ON THE RELATION OF TETANY TO THE PARATHYROID GLANDS AND TO CALCIUM METABOLISM.[1]

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Notwithstanding the fact that a great deal of study has been devoted to tetany and tetanoid conditions and to the nature of the parathyroid glands in their relation to these conditions in recent years the subject is still far from being perfectly understood. We have not yet a sufficiently large number of carefully investigated cases of some of the forms of tetany to speak with full certainty of the clinical phenomena and underlying pathological conditions, but this material is rapidly accumulating and rapidly becoming more valuable as the new light shed upon the subject by experimental work makes it possible to study the cases more intelligently.

v. Frankl-Hochwart in his notable monograph upon Tetany in Nothnagel's System subdivides the cases into a number of groups.

1. Tetany following or accompanying infectious diseases such as typhoid fever, cholera, etc.

2. Tetany in cases of gastric dilatation with stagnation of the stomach contents.

3. Tetany in infants and children thought by recent writers to be connected with nutritive disturbances and lesions of the parathyroids.

4. Tetany of so-called idiopathic nature occurring in workmen who ply certain trades such as those of the shoemaker, carpenter, etc.

5. Tetany associated with such diseases as osteomalacia, rickets, etc., possibly due as Erdheim suggests to lesions of the parathyroid gland.

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6. Tetany occurring in the course of pregnancy and lactation.

7. Tetany resulting from operative extirpation of the thyroid gland in which the parathyroids are also removed or destroyed.

In all these forms of the disease the symptoms are in their general character the same. They depend on increased excitability of the central nervous system which may be recognized by quantitative tests with faradic and galvanic currents or by the spasmodic rigidity of the muscles, frequently with violent twitchings which may even become so intense and general as to constitute an epileptiform convulsion. This is seen frequently in children, and sometimes, in dogs; such convulsions may closely resemble those of an epileptic. Fibrillary tremors of the tongue and distorting contractions of the facial muscles are often present and the jaws may be so tightly clenched that speech or the taking of food is impossible. Changes in temperature have not been well studied, but numerous instances are on record in which distinct elevation of the body temperature was observed. Our own attention has not until recently been especially directed to this point, but our casual observations have shown during the actual tetanic spasms in dogs rectal temperatures ranging from 38° C. to 43.2° C. In a recent instance in which the temperature of the dog, until the appearance of tetany, stood at the normal figure 39° C. it was found to register during the tetany 43.2° C. The administration of calcium in the way to be described, caused the muscular contractions to disappear and within half an hour the temperature sank to normal limits. The idea suggests itself that here as in cases of hyperpyrexia in tetanus, status epilepticus, intense muscular exertion as in a footrace, etc., the elevation of the temperature may be due merely to the fact that with violent muscular activity and excessive heat production, the heat regulating mechanism is for a short time inadequate and the elimination of heat is not rapid enough to compensate for the sudden heat production. Exact studies of the temperature in such animals will be published elsewhere. The pulse rate is generally quickened, but is sometimes not very greatly changed. Little mention is made in the literature of periods of tachypnoea, but in dogs this is one of the most striking features. It is doubtless an effort toward the regulation of the body temperature. But the condition has been so extensively described that it is

quite unnecessary to repeat the descriptions here since our results are concerned rather with the experimental study of the disease than with its clinical characters. It is indeed through experimental study that all of the information has been obtained which can lead to any therapy which may be of benefit in such cases and in view of the agitations designed to interfere with such studies, in this country it seems well to call attention to these results.

The fact appears to be thoroughly well established in spite of the dissenting voices of a few English investigators that the parathyroid glands are organs of independent nature and not developed from the thyroid or convertible into thyroid tissue. The evidence against this is of so insignificant a character as compared with the overwhelming evidence in its favor, that space need not be occupied here in discussing it. It may be said, however, that the argument for the unity of these two glands based on the chemical analyses of Gley, who found large amounts of iodine in the parathyroids has been disproven in the recent papers of Estes and Cecil[2] in which it was shown that the iodine content of the parathyroid glands is insignificant.

Nor is it less certain that the parathyroid glands exercise a specific function although we are as yet not perfectly informed as to that function. At least, we know well that the destruction of all the parathyroid glands results in the death of the animal with symptoms of tetany which is not in the least dependent, as was once thought, upon the destruction of the thyroid gland.

The work of Gley, Vassale, Generali, Horsely, Kocher, Erdheim, Pineles and many others sufficiently proves this, and in previous papers by one of us,[3] numerous experiments have confirmed these results and have convinced us beyond doubt or question as to the correctness of the observations. Most of our experiments have been performed upon dogs but Gley and others have extirpated the gland with similar results in rabbits, Horsley and Edmunds in monkeys, Erdheim in rats and Hagenbach in cats.

The objection has been raised that it is impossible to produce tetany in herbivorous animals, possibly on account of the difference

[2] Estes and Cecil, *Johns Hopkins Hospital Bulletin*, 1907, xviii, 331.

[3] MacCallum, *Medical News*, 1903, lxxxiii, 820; *ibid.*, 1905, lxxxvi, 625; *Centralbl. f. allg. Path.*, 1905, xvi, 385.

in the character of their food but we have shown in a recent paper[4] that if the extirpation be really complete it is possible to produce the most characteristic tetany in such animals as goats. It seems that the failures in these experiments, some of which occurred in our own hands, are probably due to the wide distribution of the parathyroid tissue which makes it difficult, if not impossible for the operator to recognize every focus of such tissue. Getzowa[5] and Michaud have recently pointed out the fact that such small masses of parathyroid tissue may occur deeply embedded in the tissue of the thyroid in human beings and we have repeatedly found this to be the case in dogs. There are, for example, several instances in which after the removal of four parathyroids, no tetany resulted, a phenomenon easily explained by the subsequent discovery of an extra mass of parathyroid tissue embedded in the thyroid or elsewhere. The extirpation of this extra nodule will bring about the development of tetany but it is surprising to note the extremely small size of the mass of parathyroid requisite to keep the animal from having tetany.

From this it is evident that the number of parathyroid glands is not by any means so constant as has generally been thought. Erdheim[6] points out that in rats their distribution is extremely variable and only the most careful study of several sections through all the organs of the neck is sufficient to give a trustworthy idea of their number. The inconstancy of the distribution of thymus and thyroid tissue is sufficient to make it probable that aberrant parathyroids might well occur also. Studies of the number and distribution of the parathyroid glands from a surgical point of view have been published by one of us[7] and by many other writers in this country and seem to show that the number and position depart from the typical form in very many cases. So, too, in dogs we have recently found cases in which six or eight distinct parathyroid glands were found in relation with the thyroid. Seldom, or never, however, have we succeeded in producing tetany by the extirpation of the parathyroid

[4] MacCallum, Thomson and Murphy, *Johns Hopkins Hospital Bulletin*, 1907, xviii, 333.

[5] Getzowa, *Virchow's Archiv*, 1907, clxxxviii, 181.

[6] Erdheim, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1906, xvi, 632.

[7] MacCallum, *Brit. Med. Jour.*, 1906, ii, 1282.

glands when we could find only three, and we have usually concluded that others were embedded in the thyroid as was proven by the subsequent extirpation of the thyroid and the production of tetany.

Nevertheless, in any long series of experiments there are some puzzling cases in which even though apparently every possible tissue which could contain parathyroid tissue has been extirpated the dog does not develop a frank tetany but may remain quite well or sink into a sort of apathy in which he is prone to infection and in which he finally dies. The exact nature of this is not clear but several things may possibly bear upon it. There may be a remnant of parathyroid tissue left too small to maintain perfect health, or the occurrence of a secondary infection, or the nature of their food may be sufficient to alter the character of the symptoms from those of outspoken tetany. We have referred at length to this matter in a previous paper[8] without reaching a conclusion and even now only those cases are clear in which at autopsy or on second operation remnants of parathyroid tissue are found embedded in the thyroid. Outspoken tetany is, however, not necessarily perfectly continuous even in those cases in which the extirpation of the parathyroids has been complete—there are intermissions in which the animal, while very sick and depressed does not show spontaneous twitching although the electrical excitability of the nerves may be increased. Others may live for a long time upon the verge of actual tetany, occasionally suffering from acute attacks but fairly well in the meanwhile. Beside this one may ameliorate the tetany for a time by bleeding and infusing salt solution so that although not permanently cured the animal is relieved from the acute symptoms for a time. On the whole it seems that the occurrence of these acute symptoms depends first of all, upon the complete removal of the parathyroid gland and then upon the degree of metabolic disturbance which results and which may perhaps be modified by the diet to a slight extent. In some instances in which dogs were kept fasting for the purpose of studying the changes in metabolism resulting from parathyroidectomy, we have been tempted to wonder whether their failure to develop tetany was due to the lack of food. This seems to be contradicted, however, by the fact that in several such cases

[8] MacCallum and Davidson, *Medical News*, 1905, lxxxvi, 625.

we have subsequently found minute masses of parathyroid embedded in the thyroids, and further by the fact that the tetany has often developed during such fasting.

It is of course possible that some of these animals, in which tetany was not observed had really passed through an attack with convulsions and tachypnœa at some time during the night when they could not be watched—indeed in some instances there were signs about the cage and in the position and general condition of the animal which would indicate this.

Although we have watched animals in which tetany had developed, for long periods and have observed as described above that they may be free from tetany except for attacks at long intervals, we have seldom seen a complete recovery after tetany had definitely appeared. It is interesting to read that v. Frankl-Hochwart[9] in his study of the ultimate fate of persons who have had tetany finds that they generally continue to show symptoms throughout their lives, but this chronic tetanoid condition can surely not refer to those cases in which transient attacks of tetany follow infectious diseases, pregnancy, lactation and nutritive disturbances.

In the previous papers referred to it was pointed out that the symptoms of tetany could be made to disappear by the subcutaneous or intravenous injection of an extract of the parathyroid gland—in other words, by an artificial replacement of the parathyroid. Since that time a number of investigators have published observations which confirm this fact and some have even proceeded farther and have found (Beebe) that the active principle of the gland is contained in the nucleo-proteid which is capable of being separated from the remaining albuminous substances by precipitation with acetic acid. The remaining albuminous substance is inert, but the solution of the nucleo-proteid is quite active in dispelling the symptoms of tetany. We have repeated this and can confirm Dr. Beebe's results to this extent. Doses of parathyroid material given by mouth have had no good effect in our hands although Dr. Halsted reports beneficial effects in a case with tetanoid symptoms which he has observed. That the subcutaneous administration of the extract of the gland has a remarkable effect was seen not long ago in a case which will doubtless be reported later by Dr. Branham.

[9] v. Frankl-Hochwart, *Wien. med. Woch.*, 1906, lvi, 309.

This was the case of a girl from whom a goitre had been extirpated together with portions, at least, of the parathyroid. The insufficiency thus produced resulted after seventy-two hours in a most violent attack of tetany in which the girl became very rigid and perfectly helpless. The fingers were contracted into the characteristic position, the feet extended and the jaws so tightly set that nothing could be forced into her mouth. An emulsion of four or five parathyroid glands of the cow was prepared aseptically and injected beneath the breast. Several hours later there was a complete relaxation of the rigid muscles and the patient fell asleep to wake up next morning feeling quite well. Four days later there occurred another similar attack which was again combated in the same way with the same good result. Strangely enough, there were no further symptoms, whether because some remnant of parathyroid gland had by that time resumed its function or for some other reason, it is difficult to decide.

There seems no doubt that with a suitable emulsion or extract of the ox parathyroid cases of tetany could be successfully relieved for a time but the method of administration is difficult and not without the possibility of unpleasant infection at the site of injection. It would, however, be of great importance to apply this therapeutic test to those forms of tetany which are not definitely known to depend upon the destruction of the parathyroids. It is to be hoped that it may be tested by some one who has the opportunity of studying cases of gastric tetany and the other conditions mentioned above. Especially interesting would be its effect upon osteomalacia and rickets.

The object of our work together this year has been to determine, if possible, the chemical nature of the processes which result from parathyroidectomy and the chemical nature of the functional activity of the parathyroid. The latter part of this problem is far more difficult of solution than the former and we have little to report upon that, but as regards the chemical nature of tetany, we can make a report which, however incomplete, we still prefer to publish now with the hope of communicating the results of further studies later.

Although it was known that some substance contained in the

watery extract of the parathyroid gland, or even in the precipitated nucleo-proteid of that gland is capable of restoring to normal whatever disturbed metabolism we might find in tetany, it was thought best to begin by the investigation of these disturbances before attempting to study the character of this extract. It was proposed, therefore, to place animals under constant conditions for several days before the parathyroidectomy and to observe the chemical characters of the excreta during those days and the whole period following the operation. Further it was thought desirable to study the chemical constitution of the blood, brain, etc., in those dogs which developed tetany as compared with that of normal control animals. The study of the central nervous system was regarded as the more important inasmuch as experiments described in a previous paper[10] seemed to show fairly clearly that the tetanic condition is not an affection of the muscles, but rather of some portion of the brain. In all this it was thought that the study of the mineral contents of the tissues and excreta might be especially important and in view of recent literature on allied conditions it seemed especially important that we should turn our attention to the calcium content. This recent literature which has been well reviewed by Bogen[11] is not extensive and has led so far, to conclusive proof of only a few points. Briefly the papers which bear directly upon the subject are as follows:

The earlier work of Forster[12] and Voit[13] upon the resorption of calcium and its significance in the animal body with the effects of deprivation of calcium in the food gave results of fundamental importance upon the general relations of calcium but gave very little suggestion as to any connection with muscular or nervous hyperexcitability. Pædiatricians had described the nervous and muscular phenomena in infantile tetany and in 1900 Gregor[14] suggested that something in the nature of the nutriment might be the underlying cause of these changes. This was followed later by many more interesting observations on the relations between the nutriment and the development of tetany which will be detailed in order.

In 1901, Sabbatani[15] observed that calcium salts had an action antagonistic

[10] MacCallum, *Medical News*, 1903, lxxxiii, 820.

[11] Bogen, *Monatschr. f. Kinderheilk.*, 1907, vi, 228.

[12] Forster, *Zeitschr. f. Biol.*, 1876, xii, 464; *Archiv f. Hygiene*, 1884, ii, 385.

[13] Voit, *Zeitschr. f. Biol.*, 1880, xvi, 55.

[14] Gregor, *Archiv f. Kinderheilk.*, 1900, xxix, 95.

[15] Sabbatani, *Rivista sper. di Freniatria*, 1901, xxvii, 946.

to that of sodium citrate which he regarded as a "chemical" and not a "pharmacological" action. These effects which concern the irritability of the nervous system are especially marked when the salts are applied directly to the surface of the brain and are as follows: when calcium chloride is applied thus to the cortical surface the irritability as estimated by mechanical or electrical stimuli is almost immediately reduced so that a much greater electrical stimulus is required to produce muscular contraction than in the case of the normal brain. The application of such substances as sodium citrate, sodium oxalate, sodium soap, etc., has the opposite effect, and greatly increases the excitability of the nervous system so that the stimuli necessary to produce muscular movements are now greatly decreased—indeed under these circumstances spontaneous twitchings and even epileptiform convulsions may occur. Subsequent application of the calcium salt will neutralize these effects and reduce once more the excitability of the nerve cells. One can apply sodium citrate on one side of the cortex and calcium chloride on the other with corresponding results on the two sides. All this is due, according to Sabbatani, to the immobilization of the calcium which has a permanent moderating function in the cortex and he suggests that it might be useful in epilepsy but his experiments in this regard were not always successful.

Jacques Loeb[16] in a paper on the production of muscular twitchings by electrolytes, finds that the injection into the animal body of any salt liable to precipitate calcium produces twitching of the muscles, and suggests that "abnormal conditions might arise in which an increase of such acids in the circulation could diminish the amount of calcium in the body. The necessary outcome would be muscular twitchings. In that case the administration of calcium salts might cure the disease." In the suppression of neurogenic twitchings, he thinks it possible that more calcium may be required than in the case of myogenic twitchings. The experiments recorded show that the immersion of a muscle nerve preparation in a solution of a salt which precipitates or renders inactive the calcium, gives rise to twitchings which are suppressed by the addition of fresh calcium to the solution or the transfer of the muscle to a calcium solution. Similarly J. B. MacCallum, in numerous papers,[17] has pointed out that peristaltic activity in the intestine and secretory activity in other organs may be stirred up by certain salts which have an action antagonistic to that of calcium and suppressed by the addition of a soluble calcium salt.

Roncoroni,[18] in 1903, confirmed Sabbatani's work and found that it is difficult to stimulate the cortex after having given intravenous injections of calcium chloride, but that injections of sodium citrate heighten its susceptibility. Histological study of the portions of the cortex treated in Sabbatani's method with various salts show only such modifications as might be due to chemical alterations.

Thiemich[19] described, in 1903, in detail the changes in electrical excitability in cases of infantile tetany which were already well enough known, but pointed

[16] Loeb, University of Chicago Decennial Publications, 1902, x, 6; *Amer. Jour. of Physiol.*, 1900, iii, 327; Garrey, *idem.*, 1905, xiii, 186.

[17] MacCallum, J. B., *University of California Publications, Physiol. Department*, 1903–1906; *Pflüger's Archiv*, 1904, civ, 421.

[18] Roncoroni, *Rivista sper. di Freniatria*, 1903, xxix, 157.

[19] Thiemich, *Rev. d'hygiene et med. infantiles*, 1903, ii, 309.

out also that it is especially in artificially fed children that such tetany occurs, and that cow's milk is especially likely to bring on this condition. Japha[20] similarly recognized, in cow's milk, an important cause of digestive disturbances and of tetany, for its withdrawal and the substitution of mother's milk or farinaceous material brings about a cure. He expressed the opinion that the influence of nourishment is a secondary result of a functional organic disturbance. Finkelstein[21] expresses very similar views in his text-book. Stoeltzner[22] met with similar cases of tetany and tried to analyze the possibilities as to the component of the cow's milk which could thus accentuate or even cause the tetany in children. The result of his experiments is that he regards the tetany as the symptom of excessive retention of calcium in the tissue—a sort of calcium poisoning probably due to intestinal disturbances which prevent the proper excretion of calcium by way of the intestine. As is pointed out by Bogen and others, however, the proof of this theory which Stoeltzner brings forward is not very convincing.

Quest,[23] interested in the work of Sabbatani and Regoli, thought it necessary to determine the calcium content of the brain in convulsive diseases and its relation to calcium metabolism in general. He found that the calcium content of the brain is high in the fœtus and new-born babies but sinks gradually with age and irritability is normally less in the cortex of the new-born than later. In tetany the calcium content of the brain is remarkably lowered. He also tried to produce electrical hyperexcitability in animals by giving them a calcium-free food with the results that the excitability of the calcium-starved dogs is remarkably increased. Weigert,[24] who had an opportunity to study two puppies of the same litter one of which suffered an attack of tetany when fed on cow's milk found that the calcium ratio in the brain was very much diminished as compared with that of the normal dog.

Cybulski[25] studied the metabolism in a child with tetany and does not agree with Stoeltzner's idea, for he found that the calcium retention was far less during tetany than during recovery.

Silvestri[26] estimated that the calcium contents of a fœtus increases rapidly toward the end of term. This must be a great drain upon the mother especially during that time. So too, the amount of calcium secreted in the milk is very high for it amounts to about 0.4 per cent. of the milk and from 1700–1800 grms. are secreted daily which would give an amount of calcium of about 6–7 grms. per day. He thinks tetany is due to a hypocalcification of the nervous centers.

Netter[27] observed good results follow the administration of calcium salts per os in three cases of tetany and thinks that Stoeltzner's views may be recon-

[20] Japha, *Berl. klin. Woch.*, 1903, xl, 1126.

[21] Finkelstein, Lehrb. der Säuglingskrankheiten, 1st half, 1905, Berlin.

[22] Stoeltzner, *Jahrb. f. Kinderheilk.*, 1906, lxiii, 661.

[23] Quest, *Jahrb. f. Kinderheilk.*, 1905, lxi, 114; *Wien. klin. Woch.*, 1906, xix, 830.

[24] Weigert, *Monatschr. f. Kinderheilk.*, 1906, v, 457.

[25] Cybulski, *idem*, 1906, v, 409.

[26] Silvestri, *Gazz. d. ospedali*, 1906, xxvii, 1005.

[27] Netter, *Comp. rend. d. l. Soc. d. Biol.*, 1907, lxii, 376.

ciled with the experimental results of others on the ground that in cow's milk one is dealing with relatively enormous doses of calcium.

Iddo and Sarles are cited by Netter as having found an increased amount of calcium in the urine of a child suffering from tetany which they regard as evidence of an increased excretion of calcium during the tetany.

v. Pirquet[28] opposes Stoeltzner's ideas also on the ground that the hyperexcitability in tetany is by no means dependent upon excessive retention of calcium since it sometimes begins when the amount of calcium taken in with the food is minimal and disappears during the administration of larger amounts of calcium. Bogen also disagrees with Stoeltzner in his idea that an excess of calcium is responsible for the tetany. Other things than cow's milk may induce tetany, the administration of calcium, even in Stoeltzner's hands, did not always result in tetany and after long and harmless administration of calcium acetate, cow's milk is sometimes found to bring on tetany. In seven patients of his own, Bogen[29] found that the administration of calcium will not bring on the tetanoid condition but tends to reduce the excitability of the nervous system and that there is no basis for the belief that tetany arises from a calcium stasis in the organism.

So far for the literature bearing directly upon these relations. Other papers treat indirectly of the same thing, thus several authors among whom Verstraeten and Vanderlinden[30] may be mentioned, make the statement that it is more difficult to produce tetany in animals fed exclusively upon milk than in those given a meat diet. The extent to which this is true will be discussed further on in this paper.

Erdheim[31] has recently attempted to show that there is a direct interdependence between osteomalacia and lesions of the parathyroid bodies and others (Kassowitz) have thought that rickets might be the underlying basis of the tetany of children. Both of these diseases in the course of which tetany is well known to occur are conditions in which there is obviously some profound disturbance of calcium metabolism and the suggestion of their relation to the parathyroid glands at least suggests the study of the relation between the parathyroid glands and calcium metabolism. Erdheim, in his experiments on the production of tetany in rats found most extraordinary changes in the teeth of the rats which

[28] v. Pirquet, *Wien. med. Woch.*, 1907, lvii, 14.

[29] Bogen, *loc. cit.*

[30] Verstraeten and Vanderlinden, *Mem. couronnés de l'Acad. royale de med. de Belgique*, 1894, xiii, 1.

[31] Erdheim, *Sitz. d. k. Acad. d. Wiss., Wien, Math. Naturwiss. kl.*, 1907, cxvi, iii, 311.

became fragile and opaque and frequently broke off short—again some disturbances of however obscure a character in the calcium metabolism.

Our own experiments fall into two groups, in one of which we endeavored to ascertain in cases of outspoken tetany produced by parathyroidectomy the effect of the administration of various substances chiefly mineral salts which might occur normally or under pathological conditions in the animal body and among these we were especially interested in the soluble calcium salts. The second group of experiments was arranged for the study of the changes in metabolism during tetany and in the chemical composition of the tissues in animals dying in that condition.

The effect of the administration of various body fluids and tissues has been mentioned in previous papers but no clear results can be deduced from these. It was shown that the transfusion of blood from a normal dog will suppress the symptoms of tetany when a sufficiently large amount is introduced. Emulsion of brain substance was injected in the same way but the effect upon the tetany was so indefinite that it was questioned in that paper whether the action of the emulsion was any more marked than would have been that of so much salt solution or emulsion of any other organ from a normal dog. Emulsions of the parathyroid gland seem to have a definitely specific effect but that appears only after the lapse of some hours whereas the effect of bleeding and infusion of relatively large amounts of salt solution or blood (200 to 400 c.c.) from a normal dog has an almost immediate effect in supressing the tetany. We could find no other explanation of this phenomenon than that some poisonous material, not destroyed or present in larger amounts than physiologically, on account of the absence of the parathyroid glands, was circulating in the blood. We could not demonstrate the presence of this poisonous substance by injecting the blood from dogs in tetany into normal animals but it may readily be imagined that it is some substance easily oxidized or otherwise changed into harmless materials in the normal body but circulating in the parathyroidectomized dog on account of the lack of some ferment-like material produced normally by the

parathyroid. The idea of a circulatory organic poison we have kept in mind throughout our subsequent experiments.[32]

Our attention was turned then to the inorganic substances which might be concerned. Salts of sodium, potassium, calcium and magnesium are of course prominent. We began with the effects of calcium subsequently experimenting with the others as follows:

2107. Thyroparathyroidectomy, four days later violent twitching of muscles—pulse, 160, respiration labored. Given 10 c.c. of a 5 per cent. solution of calcium acetate into jugular vein. Respiration became rapid, 200 to minute, twitching rare but sharp—twenty-five minutes after the injection, pulse was 80, very irregular and slow. Dog thought to be dying—occasional slight twitches. Next day dog was found walking about and fairly well but was found dead the day after. In this experiment the animal was apparently restored to life from a moribund state, but the amount of Ca salt had not been large enough to remove tetany instantly.

2207. Four parathyroids extirpated December 20. On December 22 at 3 P. M. most violent tetany, with tachypnœa, respiration 200, pulse 132, temperature 40.75. December 22 at 3.05 P. M., given 10 c.c. of 5 per cent. solution calcium acetate into jugular vein. 3.10, respiration 240–250, twitchings intense with snapping of teeth. 3.25, tachypnœa continues irregularly at a rate varying from 160–170. 3.30, breathing much quieter but still unnaturally rapid. No panting at present, twitching markedly improved, pulse 100. Dog now lies quietly and is fairly well relaxed. Twitchings very slight, felt only in shoulder. Lifts up his head and wanders about, is breathing quietly and seems comfortable—respiration 100, twitching has practically disappeared. 3.35, respiration 80, pulse 95—dog now quiet and takes intelligent interest in surroundings. 3.40, respiration 35, pulse 90, slight twitching. 3.45, respiration 21, dog resting quietly —apparently rather exhausted. 3.50, runs about actively, swaying slightly with an occasional jerk of one leg, but on the whole one could not tell that he had had tetany. Responds eagerly to petting and eats greedily. 6.30, seems quite well—no trace of twitching—is very quiet and tractable, no distinct tetany. December 23.

108. January 9, two parathyroids and one lobe of thyroid extirpated—no results. January 18, second lobe of thyroid removed. January 19, violent tetany —at 11.30 given 10 c.c. of 5 per cent. calcium lactate subcutaneously. 11.35 respiration 240, marked twitching, pulse 180, breathing very rapid and labored. 12.10, still tachypnœa and twitching. 1.10, respiration slowed, 40 to minute, muscular twitching still marked. 1.30, respiration quiet, 1.32, twitching has almost disappeared, slight muscular tremor, walks about but looks dejected. 3 P. M., respiration 24, pulse 124, dog is quite normal in appearance, no tremor nor twitching. Respiration perfectly quiet and animal has perfect control of himself and eats hungrily on being taken to cage.

It is seen from this experiment that the effect of subcutaneous injection of calcium is the same as that of intravenous injection

[32] MacCallum and Davidson, *Medical News, loc. cit.*

but appears more slowly. The dog developed tetany again next day and his further history will be given in connection with experiments with potassium salts.

208. Thyroparathyroidectomy, January 16. On January 18, at 9 A. M., found in violent tetany; tachypnœa, twitching and loss of control of legs, unable to stand. 11.30, 80 c.c. of 5 per cent. solution of calcium acetate given by stomach tube; after a short time was able to walk and tetanic spasms disappeared, but animal was found dead next day.

2208. This was one of Dr. Halsted's dogs from which he had removed the thyroids and parathyroids after having transplanted one or two parathyroid glands into the abdominal wall. After the total removal of the glands in the neck the dog developed tetany, since at that time the transplanted parathyroids were evidently not functioning actively enough to prevent it. February 14, dog is having marked tetany, at 5 P. M. respiration very rapid, pulse 120; given 100 c.c. of 4.3 per cent. calcium lactate by stomach tube. 6.30, respiration still rapid, but tetany has stopped. February 15, 10.15 A. M., dog is fairly well, but has fibrillary twitchings in tongue, respiration is rather deep and rapid, 110, pulse 100. Passage of the stomach tube elicits an attack of tetany with respiration at 304 and very rapid pulse. 10.45, 100 c.c. of 4.3 per cent. calcium lactate given by tube. 11.00, respiration 60, deep and regular—at 2 P. M. no tetany could be observed. February 17, 9 A. M., dog is having tetany—given 50 c.c. of 4.3 per cent. calcium lactate at 10.30; in afternoon was all right. February 18, no tetany, but dog was given during the day two doses of calcium lactate as a prophylactic measure. February 19, no tetany, given 40 c.c. of 5 per cent. calcium acetate. February 20, no tetany, given 50 c.c. 5 per cent. calcium acetate. February 21, no tetany. February 25, slight twitchings of muscles of head; given 100 c.c. of 4.3 per cent. solution of calcium lactate by stomach tube. March 3, no tetany.

This dog gradually developed very distinct myxœdema but up to the present, July 3, there has been no further sign of tetany. Evidently the condition which led to the tetany was tided over by the administration of calcium until the transplanted parathyroid became able to function actively enough to prevent tetany.

2508. February 27, parathyroidectomy. February 29, 9 A. M., marked tetany, pulse 128, respiration 36. 11.40, tachypnœa. 11.48, 10 c.c. 5 per cent. sodium acetate intravenously. Respiration 150, pulse 160. 11.50, rigidity, twitching increasing. 12, tachypnœa, violent twitching, no improvement whatever. 12.10, pulse 156, respiration 240, temperature 40. 12.15, 10 c.c. of 5 per cent. calcium lactate intravenously. 12.22, respiration 252, pulse 136, tetany intense. 12.30, 10 c.c. of 5 per cent. calcium lactate intravenously. Tachypnœa intermittent, throughout some periods of 5 seconds respiration is at 300, then it falls to almost nothing, starting quickly again. The muscular twitching is almost gone. 12.35,

fibrillary twitching of the tongue almost gone, muscles flaccid, practically no twitching, except in the superficial muscles. Respiration 132, not labored. Dog begins to take interest in the surroundings, respiration 132. 12.45, respiration 100, 5 c.c. calcium lactate intravenously. 12.50, respiration 60, dog seems practically normal and is allowed to run about the floor. During the next three days twitching was very slight and one dose of calcium lactate was given on March 1, large quantities of milk, 500 c.c. to 1 l., March 2, 3, 4. March 5, dog was found in violent tetany, giving 400 c.c. of milk, 10.30 A. M. At 11.10 an epileptiform convulsion occurred in which he fell to the floor, rigid and breathing stertorously. This lasted a minute or two, when he got up, shaking himself, walked away. 2 P. M., still twitching violently, respiration labored and grunting. 3 P. M., given 400 c.c. of milk by stomach tube. Passage of the tube throws the dog into an epileptiform state, in which he lies rigid on the ground with grunting respiration. Apparently the quantity of calcium administered in the milk is far too small or is not absorbed readily enough to cure or ward off tetany. Up to 5.30 P. M. still having tetany. March 6, still is stiff and twitching, but not in violent tetany. 12.30, given 400 c.c. milk. Violent spasm during introduction of tube. 6 P. M., 300 c.c. more of milk, tetany is slight. From March 7 to May 4 the dog was left out in the yard, apparently well enough, with no tetany. He was on a meat and bone diet. May 4, found in violent tetany, almost moribund and given calcium lactate by mouth and left to himself. May 5, dog is apparently normal. Up to May 15 he was quite well, when he was found in a violent attack of tetany, given 100 c.c. of 4 per cent. calcium lactate by mouth; at 6 P. M. is in violent tetany with rapid, labored respiration. Legs rigid and twitching. Respiration 128, pulse 168. At 6.20 is still in tetany. At 8 P. M. is well, can walk about, but occasional twitches in the muscles. Respiration 40, pulse 152. Dog seems pretty comfortable and it was confidently expected that he would be all right in the morning. May 16, perfectly well and remained so up to June 7, when another attack of tetany was suppressed in the same way by giving calcium lactate by mouth. Since that time he has been well up to July 15, when he was killed by ether.

3708. Another dog operated upon by Dr. Halsted for transplantation of the parathyroid gland with subsequent extirpation of all of the remaining parathyroids, was cured of several attacks of tetany by doses of calcium lactate given by mouth.

6008. Operated upon March 17, transplantation of one parathyroid into abdominal wall. Second operation May 5, transplantation of another parathyroid into abdominal wall and removal of all parathyroid and thyroid glands in the neck. May 6, 4 P. M., violent tetany, given 50 c.c. of 5 per cent. calcium chloride by mouth. May 7, slight tetany, given 50 c.c. 4 per cent. calcium lactate by month. One hour later tetany had disappeared. May 8, no tetany. May 9, slight tetany; in the morning given 50 c.c. of calcium lactate 5 per cent. by stomach tube; complete recovery. May 10, twitching on the top of the head, given 50 c.c. 5 per cent. calcium lactate. May 11, having distinct tetany with snapping jaws, given 100 c.c. of calcium lactate. May 12, no tetany. May 13, slight tetany, given 100 c.c. 4 per cent. calcium lactate per os. May 16, slight

tetany, given 100 c.c. 4 per cent. calcium lactate per os. Since this time the dog has had no further tetany and has received no further calcium.

These experiments are sufficient to demonstrate the immediate and specific curative effect of the administration of soluble calcium salt upon the tetany of parathyroidectomy, the specificity being shown by experiments which will be recorded in which the effect of calcium is striking as compared with the inefficiency of other salts in suppressing tetany. It is seen from these experiments that the effect of calcium adminstration is quite similar, no matter whether it be given intravenously or subcutaneously or by stomach tube. The rapidity with which it acts differs, however, under these different conditions. It is found that the calcium chloride is, perhaps, the most irritating of these salts and cannot well be administered subcutaneously. Furthermore, the too rapid injections of calcium lactate into the venous channels may give rise to hemorrhages in the pulmonary tissues. We have, however, observed no other ill effects in any of the animals even when very large doses of calcium were administered rapidly.

At this point it may be stated that an opportunity has occurred for the observation of the effect of calcium upon cases of tetany in human beings produced by the operative extirpation of the thyroid together with the parathyroids on account of tumor growths, etc. Dr. J. H. Musser, of Philadelphia, has been kind enough to allow us to see a case under his charge, in which violent tetany had developed as the result of the operative extirpation of an extensively invading malignant growth of the thyroid gland. In this case calcium lactate was administered in frequent and quite large doses with the result that tetany disappeared in the course of one day. When the calcium medication was withheld for two or three days, the symptoms of tetany reappeared, only to disappear on the readministration of the calcium. In a portion of thyroid removed at operation in this case we have been able to find only one parathyroid gland, but the tissue was so much cut up, and such considerable portions had been removed, that the examination can make no pretense to completeness. A similar case has been described to us by Dr. S. J. Meltzer as occurring in the practice of

a New York physician, in which the administration of calcium salts suppressed the symptoms of tetany in precisely the same way.[33]

Dr. Meltzer in recent papers has pointed out the antagonistic action which exists between calcium and magnesium salts, and has further emphasized the anæsthetic action of magnesium salts and their importance in modifying the symptoms of tetanus when injected about the central nervous system. We have, therefore, been interested in observing the effects of magnesium salts upon the symptoms of tetany, and have made a few experiments as follows:

2207. Referred to above. In this dog in which tetany first developed on December 22 a cure was brought about by the injection of calcium, but on December 24 he was again found in moderate tetany, twitching very distinct, legs very stiff and as feet continually double under him, he cannot easily stand, respiration 24, labored, pulse 144, temperature 38. At 10.35 given 10 c.c. of magnesium chloride intravenously, breathing at once became very quiet. Tetany practically stopped. The twitching is still visible, however, in the shoulders and face. 10.40, respiration 35, pulse 100. General slight tremor, but limbs are relaxed. 10.45, respiration 44, more labored, twitching much more marked, legs stretched out. 10.55, twitching just evident. Dog is very apathetic, stands with head hanging, makes slight attempts at vomiting. He is perhaps quieter and more comfortable than before the injection was given, responds slightly to a call. 11 A. M., twitching scarcely visible. Dog still stands most dejectedly with hanging head. 11.45, cowers in the corner, stiff and scared, slight tremor, breathing audible across the room. No marked tetany. 2 P. M., slight twitching, dog has anxious look and attempts to remain in a dark corner, no definite tetany. 5.30, dog was stuporous but there was no distinct twitching and no definite tetany for three days following this, when tetany began to appear and was suppressed by injection of calcium salt.

1508. February 8, thyroparathyroidectomy, one lobe of the thyroid being left. February 10, 9.30 A. M., dog in violent tetany, pulse 152, respiration very irregular with periods of apnœa. 10.45, given intravenously 10 c.c. 5 per cent. magnesium chloride. Dog stopped breathing, but was kept alive by artificial respiration, the pulse continuing fairly strong. After a time the dog began to breathe himself, but very slowly. At 11 o'clock respiration 28, pulse 132. Dog seems to be completely anæsthetized, does not move with the prick of a pin and there is hardly any corneal reflex. Tetany completely stopped. At 11.10 still perfectly unconscious and breathing quietly. 11.30, walking about but is

[33] Dr. Harvey Stone, of Charlottesville has described to us in a recent letter the case of a little girl suffering with what was apparently gastric tetany, the symptoms of which have been completely relieved by the administration of calcium. While this tends to give some support to the idea that gastric tetany is dependent upon a relative insufficiency of the parathyroid gland, the effect of the administration of parathyroid extract in such a case would be still more interesting. Dr. Stone will shortly report the case and kindly permits us to mention it here.

very ataxic. 11.50, very apathetic, lies shivering on the floor, no tetany. 5.30, in the afternoon, the dog still lay curled up in the cage, could hardly be roused. February 11, 9.30, still lies curled up without distinct tetany, but next day, February 12, tetany appeared in a most intense form.

Unfortunately up to the present, we have not made any further experiments with magnesium, but these seem to indicate that the injection of magnesium will suppress the symptoms of tetany, though its effects are somewhat confused by the ataxic and anæsthetic action of the magnesium itself. Whereas Dog 1508 was extremely stuporous the next day after the injection, another dog suffering quite severely from tetany at the same time received instead of the magnesium an injection of calcium salt, and the next day was to all appearances perfectly normal.

A few experiments have also been made on the effects of sodium and potassium salts in relation to tetany as follows:

108. Tetany developed January 19 and was suppressed by a dose of calcium given subcutaneously. Next day, January 20, tetany was again quite marked, the dog rendered helpless.. 11 A. M., respiration grunting 40 to the minute. At 11 A. M. 10 c.c. of 5 per cent. potassium acetate given subcutaneously. At 11.20 tetany, if anything, slightly more marked than during the morning, animal stretched out helpless, breathing rapid and labored. Later in the afternoon when he seemed practically moribund, he was given 10 c.c. of calcium lactate, 5 per cent. solution, subcutaneously and still later 10 c.c. intravenously; was apathetic for the rest of the afternoon, but fairly well next morning. In this case the potassium acetate seemed to have no controlling influence over the tetany.

808. January 23, four parathyroids removed. January 26, distinct tetany with twitching, very violent. Legs rigid, pulse 148, respiration very irregular. 9.50, given 10 c.c. 5 per cent. potassium acetate subcutaneously. 10.10, tetany quite violent and at 3.30 distinct violent tetany, respiration labored. 10.45 P. M., marked tetany, pulse 160, respiration 28. As his condition seemed to be very serious 10 c.c. of 5 per cent. calcium lactate was given subcutaneously. Tetany still very distinct at 10.55. At 11.45 pulse 76, extremely forcible. At 11.50 tetany had disappeared and the dog walked about and behaved quite normally. January 27, at 6 P. M. dog which had been somewhat apathetic all day again developed tetany. At 8.30 pulse 176, respiration 36, given 10 c.c. calcium lactate intravenously, pulse immediately afterwards 56, respiration 28, tetany stopped almost immediately. January 27, no tetany. January 28, 10.30, slight but distinct tetany. 10.45, given intravenously 10 c.c. 5 per cent. solution sodium acetate. Almost immediately the pulse became uncountable, respiration from 100 to 120. Tetany at once become violent. 10.55, tetany extreme. Dog is unable to rise but lies on its side with legs stretched out, twitching violently, fibrillar tremors of the tongue, rigidity of the legs renders the animal help-

less. This continued until 12.15 when 8 c.c. of calcium lactate was given intravenously; at that time the pulse was 176, respiration 100 to 120; within a few minutes the tetany completely disappeared. Pulse rate reduced to 76, respiration 36. The dog can walk about and takes an interest in things, drinks and eats. At 2 P. M. tetany reappeared to a slight degree. At. 2.20, 10 c.c. calcium acetate were injected subcutaneously. At 2.45 another 10 c.c. At 4.50 the dog seemed well enough. The tetany reappeared on each of the next two days, but was relieved almost at once each day by the intravenous doses of calcium lactate.

1908. February 7, complete thyroparathyroidectomy. February 10, dog found in violent tetany with tachypnœa, respiration 168, pulse uncountable. At 11.25 given 5 c.c. of 5 per cent. potassium acetate intravenously. 11.32, respiration 288 to 300, pulse not counted, twitchings are evidently more violent than before. Pulse at 11.40, 144, tachypnœa and twitching very violently, fibrillary contractions of the tongue, jaws clenched. 11.45, respiration 270, very labored. 11.50, respiration 300, very irregular and in periods of violent tachypnœa. After this, was given a number of doses of calcium lactate intravenously 5 c.c. at a time until one o'clock when it became quiet and the dog could walk about. At 5.30 P. M. the dog seemed perfectly well and remained so until February 13, when he was found again in moderate tetany. At 10.38, 10 c.c. of 5 per cent. sodium acetate was given intravenously which was found to have no effect whatever upon the moderate tetany. At 4 P. M. 40 c.c. calcium lactate was given by a stomach tube and tetany gradually disappeared, being quite absent next day. The dog died two days later of penumonia.

The experiments with the injection of potassium salts are unfortunately very meagre and unsatisfactory, but we hope to repeat them later with more definite results; at least the injection of potassium salts seems to exercise no definite beneficial influence upon the course of the tetany, and in case 1908 it seemed necessary to administer more calcium than usual in order to overcome the tetany. Whether this was due to the previous injection of potassium salt or not cannot be definitely stated.

The experiments were especially unsatisfactory on account of the fact that in the hope of saving the dog's life, calcium was injected in almost every instance before sufficient time had elapsed to determine the exact effect of the potassium injection. The same thing is true in a case of sodium injection in Experiment 2508 recorded above. The studies of metabolism, to be detailed later in this paper, showed that in the course of tetany the ammonium content of the blood and of the urine is somewhat increased and the idea has been prominent that possibly something resembling an acid intoxication might be responsible for the symptoms. We have,

therefore, planned the administration of large doses of sodium bicarbonate to see if this hypothesis be true and to ward off the development of tetany. Unfortunately these experiments are as yet incomplete, but such as they are may be recorded here.

4808. Complete thyroparathyroidectomy April 25. April 26, given 25 gms. sodium bicarbonate, dissolved in water, by stomach tube. April 27, no symptoms, given 50 gms. of sodium bicarbonate by stomach tube. April 29, no twitching, no tremor of tongue, given 25 gms. sodium bicarbonate; dog was found dead next day without having developed any symptoms of tetany.

4908. April 25, complete thyroparathyroidectomy. April 26, given 50 gms. sodium bicarbonate by stomach tube. April 27, no distinct symptoms of tetany, given 50 gms. sodium bicarbonate by stomach tube. The passage of the tube elicited a sort of epileptiform attack, in which the dog quickly recovered. April 28, no symptoms. April 29, slight twitching of the muscles of back and of the tongue, given 25 gms. sodium bicarbonate by stomach tube. 6 P. M., distinct tetanic twitching about head. May 6, dog has shown no tetany during the past six days. Died subsequently without having shown any such symptoms.

5708. May 14, four parathyroids removed. May 16, 6 P. M., distinct signs of tetany. 11.15 P. M., tetany quite violent, respiration 280, legs very stiff, pulse 156. 11.30, great rigidity, extreme tachypnœa, pulse 230. 12.00 midnight, pulse 168, respiration 240, occasionally twitching in hind legs, 25 c.c. of 5 per cent. sodium bicarbonate injected into jugular vein, tetany during this more violent than before, respiration less regular, but less continuously rapid, 200 or less. 12.15, respiration 240, twitching still quite violent. 12.30, respiration 112, alternating with brief intervals of 218. 12.35, tetany is reduced but tachypnœa is still very marked, fibrillar twitchings of the tongue, intense retraction of the eye-lids, respiration 248, with rarer intervals of slow breathing. 12.45, is somewhat better, no noticeable twitching, tachypnœa recurs at intervals but stops when his attention is attracted, fibrillar tremors of the tongue persists. 1 A. M., continuous tachypnœa, 240. Dog is very awkward and stiff, conjunctivæ exposed, marked tremors and twitching in the legs, which are moderately stiff. 1.30, still a continuous marked tachypnœa, can walk only with difficulty owing to the lack of control of the legs. May 17, 9.30 A. M., dog seemed perfectly well, no twitching or fibrillary tremors of the tongue and no tachypnœa. May 18, no tetany. May 19, slight transient tetany. After this the dog was practically well until May 29, when he showed slight twitching.

6108. May 18, two parathyroids and one thyroid lobe were removed. May 20, tetany. 11 A. M., marked tetany with tachypnœa. 11.50, 25 c.c. 5 per cent. sodium bicarbonate injected into jugular vein. 11.55, twitching more violent, respiration 220. 12.00, respiration 232, tetanic spasms much more violent, injection of the sodium bicarbonate complete at 12 o'clock. At 12.15 respiration 240, twitchings very violent. 12.30, still in violent tetany with occasional tachypnœa and rigidity extreme. This continued until 8 P. M., during which time the respiration was very labored and twitchings persisted, though they became less violent toward evening. May 21, no tetany, dog is very apathetic and stuporous. May 23, dog found in violent tetany, respiration labored, 52

to a minute, extreme fibrillar twitchings of the tongue. 10.15, 25 c.c. of 5 per cent. sodium bicarbonate injected intravenously. 11.10, the twitching persisted, breathing not so labored. May 24, slight tremor but no distinct tetany. There was no tetany again, dog died June 1, after having lain in the cage in a stuporous condition during that time.

6308. May 19, thyroparathyroidectomy. May 20, marked tetany. At 12.06 respiration 240, violent muscular twitching and rigidity, fibrillar tremors of tongue. From 12.14 to 12.21, 25 c.c. 5 per cent. sodium bicarbonate were injected intravenously. At 12.22 convulsive twitchings were most violent and rigidity was extreme. 12.40, condition is similar but rather worse. 1.20, most violent tetany. 2 P. M., extremely violent attacks of tetany lasting about 5 minutes and succeeded by exhaustion. From 2.00 until 3.15 the twitchings became less marked, the body relaxed. The dog became unconscious; death took place at 3.15.

It is to be seen from these experiments that there is a very striking contrast between the effects of even very large doses of sodium bicarbonate and those of the salts of calcium in those animals in which tetany has already developed. For, while some of the animals recovered and showed no tetany next day, one at least died in the tetany without experiencing the slightest relief, and all of the others continued to show violent symptoms of tetany for hours without any such relief as was invariably observed to follow the administration of calcium.

If we imagine that there is an acid intoxication with the setting free in the tissues of excessive amounts of organic acids[34] which must be neutralized by some alkaline substances withdrawn from the tissue, among which are calcium and ammonium, it seems possible that as far as this is concerned the administration of other calcium or sodium might furnish the necessary material, but the administration of sodium would not replace in the tissues the calcium which has already been abstracted in dogs in which tetany has already developed. A minimum amount of calcium seems to be absolutely necessary for the normal function of the nervous system, and sodium cannot take its place. The administration of sodium directly after the operation, however, might well prevent any such abstraction of calcium from the tissues. More experiments than the two recorded must be performed in order to determine this point. The administration of calcium, however, would in addition to the restoring of the balance, directly restore the

[34] Lactic acid was found in blood in one case.

calcium to the impoverished tissues. Since we know that the injection of such salts as sodium chloride is without definite effects upon the tetany, it is probable that whatever beneficial influence is obtained from the injection of sodium bicarbonate is due to its basic properties after being split into sodium carbonate and carbon-dioxide.

In a number of cases an attempt was made to study the changes in metabolism which result from parathyroidectomy. In order to do this it was thought necessary to reduce as much as possible the calcium content of the food so that any error in the estimation of the amount of calcium excreted might be as small as possible. It was finally decided that the error involved in the possibility that some of the calcium of the food might pass through the intestine without having been absorbed could be eliminated best by causing the animals to fast entirely for several days before the operation, and also after the operation; they were therefore put in metabolism cages, given daily a measured amount of water but no food. Diarrhœa was prevented by the administration of kaoline or kieselguhr (free of calcium) in the water. The dog was catheterized every morning at the same hour, and 24 hour specimens of urine as well as the fæces were collected. It remained then only to analyze the urine and fæces of these dogs with respect to their ammonium content, calcium content, etc. In some of the experiments the dogs were bled at the end of the period of tetany and the calcium content of the blood determined. At autopsy the calcium content of the brain was also determined. The results of these experiments will be more clearly understood from the study of the tables which are given at the end of this paper.

As large a number of dogs as could be was studied in this way, during the time at our disposal, for the process is an extremely laborious one. This is mentioned on account of the fact that successful experiments in our series are so few. So many vicissitudes were encountered and such a large proportion of the dogs thus operated upon proved to have accessory parathyroids in their thyroid glands, that the number of complete and proved experiments is very small. In only three dogs have we succeeded in producing tetany under these conditions, and in obtaining complete records of the

analyses of the urine and fæces. In two others we have analyses of the urine and fæces after a partial extirpation of the parathyroids but without the development of tetany. In another we have the analysis of urine and fæces after the operation for the removal of the parathyroid which was not successful in bringing about tetany but which was followed by the second operation by removal of the thyroid lobes which did result in tetany from a coincident destruction of the remaining parathyroid tissue. The absence of the thyroid gland doubtless modifies the metabolic changes in this case. The analyses of the blood and of the brains were sometimes made from the dogs used for urinary and fæcal analysis, but other animals, both normal controls, and animals suffering from tetany were also used for this purpose. Objection might possibly be raised to the employment of this method of fasting of animals during the experiment, on the ground that in human beings, at least, fasting is very likely to bring about an acid intoxication with changes in the ammonium ratio in the blood and with the excretion of acetone in the urine. Numerous experiments have, however, shown that this does not follow starvation in the dog. In gross the results of the analyses which are detailed in the tables are about as follows: The blood of the dogs which were bled during an attack of tetany shows a content of calcium which is only about one-half of that of the normal dog. The ammonium content is on the other hand enormously increased, and may reach a value ten times as high as that of the normal animal. The analyses of the brain of dogs during tetany, shows the presence of a very greatly diminished amount of calcium; it being not more than about half of that found in the normal brain. The analysis of the urine and fæces should be considered in one series as representing a total excretion of calcium, etc. It is found in general, that the amount of calcium excreted in the urine decreases during the first two or three days of fasting, finally reaching a fairly constant low level. After the operation, as far as our curves indicate, there appears, during tetany a gradual rise in the amount of calcium excreted. The estimation of the total excretion of calcium is rendered difficult by the fact that the passage of fæces is extremely irregular and the calcium actually excreted into the intestines may accumulate

there during several days, so that the construction of an accurate curve is almost impossible. In order to make such a curve more accurate a much longer period of observation is required. It seems possible in future experiments that a fairly accurate idea might be obtained by washing out the intestines every day. On the whole the general impression which was received from these studies is that in the course of tetany, following parathyroidectomy, the excretion of calcium salts in the urine and fæces is somewhat increased, and the tissues of which we have examined the blood and brain, are remarkably impoverished with regard to calcium. In this way the condition described by Sabbatani and Loeb and others appears to be produced and the symptoms of tetany may well be explained on the basis of this impoverishment of calcium in the tissues. The actual amount of calcium in the tissues is so small that the loss of calcium which may appear almost infinitesimal may still be sufficient to overthrow the balance and give rise to the hyper-excitability which one observes in tetany.

It is on this basis, therefore, that the administration of large doses of a soluble calcium salt might be expected to restore the calcium content of the over-excitable tissue and thus to suppress the symptoms produced by this impoverishment. It must be observed that the administration of calcium by no means acts as a cure but merely suppresses the symptoms of a disease, the actual cure of which could be brought about only by the implantation of the parathyroid gland, or temporarily by the injection of an extract of the parathyroid gland. Nevertheless, the relief afforded by the administration of calcium, in cases of tetany, is so complete, and the animal is apparently so nearly normal under the continued administration of calcium, that it may well prove to be a therapeutic agent of some value in tiding over the period of violent tetany until some more permanent cure may be instituted.

The calcium content of the parathyroid glands themselves has been studied and found extremely minute, about equal to that of the voluntary muscle.

The bearing of these results, in so far as they offer an explanation of the various types of tetany mentioned in the beginning, is clear enough in certain classes of cases, but in others, for example

the cases of gastric tetany, it is by no means easy to understand. In osteomalacia and rickets we have evidently a common cause which leads to the decalcification of the bones and other tissues and consequently to tetany. Whether this depends upon a lesion of the parathyroids as Erdheim suggests remains to be determined. In the tetany which accompanies pregnancy and lactation, however, we can easily believe that there is no organic lesion of the parathyroid gland but that the decalcification of the tissues is directly due to the extraordinary drain upon them in the production of the bones and other calcium-rich tissues of the fœtus or in the secretion of milk which has a large calcium content. It would be of interest at least to make a therapeutic test by the administration of large doses of lime water or of any other soluble calcium salt in these cases.[35]

TABLE I.

Calcium Content of 100 c.c. of Arterial Blood.

(Obtained from carotid artery.)

Normal Control Dogs.		Tetany Dogs.	
No. 608	0.0122 gr. Ca.	No. 1108	0.0053 gr. Ca.
No. 3608	0.0140 gr. Ca.	No. 508	0.0065 gr. Ca.
No. 1608	0.0138 gr. Ca.	No. 308	0.0056 gr. Ca.
		No. 2708	0.0046 gr. Ca.
		No. 5708	0.0052 gr. Ca.

Calcium Content of 100 gr. of Dried Brain.

Control Dogs.		Tetany Dogs.	
Cerebrum	0.0841 gr. Ca.	Cerebrum	0.0472 gr. Ca.
	0.0750 gr. Ca.		0.0433 gr. Ca.
	0.0792 gr. Ca.		0.0531 gr. Ca.
			0.0510 gr. Ca.
Cerebellum	0.0560 gr. Ca.	Cerebellum	0.0326 gr. Ca.
Medulla	0.0410 gr. Ca.	Medulla	0.0323 gr. Ca.

[35] Since the publication of our preliminary report we have noticed a review in *Folia Hæmatologica,* 1908, v, 101, of an investigation by G. Parhon and C. S. Ureche, on the influence of calcium and sodium salts upon the course of experimental tetany. This was published in the *Revista Stiintelor Medical,* 1907, July and August, a journal which is unknown to the librarian of the Surgeon General's Library. They produced tetany in dogs by removing thyroids and parathyroids and found that injections of sodium chloride rather increased the symptoms, while injections of calcium chloride tended to quiet them. In both cases, however, the animals died of tetany much more quickly than the controls which had received no injections.

Ammonia Content of Blood.

50 c.c. of blood taken during tetany contain.....0.0051 gr. NH_3.
50 c.c. of blood taken from normal dog contain....0.00206 gr. NH_3.

TABLE II.

Showing Effect of Parathyroidectomy in Dogs No. 5008 and No. 5108 on Nitrogen Metabolism.[86]

Methods used for metabolism experiments were as follows:

Total nitrogen.....Kjeldahl's method.
Ammonia.....Folin's method.
Chlorides.....Titration with ammonium sulphocyanide.
Phosphates.....Titration with uranium acetate.
Creatinin.....Folin's method.

Calcium was determined as follows: Incineration of organic material, precipitation of dissolved ash with ammonium oxalate and titration of oxalic acid contained in resulting calcium oxalate with potassium permanganate. This method gives accurate results, while the amounts of calcium concerned were too small for accurate estimation by gravimetric methods.

Date.	No. 5008.				No. 5108.			
	Volume of Urine, c.c.	Total Nitrogen in gr.	NH_3-Ratio.	Remarks.	Volume of Urine, c.c.	Total Nitrogen in gr.	NH_3-Ratio.	Remarks.
May 2	185	2.51	7.26		265	3.92	6.34	
3	355	4.31	7.28		420	3.37	5.40	
4	300	3.59	7.02		320	2.40	18.41	Operation.
5	305	4.35	10.91	Operation.	325	2.43	41.84	
6	420	4.65	6.82		270	2.94	25.45	
7	315	3.54	9.21		435	3.81	20.94	
8	375	5.00	4.51		430	4.90	23.58	
9	305	4.61	4.77		210	7.61	13.63	Tetany violent.
10	365	4.44	7.14		245	4.81	29.58	Tetany slight.
11	430	2.98	10.33	Tetany slight.	255	4.86	37.31	Tetany slight.
12	475	5.99	12.00		250	5.10	33.00	Tetany slight.

Explanation of Table II.—Notice rise in total nitrogen and ammonia ratio in dog No. 5108. This animal had no parathyroids left after operation and began to show tetany May 9, and was found dead May 13. With onset of tetany volume of urine is decreased very markedly.

In dog No. 5008 operation was not altogether successful, as some parathyroid tissue was left behind. Insufficiency produced changed composition of urine to a less extent than in No. 5108. Dog showed tetany on one day only and recovered afterwards to live for a number of days without any apparent discomfort, when the thyroid was extirpated, and tetany appeared in a violent form, showing that some interior parathyroid which had not been removed at first operation was extirpated together with thyroid.

[86] *General characters of the urine after the appearance of tetany.*—The urine shows a high specific gravity and is correspondingly decreased in amount. There is a cloudy precipitate, no albumen, acetone, diacetic acid, nor sugar could be detected in any of the cases.

TABLE III.

Female Dog No. 1807. Weight 21.1 Kilos. Was Fed for the First Five Days on 800 c.c. of Milk Daily. Then Operated for Parathyroidectomy and Starved. Gets only 800 c.c. of Water now. Composition of Urine:

Date.	Volume, c.c.	Spec. gr.	Total nitrogen.	NH_3—N	NH_3 ratio.	Ca	NaCl	P_2O_5	Creatinin.	Total Acidity.
Dec. 19	710	1036	4.73	0.86	8.00	0.079	21.3	1.17	0.71	2.30
20	785	1024	5.77	0.39	6.88	0.030	17.6	0.95	0.46	1.25
21	555	1024	4.16	0.26	6.35	0.026	6.1	0.48	0.29	.44
22	410	1020	2.53	0.10	4.06	0.011	4.3	0.25	0.23	.20
23	490	1032	6.42	0.65	10.2	0.035	5.9	0.78	0.46	.49
24	350	1033	7.20	0.67	9.30	0.036	6.5	1.36	0.42	.53
25	355	1030	6.80	0.70	10.29	0.041	7.5	1.40	0.55	.59

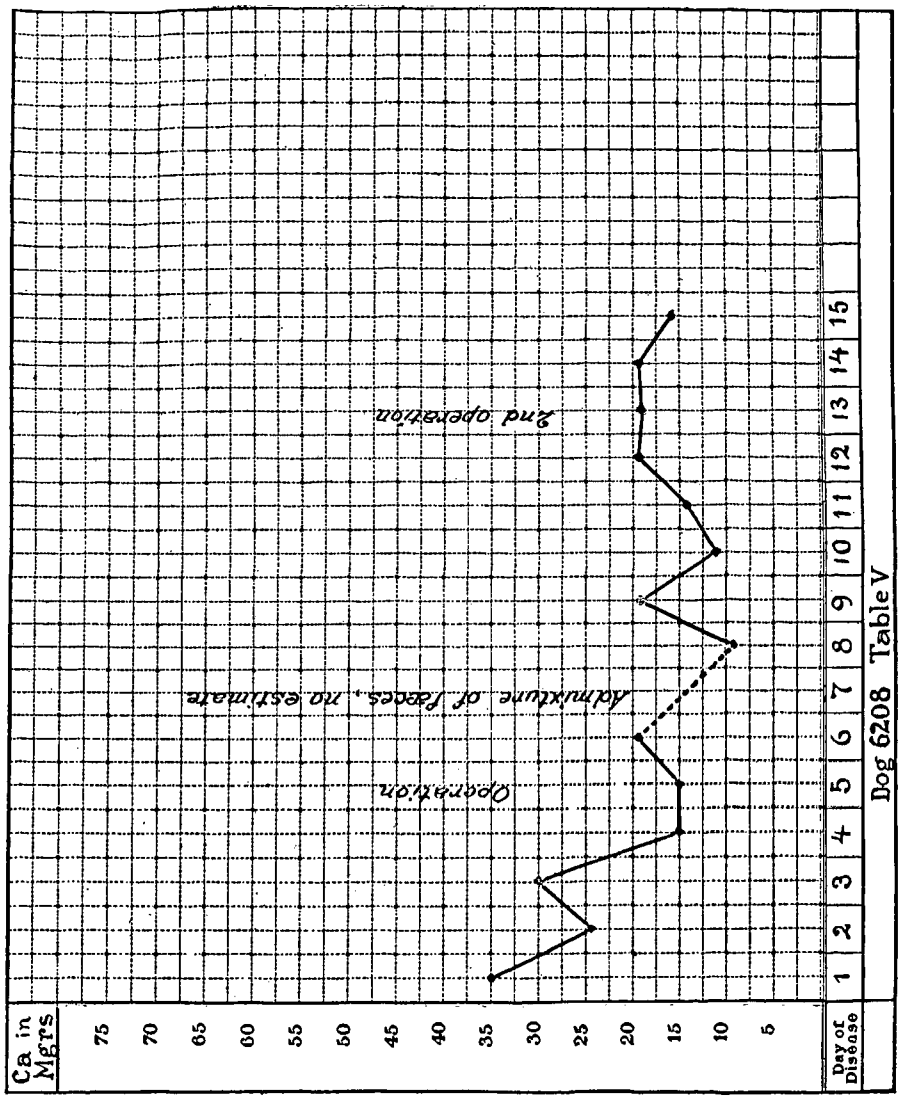
Explanation of Table III.—Dog was operated December 22. Violent tetany was observed December 24 for first time. Had several severe attacks and was found dead December 26. No fæces were obtained. Before operation animal adjusted metabolism to the low diet. From day to day less is excreted with urine. After operation all of the constituents determined are found to be present in larger quantities, in spite of the fact that animal is starving.

TABLE IV.

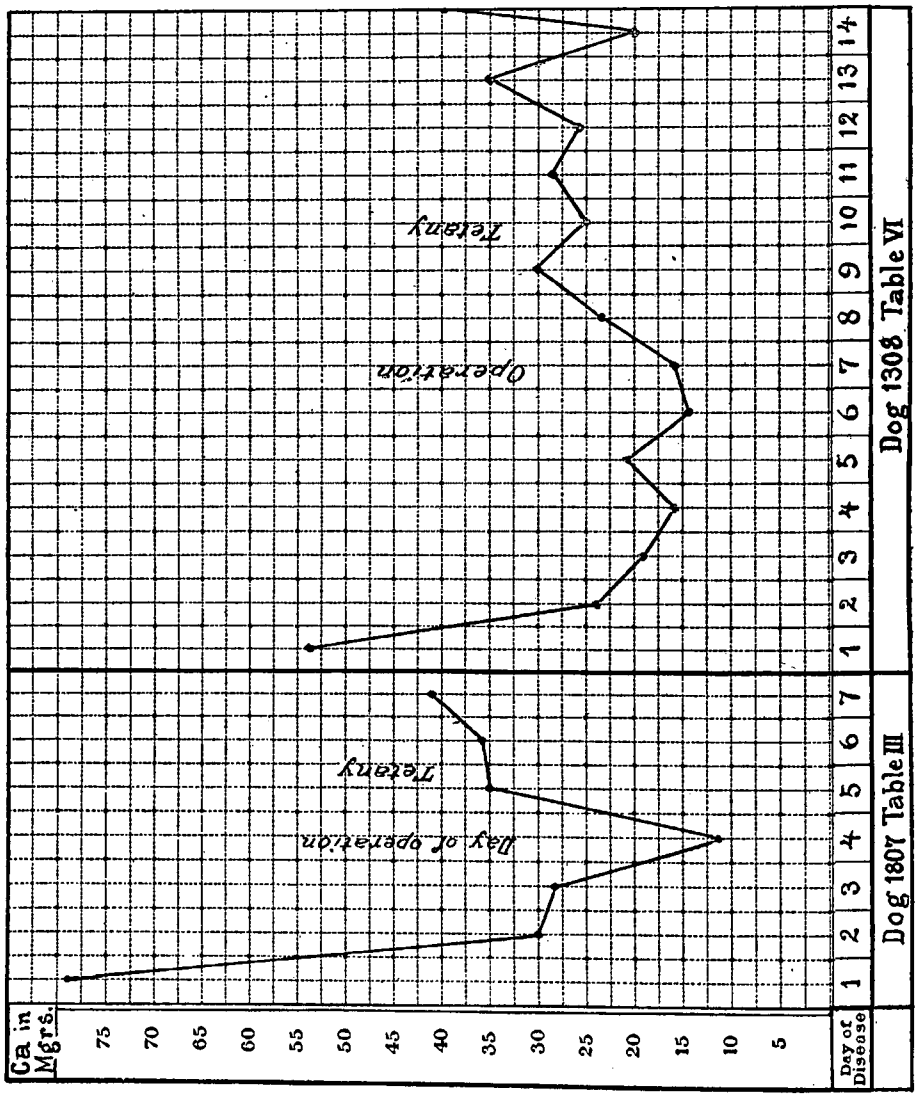
Female Dog No. 7208. Received 400 c.c. Water Daily.

Date.	Urine.		Fæces.
	Volume, c.c.	Ca in gr.	Ca in gr.
June 24	254	0.0081	
25	240	.0086	0.3279
26	265	.0098	2.5450
27	254	.0085	
28	248	.0083	1.8722
29	258	.0092	
30	300	.0092	
July 1	300	.0052	
2	230	.0061	0.7882
3	305	.0057	
4	295	.0108	
5	365	.0092	
6	285	.0087	
7	245	.0084	
8	230	.0082	

Explanation of Table IV.—This animal was kept as a control under absolutely the same condition as the ones on which parathyroidectomy was performed. Variations in volume of urine are very slight. Calcium excretion with the urine remains on about the same level with the exception of three days (June 1, 2 and 3), when calcium output is reduced approximately 30 per cent. The calcium of the fæces is decreased considerably during the course of the experiment.



CURVE 1.—The curve illustrates Table V, Dog 6208, in which parathyroidectomy was incomplete and did not result in tetany.



CURVES 2 AND 3.—Curve 2 illustrates Table III, Dog 1807. Curve 3 illustrates Table VI, Dog 1308. Both curves show the variation in the calcium output in the urine before and after the development of tetany.

TABLE V.

Large Female Dog No. 6208. Received 500 c.c. Water Daily.

Date.	Urine.				Fæces.	Remarks.
	Volume, c.c.	Sp. Gr.	Total N, gr.	Ca gr.	Ca	
May 24	585	1010	4.82	0.035	0.533	
25	520	1010	3.88	.024		
26	560	1010	3.95	.030		
27	460	1008	3.79	.015		
28	480	1000	3.72	.015		First operation.
29	670	1006	4.19	.019		
30	370	1009	3.09	.048	1.177	Urine contains small amount of intestinal mucus fæces.
31	500	1010	4.41	.009		
June 1	390	1010	3.93	.018		
2	410	1008	3.59	.011		
3	480	1006	3.94	.013		
4	470	1008	3.81	.019	2.263	
5	440	1008	—	.018		Second operation.
6	450	1009	—	.019		
7	460	1010	—	.016		

Explanation of Table V.—At first operation four parathyroids were removed, but no signs of tetany appeared afterwards. June 5 another operation was performed, but no parathyroid could be found. On June 17 both thyroid lobes were removed and tetany appeared, showing that some interior parathyroid was extirpated together with thyroid. This shows clearly that a comparatively small amount of parathyroid tissue is able to keep up metabolic processes well enough to prevent the appearance of tetany. The composition of the urine of this animal is practically the same as in the normal control (Table IV) whereas the calcium in the fæces shows an increase.

TABLE VI.

Large Female Dog No. 1308. Put into Cage March 13. 500 c.c. Water Daily. Weight at Beginning of Experiment 19.2 kilos.

Date.	Urine.					Fæces.	
	Volume c.c.	Spec. gr.	Total N	Cl as NaCl	Ca	Ca	Remarks.
March 15	610	1021	4.86	4.10	0.053		
16	480	1020	4.72	3.2	0.024		
17	355	1022	4.88	2.2	0.018		
18	425	1021	4.28	2.6	0.016		
19	440	1020	4.84	2.7	0.021	0.127	
20	430	1019	3.69	2.6	0.014	0.003	
21	450	1018	3.15	3.1	0.016	0.153	Operation.
22	435	1018	3.94	2.9	0.023		
23	505	1013	4.28	3.2	0.030		
24	430	1020	6.73	2.9	0.025		Violent tetany.
25	330	1030	9.26	2.3	0.028		
26	350	1042	7.79	2.4	0.026		
27	340	1042	10.50	2.3	0.035		
28	170	1042	5.62	1.1	0.019		
29	140	1055	4.33	0.94	0.039	1.368	

Explanation of Table VI.—March 21, eleven distinct parathyroids are removed. March 24, tetany appears and can be noticed daily until exitus, March 29. Notice great decrease in volume of urine at onset of tetany. Specific gravity is correspondingly increased. After operation total nitrogen begins to rise and this becomes especially prominent when tetany sets in. Calcium output in urine is increased by 90 to 100 per cent. of the amount before operation. The daily output of calcium in fæces before operation 0.04 gr., after operation 0.17 gr.

TABLE VII.

Large Female Dog No. 2708. Weight 20.5 kilos. 500 c.c. Water Daily.

Date.	Urine.						Fæces.	Remarks.
	Volume c.c.	Spec. gr.	Total N.	NH_3N	NH_3 ratio.	Ca	Ca	
March 15	580	1010	3.98	0.22	5.6	0.016		
16	540	1016	3.63	0.26	7.3	0.013		
17	490	1016	4.35	0.24	5.5	0.015	1.754	
18	510	1017	6.63	0.31	4.7	0.013		
19	470	1016	3.42	0.23	6.7	0.021		
20	470	1017	3.68	0.21	5.8	0.021		Operation.
21	410	1020	4.29	0.33	7.8	0.025	0.936	
22	560	1010	3.17	0.28	9.1	0.014		
23	480	1012	4.05	0.26	6.5	0.011		
24	430	1010	3.67	0.43	11.5	0.011		
25	515	1012	3.69	2.06	55.9	0.011		
26	440	1016	3.68	1.98	53.9	0.010		
27	650	1010	3.66	1.46	40.0	0.013		
28	460	1012	3.59	1.71	47.4	0.012		
29	320	1012	2.38	1.16	48.9	0.016		
30	370	1012	3.55	1.78	50.2	0.008		
31	500	1008	3.46	1.67	48.3	0.015	2.173	Operation.
April 1	345	1020	3.26	1.43	43.8	0.016		
2	600	1012	3.31	1.62	48.8	0.092		Tetany.
3	375	1029	4.43	2.04	46.1	0.012		"
4	260	1032	4.45	1.75	39.3	0.019		"
5	620	1010	4.13	0.45	10.9	0.014		"
6	180	1036	4.96			0.015		"
7	187	1039	5.49			0.015		"
8	190	1038	5.82			0.012		"
9	185	1031	3.33			0.013		"
10	160	1032	2.67			0.011		"

Explanation of Table VII.—March 19, incomplete parathyroidectomy was performed. No tetany followed operation, but ammonia ratio was increased very much. No abnormality in other constituents of urine. March 31, complete thyroidectomy. Second day after operation violent tetany, accompanied by a great rise in the urinary calcium for one day only. Volume of urine became extremely small and specific gravity correspondingly high. Total nitrogen increased until the last two days when animal was found exhausted. Nothing conclusive can be found in the calcium excretion with the fæces. One point of special interest in this experiment is the behavior of the ammonia ratio. This latter increases rapidly after the production of parathyroid insufficiency, in spite of the fact that no clinical symptoms can be observed. After complete thyroparathyroidectomy ammonia ratio shows a tendency to fall.

CONCLUSIONS.

1. Tetany occurs spontaneously in many forms and may also be produced by the destruction of the parathyroid glands. Recent researches tend to demonstrate an intimate relation between the various forms of tetany and relative or absolute insufficiency of the parathyroid gland.

2. The parathyroid glands are independent organs with definite specific function. Whether or not this function is intimately related to that of other organs of internal secretion is not as yet proven.

3. The number and distribution of the parathyroid glands varies. Failure to produce tetany experimentally is probably due to the fact that some parathyroid tissue remains after an apparently complete extirpation. When extirpation is complete tetany appears, even in herbivora. Only a very small amount of parathyroid tissue is required to prevent this.

4. The effect of the extirpation of the parathyroid glands may be annulled by the reintroduction of an extract of these glands even from an animal of widely different character. The active principle is associated with a nucleo-proteid in the extract and may be separated with this nucleo-proteid from the remaining inert albuminous substances. Its effect in counteracting tetany appears some hours after injection and lasts several days.

5. The parathyroid glands contain no considerable amount of iodine. The parathyroid extract is not an iodine containing compound.

6. In tetany there is apparently some disturbance of the composition of the circulating fluids ordinarily prevented by the secretion of the parathyroid, which disarranges the balance of the mineral constituents of the tissues. Possibly this consists in the appearance of an injurious substance of an acid nature for such tetany may be relieved by extensive bleeding with replacement of the blood by salt solution. No actual poisonous material has, however, been demonstrated by the transference of the blood of a tetanic animal to the veins of a normal one.

7. Numerous researches have shown the important relation of the calcium salts to the excitability of the central nervous system.

Their withdrawal leaves the nerve cells in a state of hyperexcitability which can be made to disappear by supplying them with a solution of a calcium salt.

8. Tetany may be regarded as an expression of hyperexcitability of the nerve cells from some such cause.

9. The injection of a solution of a salt of calcium into the circulation of an animal in tetany promptly checks all the symptoms and restores the animal to an apparently normal condition.

10. Injections of magnesium salts probably have a similar effect but these effects are masked by the toxic action of the salt.

11. The injection of sodium or potassium salts has no such beneficial effect but rather tends to intensify the symptoms. This is true also of the alkaline salts of sodium which were studied especially in respect to their basic properties.

12. The effect of calcium is of value in human therapeutics in combating the symptoms of spontaneous forms of tetany and in relieving the symptoms in cases of operative tetany and thus tiding over the period of acute parathyroid insufficiency until remnants of parathyroid tissue can recover their function or new parathyroid tissue can be transplanted. It is in this way an important and convenient ally of the method of injecting parathyroid extract.

13. Studies of the metabolism in parathyroidectomized animals show:

1. A marked reduction in the calcium content of the tissues especially of the blood and brain, during tetany.
2. An increased output of calcium in the urine and fæces on the development of tetany.
3. An increased output of nitrogen in the urine.
4. An increased output of ammonia in the urine with

4*a*. an increased ammonia ratio in the urine.

5. An increased amount of ammonia in the blood.

Much of this affords evidence of the existence of some type of acid intoxication. Its effects are, however, not neutralized by the introduction of alkaline sodium salts and may perhaps be regarded as especially important in producing a drainage of calcium salts from the tissues which can be remedied by the reintroduction of calcium salts.

14. Emphasis must be laid upon the remarkable difference which exists between the alterations in metabolism following thyroidectomy and those following parathyroidectomy. In myxoedema there is lowered metabolism, decreased respiratory changes and lowered nitrogen output with depression of body temperature. In tetany there is increased metabolism, probably increased respiratory changes, certainly increase in nitrogen output and elevation of the temperature.

15. It is important, therefore, that in any experiments upon metabolism in relation to the thyroid and parathyroid gland, these glands should be clearly distinguished as structures exercising very different and in large part contrary effects upon metabolism.

16. In general the role of the calcium salts in connection with tetany may be conceived of as follows: These salts have a moderating influence upon the nerve cells. The parathyroid secretion in some way controls the calcium exchange in the body. It may possibly be that in the absence of the parathyroid secretion, substances arise which can combine with calcium, abstract it from the tissues and cause its excretion and that the parathyroid secretion prevents the appearance of such bodies. The mechanism of the parathyroid action is not determined, but the result, the impoverishment of the tissues with respect to calcium and the consequent development of hyperexcitability of the nerve cells, and tetany is proven. Only the restoration of calcium to the tissues can prevent this.

17. This explanation is readily applicable to spontaneous forms of tetany in which there is a drain of calcium for physiological purposes, or in which some other condition causes a drain of calcium. In such cases the parathyroid glands may be relatively insufficient.