STUDIES ON PARATHYROID TETANY

by

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A Thesis

Presented to the Faculty of the Graduate School of the

University of Oregon.

In partial fulfillment of requirements for the degree of

MASTER OF ARTS.

JUNE 1927.

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Introduction

The parathyroid glands in the dog consist of four small bodies so intimately associated with the thyroid glands that when the latter are removed the former are almost invariably included. The glands are oval shaped and measure about six millimeters in length, three millimeters in width and two millimeters in thickness. They weigh, in all, about fifty centigrams. The dimensions and location are subject to marked variation according to Cowdry (12). In fifty per cent of the cases studied in dogs by Berkeley and Beebe (3) it was found that the internal or superior pair of parathyroid glands was located on the cephalic pole between the branchings of the superior thyroid artery. The external or inferior pair was found on the lateral aspect of each lobe midway between the poles. In the human, according to Cowdry, the location of the superior pair of parathyroids occurs on the medial aspect of the dorsal surface of each lateral lobe of the thyroid gland at about the junction of its upper and middle thirds. The inferior pair have a similar location but are more caudad.

The parathyroids receive a rich blood supply from the inferior thyroid artery, and are innervated by the sympathetics. Two types of glandular elements are present, namely: (a) the chief cells which are large polygonal cells having clear cytoplasm with faintly staining nuclei; (b) the oxyphyl cells, the cytoplasm of which stains strongly with eosin and the nucleus with hematoxylin.

Embryologically the parathyroid glands are derived from thickenings of the endoderm of the third and fourth branchial clefts. The glandular histology is described as consisting of columns or clumps of epithelial cells separated more or less by bands of connective tissue which are continuous with the capsule, which is also of connective tissue.

The physiological importance of muscle is in direct ratio to its size. This cannot be said of parathyroid tissue for its importance is in indirect ratio to its mass. Limited as this tissue is, its presence in the body in an unaltered state is absolutely essential for its normal functioning. The removal of these glands leads to a group of symptoms spoken of as tetania parathyropriva. This tetany, as defined by Barker (2), is a clinical syndrome characterized by a peculiar hyperexcitability of the nervous system (motor, sensory and autonomic) and in marked cases by spontaneous attacks of peculiar tonic spasms which involve either certain groups of muscles or the entire body musculature. A characteristic point in the diagnosis of experimental and clinical tetany of parathyroid origin is the ability to demonstrate Erb's phenomenon.

Parathyroid tetany varies in severity in different species, the most severe form occurring in carnivorous animals such as the dog, fox and cat. In untreated parathyroidectomized dogs, a syndrome develops which leads to death in from five to ten days. In dogs treated by any one of the several methods mentioned below, life may be sustained for indefinite periods of time.

The first symptoms to develop appear on an average within twelve to seventy-two hours. These are anorexia, restlessness, excitability, anxiety and itching of the nose. Later there develops

an inflammation of the conjunctival and nictitating membraned and an increase in the respiratory rate. This latter group of symptoms vary in their severity and in the constancy of their appearance. Following the preliminary symptoms there appear at intervals varying from one to five hours, clonic muscular twitchings which are usually seen in the isolated muscles of the back. Frequently, however, the posterior extremities and sometimes the anterior become involved in these early clonic spasms. The animal at this time is usually stiff gaited and awkward. Unless treatment is given, the clonic spasms soon become tetanic and these fast develop into complete body rigidity. The respirations increase rapidly until at last the animal is prostrated with the rigidity and air hunger. He may die in this first attack from laryngeal spasm but usually will recover and no signs of tetany will be manifested until two or three days later when another attack of severer character develops.

Often times, before entering the stage of prostration there is frequent snapping of the jaws which may injure the tongue severely since it is usually protruding. In many cases saliva, at this time, flows copiously from the mouth. During the first attack the rectal temperature reaches 104 to 105 degrees. In the second attack, in addition to the more severe convulsions, the rectal temperature may rise to as high as 108 to 109 degrees. With the increase in respirations, there occurs also a mild or severe frothing at the mouth and involuntary acts of urination and defecation. During the height of the attacks the animal will sometimes throw himself into the air repeatedly. This aggravates the air hunger and hastens the prostration. In the latter condition the legs are stretched out rigidly and the head is drawn back upon the neck. Respirations

may actually stop for a few moments to be gradually resumed if the animal is to recover. After a time the legs will relax, breathing will become easier and the animal will get up and walk about. The attacks follow one another with increasing severity and frequency. The spasm involves the muscles of respiration which, if severe enough and sufficiently prolonged, will result in a decrease in oxidations, a drop in body temperature and death. The contrast exhibited by a dog over a short time is very marked. One hour he may appear normal in every respect and the next hour be lying in his death struggle.

In contrast to this picture of violent tetany is the description given in 1908 by Thompsom and Leighton (81) who found that after ligation of all the blood vessels to the parathyroids, the dog did not develop tetany and passed through the usual critical post-operative period with practically no untoward symptoms. Gradually, however, there was a progressive loss of weight and strength, a greatly diminished resistance to infection and a final stuporous condition terminating in death without tetany. MacCallum (58) in 1903 noted that the acute symptoms were occasionally followed by a stuporous condition which gradually increased in severity and led to death without tetany.

It has been thought that the cachexia noted by Thompson and Leighton and by MacCallum was due to the loss of the thyroids, but this cannot be true since it developed when only the parathyroids rere removed. The true explanation for this condition is, at present, not apparent.

Until recently, in our own experience, the animals that had recovered from the stage of acute tetany were never as active or

playful as normal animals. They manifested various degrees of malaise and depression. The only exception to this statement is in regard to more recent work in which animals were given yeast and cod liver oil, the details of which will be given later. These dogs remained more active than any others so far observed.

As a further summary of the various types of tetany, the following may be enumerated:

1. Infantile tetany (spasmophilia).
2. Tetania strumipriva (parathyreopriva).
3. Gastro-intestinal tetany.
   (a) Tetany due to stenosis of the duodenum.
   (b) Tetany due to spasm or stenosis of the pylorus.
   (c) Tetany in colonic dilatation.
   (d) Tetany in Helminthiasis.
4. Tetany due to hyperpnea.
5. Idiopathic tetany.
6. Rachitic tetany.
7. Tetany of alkalosis.
8. Methyl Guanidin tetany.
9. Tetany of anoxemia.
10. Tetany due to administration of alkaline or neutral phosphate
11. High sodium chloride tetany.
12. Low Calcium tetany.
13. Tetany associated with infectious diseases.
14. Tetany associated with intoxications.
15. Maternity tetany.
   (a) Lactation.
   (b) Pregnancy.
   (c) Puerperal.

Historical.

The earliest recorded experiments bearing on the parathyroid glands are those of Raynard (72) in 1835. He removed the thyroid glands from a number of dogs and found that death frequently resulted in the course of a few days. Schiff (76) in 1859 removed the thyroids from various animals and concluded from his results that the removal of the thyroid glands of rats and rabbits was followed by no untoward symptoms but in dogs and cats death invariably followed within a few days. Sandström (74) in 1880 is credited with being the first to describe the parathyroid glands. In 1891 Gley (33), in removing the thyroid gland in a goiter operation, described a condition of tetany that followed. This resulted in the rediscovery of the superior pair of parathyroid glands, knowledge of which had been lost for eleven years.

Gley, following his discovery of the external pair of parathyroid glands, demonstrated that the acute symptoms of muscular twitching, dyspnea and death were due to the removal of the parathyroids and not to the thyroids alone. Kohn (50) in 1895 discovered the inferior or external parathyroid glands. He recognized that every animal had four parathyroid glands and believed them to be different in structure and function from the thyroids with which they were so closely related. Gley at this time, however, held that the parathyroids represented embryonic thyroid tissue. In 1900 Vasalle and Generale (82) parathyroidectomized ten cats and nine dogs, leaving the thyroid practically intact. Nine of the cats died within ten days, after exhibiting anorexia, a peculiar stiffness in gait, depression, muscular spasms, tachycardia, emaciation and a fall in temperature. The nine dogs showed their first

symptoms on the second or third day following the operation and were all dead within eight days. Vassale and Generale recognized that these glands were essential to life and that they were the first to employ the toxin theory in explaining the cause of tetany. To the parathyroid glands were attributed the function of neutralizing the toxin.

Jeandelize (47) in 1902, noted that parathyroidectomy caused death from the development of acute tetany. Vincent (84) in 1904, reported that neither the thyroids nor the parathyroids were essential for life. He believed that when the thyroids were removed the parathyroids became capable of functionally replacing them to a certain extent and that their histological structure changed accordingly. Forsythe (30) in 1908, in his study of the parathyroids, came to the conclusion that they were embryonic forms of the thyroids and that they might assume the structure and function of the thyroids at times when the latter might be functionally deficient.

The physiology of the parathyroid glands is now understood somewhat better than at the time of Vincent and Forsythe. Certain functions ascribed to them can be definitely demonstrated but there still remains much that is unknown. One of the functions which is known to be possessed by the parathyroids is the regulation of such metabolic affairs as are necessary for the non-appearance of tetany. The multiplicity of hypotheses and theories which are offered in explanation of this role of the parathyroid glands is a confession of an ignorance of their real functioning in this respect. A discussion of the different theories of the pathogenesis of tetania parathyreopriva is best made upon a chronological basis.

Loeb (55) and Howell (41) in 1899, by depriving excised muscles of calcium and exposing them to a solution of calcium free

salts, observed rhythmical contractions in the muscles which occasionally left them in a state of tonic contraction. Sabbantini (75) in 1901, observed that convulsions and muscular twitchings were produced by the intravenous injection of trisodic citrate solution. He relieved this condition by the administration of calcium intravenously. Binger (7) observed that oxalates and fluorides precipitated calcium in vivo and produced tetany. He also found that neutral phosphate injected by vein caused blood calcium to drop from 11.3 milligrams to 5.6 milligrams one hour after the injection.

In 1908, MacCallum and Voegtlin (59) observed an increased excretion of calcium both in the urine and the feces, following parathyroidectomy. They also reported a reduction in the calcium content of the brain of a dog that had died from parathyroid tetany. These workers furthermore found that intravenous injections of a soluble calcium salt relieved violent tetany. One year later they (60) demonstrated that in parathyroid tetany there was a lowered calcium content of the tissues and body fluids, especially of the blood. They also demonstrated that calcium salts injected intravenously caused the convulsions of tetany to cease and the animal to be restored to a normal condition. From such data as the foregoing MacCallum and Voegtlin (59) formulated the calcium deficiency hypothesis as best meeting the requirements of an explanation of these phenomena.

In the treatment of tetania parathyreopriva, many different calcium salts have been used. Compere and Luckhardt (13) studied the efficiency of various salts and reported that calcium lactate, nitrate and acetate were equally potent in relieving tetany. Calcium carbonate is effective to a less degree and, in addition, is more constipating than the lactate, acetate or nitrate. Calcium

chloride is effective but is too irritating for continuous use. Since the lower bowel is the site of elimination of the major portion of the excreted calcium, Ivy (44) and Oldberg (45) have furnished further evidence in favor of the calcium deficiency hypothesis by showing that in most dogs parathyroidectomy did not result in tetany if the colon had been entirely removed some two weeks previously. Salvesen (73) believes the function of the parathyroids is to control the calcium level of the blood. He not only found that calcium is very rapidly excreted through the intestines and the urine in tetany but that there is an increase in blood phosphate. He was able to keep his dogs alive for many months after thyreo-parathyroidectomy by giving them calcium and milk. As a result of his experiments, Salvesen does not believe that recovery of parathyroidectomized dogs is due to a compensatory hypertrophy of accessory glands because if such were the case the blood calcium would return to normal. Collip (14), however, does not accept this in toto and offers no justification for his stand. He and his coworkers (15) (16) (17) (18) support the calcium deficiency theory and have added much to advance the knowledge of the physiology of the parathyroid glands.

Luckhardt and Goldberg (56) have prevented tetany in completely parathyroidectomized dogs by the administration of ten grams of calcium lactate in water by stomach tube twice daily. The diet, which consisted of meat and water, is known to augment the development of violent tetany in parathyroidectomized dogs. By withholding the calcium twenty-four hours severe tetany developed. They have also treated their dogs with peroral administration of calcium lactate and milk and have thus prevented tetany and death. Previous to the work of Luckhardt and Goldberg, it was held that calcium

salts were of value only in the relief of tetany and not in its prevention.

Greenwald (35) consistently found a lowered calcium content of the serum and a diminished excretion of phosphates in the urine following parathyroidectomy. Martin (64) states that the spasms of tetany are intrinsically muscular and are due to the breaking down by chemical influence of the lactacidogen of the muscles involved. He believes that calcium at its normal concentration in the blood inhibits this break down. Bergeim (4) has shown that lactose promotes a greater absorption of calcium than does other sugars. This is a significant fact in view of the work done by Dragstedt et al (24) (25) (26) who were able to prevent tetany by the use of a diet made up of lactose, milk and white bread.

Opposed to the calcium theory is the fact demonstrated by Luckhardt and Rosenbloom (57) that calcium free Ringer's solution when perfused freely into the animal will prevent or control parathyroid tetany over a considerable period of time. Relief of tetany by the intravenous injection of normal blood, normal saline, by bleeding or by transfusion of normal blood is further evidence against the calcium deficiency theory.

As further confirmation of the calcium theory must be cited the discovery of a potent parathyroid extract which, when administered to either normal or parathyroidectomized dogs, will raise the calcium content of the blood or, when given to the latter alone, will relieve or prevent tetany. Parathyroid extracts were employed by Vincent and Jolly (85) in 1904, Moussu (65) in 1898, MacCallum (58) in 1905 and Berkeley and Beebe (3) in 1909.

In 1924 Hansen (39) prepared a hydrochloric acid extract of bovine parathyroid glands which he used in the relief of parathyroid

tetany and also in the treatment of many other diseases. Collip (19) in 1925 obtained a parathyroid hormone which prevented and controlled parathyroid tetany and also produced hypercalcemia in normal dogs.

In 1900 the toxin theory was advanced by Vassali and Generali (82) as an explanation of parathyroid tetany. They made some very excellent observations in support of this theory such, for example, as the greater severity of tetany in young dogs than in old ones. Young animals, in general, are more susceptible to infections and toxemias than old ones because those very experiences, in a mild degree, constitute the process they must go through in order to build up the resistance which characterizes the older animals. In 1909 MacCallum and Voegtlin (62) observed that the withdrawal of approximately one-third of the blood from an animal in the acute stages of parathyroid tetany and replacement of the same with normal saline solution promptly relieved the symptoms. This was confirmed by Berkeley and Beebe (3) in the same year. The latter also observed that a substance which they assumed to be a toxin acted centrally in a manner similar to strychnine, ammonia and the xanthin substitution products. MacCallum (58) further demonstrated that severance of the motor nerve to any group of muscles prevented those muscles from taking part in the tetany. Later (in 1912) by causing blood from a dog in tetany to flow through the leg vessels of a normal dog, he (61) demonstrated an excitability identical to that found during parathyroid tetany. In 1911 Joseph and Meltzer (48) showed that the injection of sodium chloride solution without previous bleeding would allay the muscular twitchings of parathyroid tetany. Dragstedt (27) demonstrated that intravenous injections of sodium chloride and glucose as well as Ringer's solution also were beneficial in the treatment of tetany.

Further support to the toxin theory is given by the work of Clara Jacobsen (46) who transfused the blood from a dog in tetany to a normal dog and produced a demonstrable increase in the excitability of the nerves of the leg receiving the blood.

In 1909 MacCallum and Voegtlin shifted their allegiance from the calcium deficiency hypothesis to an acid toxin theory. They were unable to show, however, that tetany could be relieved by the administration of sodium bicarbonate although in a few cases it seemed to exert a beneficial effect.

Dragstedt and coworkers (24) (25) (26) came to the conclusion that the parathyroids constitute a detoxicating mechanism and furthermore found evidence that the liver may assume the function of the parathyroids. The fact that they were able to keep dogs alive indefinitely without showing tetany by feeding them a diet of milk bread and lactose furnished evidence which led them to formulate the idea that under certain conditions, due to bacterial activity in the intestines, certain products are formed in excess which, when absorbed, lead to a toxic condition resulting in tetany. It should be observed,however, that the diet used by Dragstedt offers as much, if not more, support to the calcium deficiency hypothesis than it does to the toxin theory for it not only supplies calcium but, because of its lactose content increases, according to Bergeim (4), the absorption of calcium from the intestine.

Blumenstock and Ickstadt (8) in 1924 studied the effects of parathyroidectomy on dogs following the establishment of Eck fistulae and found that tetany was delayed in appearance and that there was a diminution in the severity of the characteristic symptoms. This, they believe, contributes evidence in favor of the theory of the toxemia. They ascribe to the liver the function of modifying the

toxins absorbed from the intestine thus rendering them more toxic. In the absence of the parathyroid glands, the toxins are not neutralized and tetany results.

Greenwald (35) takes the view that there is no toxin in the blood which can be considered as being the cause of tetany.

Early investigators observed the similarity existing between parathyroid tetany and tetany resulting from the injection of certain guanidines. As early as 1909, Berkeley and Beebe (3) found that the tetany produced by the administration of ammonia and xanthin was promptly relieved by calcium and strontium salts.

MacCallum and Voegtlin (62) in 1909 after they had abandoned the idea that parathyroid tetany was due to a deficiency of calcium, were able to demonstrate an increased output of ammonia nitrogen in the urine of dogs whose parathyroids had been removed. They interpreted this as indicating that in the absence of the parathyroids there occurred an increase in guanidin derivatives in the blood. Koch (51) in 1912 and 1913 described the presence of methyl guanidin and other bases in the urine following parathyroidectomy. Paton and his co-workers found a similar increase in methyl guanidin in the blood and supported the conception that tetany was due to increases in these bases in the blood. Findlay and Sharpe in 1920 (29) and Nattras and Sharpe (66) in 1921 observed an increased amount of guanidin in the urine of adults suffering with tetany. Lestocquoy (54) believes that the increase in guanidin following parathyroidectomy is significant.

Wilson, Stearns and Janey (86) showed that the increased excretion of ammonia only begins after muscular action is in evidence and probably is produced in an attempt to neutralize the resultant acidosis. This would discredit the guanidin theory. Greenwald (36)

in 1911 found that the excretion of nitrogen was increased only after the onset of tetany when the muscular action was increased and that the proportion of total nitrogen excreted in the form of ammonia was very little if at all increased. He stated that the concentration of ammonia in the blood during tetany was not higher than in normal animals.

Carlson and Jacobsen (11) observed that the ammonia content of the blood of dogs suffering from parathyroid tetany is not appreciably greater than that of normal dogs and that the intravenous injection of calcium salts in quantities sufficient to suppress completely the spasmodic symptoms in these animals does not reduce the concentration of ammonia in the blood. They have noted the fact that calcium salts have a much slighter effect on tetany produced by ammonia than on parathyroid tetany. Voegtlin and MacCallum noted in incipient parathyroid tetany that the peripheral nerve excitability was increased and that the intravenous injection of ammonia salts had a preventive effect rather than the opposite.

Collip, basing his judgment on his own observations, is of the opinion that guanidin intoxication bears no relationship to parathyroid tetany. He was unable to demonstrate an increase in methyl guanidin in the blood of parathyroidectomized animals and could find no antagonism between the parathyroid hormone and guanidin

Salvesen found that the non-protein nitrogen and urea in the blood was normal during tetany.

In view of these results it would seem that there is sufficient evidence to disprove the guanidine theory although the findings of Paton and his coworkers present a strong argument for it.

In 1925 Wilson and his collaborators (86) advanced the opinion that parathyroid tetany was due to an upset in the acid-base balance

of the body. They found that the ammonia excretion following parathyroidectomy diminishes at first but that it increases with the onset of convulsions. This, they hold, points to the development of an alkalosis after parathyroidectomy which is relieved by the acidosis produced during the convulsions. The convulsions are therefore interpreted as being due to a physiological response on the part of the body by which it produces a compensatory acidosis.

Togawa (80) also supports the contention that tetany is caused by a derangement in the acid-base balance since he has found an acidosis in tetany accompanied by an increased excretion of ammonia. The work of Dragstedt (24) also may be cited as further support for this view. This worker administered hydrochloric acid by vein and thereby raised the blood serum calcium which temporarily relieved tetany. The period of survival of such animals is considerably prolonged but recovery as a rule does not occur. Moreover Dragstedt was not able to obtain a consistent rise in the serum calcium concentration.

Gamble and Ross (31) found that the ingestion of ammonium chloride and hydrochloric acid led to an increased excretion of phosphates and fixed alkalies in the urine and that calcium chloride and hydrochloric acid caused an increase in the total calcium of the plasma. However, the administration of ammonium chloride did not raise the lowered calcium content of the plasma found in tetany. Gamble, Ross and Tisdall (32) further reported that the ingestion of hydrochloric acid producing substances increased the serum calcium level, and formulated the statement that the less the phosphate of the blood , the greater will be the calcium, and the greater the calcium the more will the phosphates be excreted in the urine and feces.

Bogert and Kirkpatrick (9) found that the total excretion of calcium during a period on a base forming diet was lower than when an acid forming diet was used. It would thus appear that calcium is retained better on a basic diet than on an acid one.

Voluntary hyperpnea, by washing out the carbon dioxide of the blood, will cause a corresponding rise in blood phosphate ultimately leading to the production of tetany. In 1920 Collip and Backus (21), Grant and Goldman (34) and Stewart and Haldane (78) found that the calcium content of human serum could be raised ten to twenty per - cent by the ingestion of calcium chloride or ammonium chloride or by breathing six to seven per cent carbon dioxide. They showed that it could also be lowered ten to twenty percent by the ingestion of sodium bicarbonate.

Boyd, Austin and Ducey (10) showed that the frequency and severity of tetanic attacks could be reduced by oral administration of ammonium chloride.

MacCallum (61) and Berkeley and Beebe (3) by employing calcium, strontium, magnesium and barium salts were able to relieve tetany. However, the magnesium salts were very depressing and the barium compounds so toxic that only small doses could be given without fatal results. The calcium and strontium salts were found to be harmless when administered by vein. Sodium and potassium salts were shown by MacCallum and Voegtlin (62) to be without beneficial effect.

Sloane (77) was able to successfully carry completely parathyroidectomized dogs through four or five successive attacks of tetany occurring at intervals of four to seven days by injections of morphine sulphate. Both morphine sulphate and magnesium chloride owe their activity to their depressing action.

Experimental.

The purpose of this work was an attempt to ascertain the mechanism or mechanisms by which dogs were enabled to establish a compensation following parathyroidectomy and thus be able to live indefinitely thereafter. This problem was pursued along two main lines. One was the use of various therapeutic measures as an aid in enabling dogs to compensate for the loss of their parathyroids, and the other was the employment of different methods calculated to produce tetany in dogs who had established a compensation and showed no tetany even though on a mixed diet. It was hoped that each method would throw light on the mechanism of compensation that could not be obtained from the study of one alone.

For purposes of brevity and to obviate repetition, no detail of the different methods used in the treatment of these experimental animals or of the results obtained will be given.

Thirty-two dogs have been thyroparathyroidectomized in the course of this study. Atropine and usually morphine were administered before each operation. Ether was the anesthetic used. Serum calcium estimations were made by Collip and Clark's (17) modification of the Kramer and Tisdall method (52). For the estimation five cubic centimeters of blood were drawn from the saphenous vein or from heart puncture.

All of the animals except those on cod liver oil and yeast received the same stock diet. This consisted of a daily portion of 1000 grams of rolled oats mush cooked in beef broth and 500 to 600 c.c. of milk. In addition to this 250 grams of hamburger was given twice a week along with a variable number of bones having on them small amounts of meat. The dogs receiving the yeast and oil were given daily a stock diet of 500 to 600 c.c. of milk and 140 to 150

grams of dog biscuit. As a supplemental feeding, 250 grams of hamburger was added twice a week.

Observations of the animals were made daily except for one or two occassions when absences were unavoidable. Attendance upon these animals was not maintained at night.

Of the thirty-two parathyroidectomized dogs only five thus far have established a permanent compensation. Because of the development of mange it was necessary to kill one of these, six months and seven days after the operation. Fourteen animals were unable to establish any compensation and died within a few days after the operation. The thirteen remaining dogs were able to build up a partial compensation and lived from sixteen to forty-one days. They died either during the night or at other times when I was obliged to be absent. Because of the uniform success which attended most of the efforts to relieve tetany when it occurred during the day, I feel that they would have been equally as successful if applied at night and since most of this latter group died at night or other times when I was absent, I feel that this group should be classed along with those that established a permanent compensation. They were, of course, unavailable for the pursuit of the second phase of the experiment.

The different substances used to enable the dogs to compensate for the loss of their parathyroid glands were: calcium lactate, adrenalin and atropine, dessicated spleen, insulin, parathormone and oleum morruhae with and without yeast. This constituted the first phase of the study. The second was to take the compensated animals and study the proceedure necessary to upset the compensation. Four animals were available for this. The methods used were as follows: Splenectomy was performed to determine to what extent, if

any, the spleen is concerned in assuming the functions of the parathyroids, and sodium acid phosphate was injected intravenously to see what effect an upset of the newly established calcium-phosphate ratio would have.

Sixteen parathyroidectomized animals received 40 c.c. of a ten per cent solution of calcium lactate in their stock diet daily. This constituted the only preventive therapy employed with these dogs but it had to be modified on several occassions. When anorexia became manifest the calcium lactate was added to the milk and both were administered by stomach tube. If vomiting occurred so that there was no retention of the calcium, a five per cent solution of calcium lactate was given intravenously. The five dogs mentioned above as having established a compensation are from this group. Although they showed no tetany after compensation, yet they lost weight which was never completely recovered and were less active and more subject to secondary infections.

Two parathyroidectomized animals received as their treatment for the prevention of tetany, adrenalin and atropin. By this means it was thought that tetany might be delayed in onset or alleviated in severity because of a decrease in the motility of the intestine which would permit a greater absorption of calcium. Another factor that might also play a desirable part is the resultant hyperglycemia which might combine with the retained phosphates by forming di-hexose phosphate and thus, through its inverse relationship with calcium cause an increase of the latter in the blood. These drugs did not delay the onset of tetany but apparently exerted a beneficial action in ameliorating the severity of the symptoms. This probably can be accounted for on the basis of a transitory increase in blood calcium which is effected by these measures. It was demonstrated

in normal animals later that both atropin and adrenalin are capable of increasing blood calcium. The mechanism for this action cannot be conclusively stated.

In view of the work of such men as Hess (40), Steenbock (42) and others (79) (67) (43) on the apparent relationship that exists between ultra violet light, sunlight, oleum morruhae, calcium and phosphorus metabolism and rickets, it was desired to learn what effect cod liver oil might have in the treatment of parathyroid tetany. To this end three of the parathyroidectomized animals were given, in addition to their stock diet, a daily dose of 15 c.c. of Oleum Morruhae. On an average mild tetany developed in 7.7 days whereas in twenty other parathyroidectomized dogs fed the same diet without the oil inclusion, tetany developed in an average of 2.55 days. None of the dogs fed oleum morruhae developed violent tetany and whatever symptoms of that nature that did appear were easily controlled by the oral administration of milk and cod liver oil.

Jones (49) used cod liver oil both before and after operation in the treatment of parathyroid tetany. He was able to prevent the development of tetany in those dogs which had received cod liver oil two weeks before operation although two of them developed anorexia on the sixth and seventh days which indicated parathyroid deficiency. He concluded that post operative use only of cod liver oil was of no value. Although we do not agree in the details of our observations yet our results essentially corroborate each other and lead us to believe that cod liver oil plays an important part in calcium metabolism either by increasing its absorption or bettering its utilization.

Two parathyroidectomized dogs were fed milk containing dessicated spleen (Armour). The onset of acute tetany was not delayed nor

were the symptoms ameliorated. In normal dogs, however, we have found that splenic extract raises the blood calcium. Splenic extract would therefore seem to be able to produce changes in blood calcium only when the parathyroids are intact. It would also appear that a small increase in blood calcium is not a controlling factor in the prevention of tetany. Further experimental work concerning the bearing the spleen may have to parathyroid tetany will be mentioned later.

Some of the recent outstanding advances in our knowledge of the parathyroids has been made by Collip and his coworkers. He prepared an acid extract of the parathyroid glands which is effective in raising serum calcium and in preventing and relieving tetany. We did not use it over a long enough period to enable the animals so treated to establish a compensation. Collip (19) states that animals after receiving the extract for six weeks, can very often do without it and that no tetany will result if the diet is properly regulated. He further adds that the oestral cycle will bring on convulsions.

One of the outstanding features of parathyroid tetany is a marked anorexia. This constitutes the chief difficulty to be overcome in any therapeutic measure depending for its success upon the ingestion of food and drugs by mouth. For example, dog #20 persistently refused his food so that it was necessary, each day, to give him milk and calcium by stomach tube. Knowing that insulin produces a hypoglycemia and a resultant increase in appetite, the idea was conceived that possibly it might produce desirable results by correcting the anorexia. Accordingly twenty units of insulin (Lilly) were administered subcutaneously. Fifteen minutes later the dog drank his milk, became more active and looked better than he had for several days.

Following this experience two other parathyroidectomized dogs exhibiting a marked anorexia were given insulin and in both cases desirable results were obtained. These animals, in addition to their stock diet, were given twenty units of insulin daily. Dog #22 lived eighteen days with no signs of tetany but died suddenly one day when insulin was omitted. Dog #27 showed no signs of tetany for seventeen days and was killed the following day in a fight with another dog.

These results appeared so favorable that four more animals were added to this group. Insulin was administered at four hour intervals during the day only. In two of these animals tetany developed early and was severe enough to cause death. In another death resulted from convulsions occurring at night when insulin was not available. The fourth animal was changed to another type of therapy after a few days when it was seen that there was no apparent benefit being derived from the insulin treatments. These results almost nullify the conclusions obtained from the first group but, owing to the distinct benefit derived by those animals, we feel that the administration of insulin at such times is of sufficient value to warrant further work along this line.

All seven of the animals treated with insulin showed a marked improvement in the anorexia that usually follows loss of the parathyroids. None of these animals had to be fed by stomach tube. In this respect, at least, insulin has been of decided value. Further confirmation of the idea that the pancreas does not take on the function of the missing parathyroids is seen in the fact that the Islets of Langerhans show no histological evidence of hypertrophy.

Blood calcium estimations were made at fifteen minute intervals over a period of three and one half hours in dogs, both normal and parathyroidectomized, that had received insulin. In ten such animals we have observed an increase in serum calcium which reached its height in two hours and which usually returned to normal within three and one-half hours. This again is confirmatory evidence in favor of the use of insulin in parathyroidectomized dogs.

Davies, Dickens and Dodds (23) obtained results similar to the above in rabbits. The idea to use insulin occurred to them because of the chemical similarity between it and parathormone. It appealed more to us because of its physiological action.

At present the efficacy of cod liver oil plus yeast in preventing tetany and in enabling dogs to establish a compensation, is being tried. These animals are doing better on this therapy and are loosing less weight than when insulin or calcium lactate or oleum morrhuae alone were used.

It is possible that, as a result of parathyroidectomy, the cerebro-spinal fluid might be under an increased pressure and that this might have some bearing on the etiology of tetania parathyreopriva. To elucidate this point, lumbar puncture was performed on two dogs (Nos. 3 and 28). No increased pressure was found, there being an average of 3.3 drops per minute.

Critchley and O'Flynn (22), in an examination of 115 cerebro-spinal fluids from man, found the normal calcium content to be 6.2 milligrams per 100 c.c. During tetany they found a marked decrease. The calcium of the cerebro-spinal fluid of dog #3 two hours after the administration of 53 c.c. of sodium-acid phosphate intravenously, was 3.24 milligrams. This animal developed, as a result of the injection, a mild tetany and a stiff gait which was followed in a few hours by complete paraplegia of the posterior extremities. Previous

to the injection of phosphate solution, he had shown no tetany for five and one half months. Apparently tetany is not due to an increase in pressure in the cerebro-spinal fluid but a drop in the calcium value is of extreme significance.

Reference has been made above to the fact that increases in acidity are accompanied by relief of tetany and increases in alkalinity are associated with increases in severity of the same symptoms. This is supposed to be due to the influence the H-ion concentration has on the ionization of calcium. A highly ionized calcium being more available by the tissues than a condition where it is not so activated. Ionization of calcium apparently does not need to be associated with either an increase or decrease in the total serum calcium. With these facts in mind, an attempt was made to increase the ionization of calcium by increasing the acidity of the blood. This was accomplished by administering sodium chloride. After removal of the parathyroids , Dog #46 was given some ammonium chloride and blood calcium estimations made. As a result it was found that, although the serum calcium was not raised, the onset of tetany was delayed. This agrees with the finding of Gamble and Ross (31) and Boyd, Austin and Ducey (10).

In an attempt to determine whether or not some other organ might be compensating for the loss of the parathyroids, three animals that had completely recovered from parathyroidectomy were studied in the following manner: (a) a laparotomy only was performed and blood serum calcium estimations made before and after the operation. (b) Ten days later the operation was repeated and the spleen removed. Serum calcium estimations were made after this operation also. The serum calcium was persistently low in all of these animals

and was not affected by the laparotomy. The removal of the spleen, however, resulted in a drop in the serum calcium of 2 to 3 milligrams. Between the third and fifth day there developed symptoms which simulated mild tetany such as muscle twitchings, a profound depression and a loss of appetite. In no case did violent tetany result except in the dog described below.

From Dog #1 of the above series, the spleen was removed forty-nine days after thyroparathyroidectomy. This animal had shown no signs of tetany for twenty-three days and was in excellent condition. Four days after the operation slight anorexia and malaise developed. Calcium lactate was administered by vein and an hour later milk containing more calcium lactate was given by stomach tube. This caused a disappearance of the tetany and stiffness. The serum calcium at this time was 6.36 milligrams per 100 c.c of blood. The following ten days the dog appeared better and took his food well. His serum calcium had increased to 8.48 milligrams. During the next two or three days his condition seemed to fluctuate between good and bad. At the end of this time it was found that his serum calcium had dropped to 6.16 milligrams. On the afternoon of the following day he died very suddenly in tetany although he had drunk his milk and eaten his mush.

The results are similar to those of Hall and Ablahadian (38) who found that splenic extract raised the serum calcium in rabbits and that parathyroidectomy caused it to drop about fifty per cent. Krumbhaar (53) states that in some unfinished work of his the results tend to support the work of Hall and Ablahaidian and believes that there may be a possible relationship between the spleen and the parathyroids.

Several workers (1) (68) (71) believe that there exists an

important relationship between calcium, phosphorus and carbohydrate metabolism. They refer to a reciprocal relationship that seems to exist between calcium and phosphorus, With this relationship in mind, sodium acid-phosphate was administered to three compensated parathyroidectomized dogs. As a result they all developed muscular twitchings and tetany. The serum calcium was depressed to 5 to 6 milligrams per 100 cc. of blood. Violent tetany, followed by death , occurred in two of the animals. The third, as mentioned above in a different connection, developed a paraplegia which was relieved by intravenous administration of calcium lactate. This dog did not die. His compensation had been for a longer period than the others which may have enabled him to be more resistant to the phosphate ion.

The above three animals received from twenty to fifty c.c. of the acid-phosphate within one to twenty minutes time. In contrast to this are two normal animals that received five to fifteen c.c. within one minute and died in convulsions within three minutes. Although this work is not well controlled as far as the size of the animal and the dosage is concerned, the contrast in results is so sharp that it deserves attention. However, two of the animals, one a normal and one an experimental, were of equal size which would lend further support to the contrast which we believe exists in the response of normal and of parathyroidectomized dogs to acid-phosphate solutions. Attention should again be called to the fact already mentioned above, that acid-phosphate caused a decrease in the calcium in the cerebro-spinal fluid as well as in the blood.

We are at present interested in learning more about the relationship that exists between calcium and phosphorus before and after parathyroidectomy and the relationship of the phosphate ion to tetania parathyreopriva. Greenwald and Collip believe that too

little attention has been paid to the study of phosphates as they may be concerned in the etiology of parathyroid tetany.

Conclusions.

Different methods have been employed in an attempt to assist thyro-parathyroidectomized dogs to recover from the loss of these glands which normally are so necessary to life.

The following results have been obtained:

1. Calcium lactate is effective in the prevention and treatment of parathyroid tetany.
2. Adrenalin and atropin play a small part in the alleviation of tetania parathyreopriva.
3. Oleum morruhae apparently aids in the calcium metabolism of the body. It probably exerts its effect through an incompletely understood regulatory influence on calcium metabolism.
4. Dessicated spleen raises serum calcium but it does not provide the necessary factor that will enable parathyroidectomized dogs to establish a compensation.
5. Insulin relieves the anorexia of parathyroidectomized dogs and thus enables the animal to derive full benefit of his food; it is not a hormone that will replace the secretion of the parathyroids; it causes a temporary increase in blood calcium and thereby relieves the symptoms of parathyroid tetany.
6. Parathormone is an effective hormone in the treatment of parathyroid tetany.
7. Yeast, in addition to cod liver oil, in some way enables parathyroidectomized dogs to live on a mixed diet with fewer

symptoms of parathyroid deficiency. This is especially true in regard to the loss in weight, weakness, conjunctival inflammation, anorexia and depression.

8. Splenectomy, following compensation for the loss of the parathyroids, results in the reappearance of tetany. Apparently the spleen plays some part in enabling dogs to live without their parathyroids.

9. Acid phosphate lowers serum calcium and produces a train of symptoms resembling those of acute tetania parathyreopriva. The cerebro-spinal fluid calcium is also lowered.

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