready means of therapy. Therefore, palliative methods alone are at present generally possible; and they lie in the protection of the cells against guanidin entrance by means of calcium therapy, and the lessening of guanidin production by acid administration. For it is evident that where alkalosis is present, sufficient ammonia is also present to react with the cyanamides to, produce guanidins in toxic quantities. The acid treatment has the advantage over calcium therapy in that it reduces the symptoms without diminishing, cell nutrition. It should be so regulated as to keep guanidin production below the threshold of toxicity without producing a distinct acidosis. All that is necessary is to maintain the normal electric neutrality of the blood. Of course, the findings of the careful clinician upon this point must determine its value. We are so hard pressed for therapeutic measures in this condition that the above remarks require application.

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