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The pathogenesis of spasmophilia

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THE PATHOGENESIS
of
SPASMOPHILIA

Senior Thesis

Robert Hankerson

1932.

THE PATHOGENESIS OF SPASMIOPHILIA

A definition of spasmophilia or infant tetany is desirable but difficult, as workers in this field differ, both in their findings and in the interpretation of findings that are similar. It is perhaps impossible, for this reason, to give a comprehensive definition.

Marriott (1) defines it thusly:

"Tetany, or spasmophilia, is a condition dependent upon a disturbance in mineral metabolism characterized by neuro-muscular hyperexcitability leading to characteristic tonic spasms of the muscles of the extremities and of the larynx or, in severe cases, to generalized convulsions. It may be latent and characterized only by increased excitability of the motor nerves to the galvanic current or to mechanical stimuli."

Woringer (2) describes spasmophilia as a condition in which there is abnormal response to mechanical and electrical excitation accompanied by disturbances in the mineral equilibrium of the blood which responds to appropriate treatment.

The various manifestations of spasmophilia are so striking that we should hardly expect them to be overlooked by the earlier physicians. Carpopedal spasm was described as early as 1699 by Etmuller (3) but it was only in the beginning of the last century that the various symptoms were described as a definite entity. Clark (4), in 1815, devoted a chapter to a peculiar species of convulsions in which he describes laryngismus stridulus ac-

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accompanied by carpopedal spasm. He noted that the latter was often the forerunner of convulsive disorders. He comments upon the fact that convulsions rarely occur after the third year and if the baby suckles until they have teeth.

Hall again, in 1842 (5), described the syndrome as one disease. It is probable that Trousseau (6), in 1860, was the most influential in establishing a fuller understanding of the disease, although he seemed somewhat confused as he described laryngospasm as a definite disease and also incorporated it in his description of tetany. It might be mentioned that the discovery and use of his sign by him was upon adults. From Trousseau's time the syndrome of spasmophilia or infantile tetany seems fairly well recognized and is described in 1867 by Hensch (7) and in 1887 by Cheodle (8).

Other memorial dates may be briefly mentioned. In 1876 Chevostek (9) described his sign and in 1890 Escherich (10) demonstrated the presence of increased electrical irritability in infantile tetany. It may be said, however, that Escherich gave credit to Stewart (11), an American who demonstrated Erb's sign in children with tetany. Stewart seemed, however, to have a very imperfect understanding of the prevalence and importance of infantile tetany.

As spasmophilia occurs during the teething of the child, and, as we now know, accompanies rickets in a

great share of cases, it is not hard to understand why the early writers (and some not so early (12)) attributed the manifestations to abnormal dentition. Thus we find Etmuller (3), 1699, ascribing convulsions to the breeding of teeth, especially the sharp eyeteeth, and Hamilton, 1813, (13), speaks of the spasm of the larynx as occurring during dentition. Clark (4) ascribed the syndrome as due to disease of the brain. Trousseau (6) reflected the opinion of the time when he attributed spasmophilia to difficult dentition, indigestion and worms. He seemed inclined to favor hereditary and poor feeding, saying:

"It must be remembered that the dependence of the nervous system on the blood and nutritive functions is strikingly marked in children."

He also mentioned enlargement of the thymus as causing laryngospasm but remarked he had never seen an enlarged thymus give the peculiar symptoms of laryngospasm. Henoeh (7) suggested an error of metabolism as the cause, while Cheodle (8), noting the simultaneous occurrence of rickets, held spasmophilia was a nervous manifestation of rickets. It is interesting to note that, in Cheodle's excellent discussion of spasmophilia, he is surprisingly modern, even advocating as treatment cod liver oil and lacto-phosphate of lime!

About Cheodle's time, Victor Horsely (14) discussed the function of the thyroid gland and called attention to the already-known fact that extirpation of the

thyroid will lead to myxedema and convulsions and pointed out the latter were very similar to tetany of adults. The results of Horsely and others led Van Eiselsberg (15) to conclude tetany of adults was due to defective thyroid action. In 1895, five years later, Kahn (16) brought to the attention of the medical world the fact that the thyroid and parathyroid are independent glands. Their independent function was demonstrated by Vassale and Generale (17), who showed the nervous symptoms of thyroidectomy were due to removal of the parathyroids. This led Yanase (18) in 1907 to an investigation of the parathyroid glands of children who had showed signs of tetany. He came to the conclusion that hemorrhage into the glands was the direct cause of the spasmophilia.

At the same time the endocrine explanation was being developed, the situation was attacked from another angle. This work appears to have developed from Ringer's (19) pioneer studies upon the effect of various salts on spontaneous movements of muscle. He showed the addition of calcium to perfusion fluid would prevent the twitching of excised muscle strips that pure saline perfusion fluid caused. Loeb (20), in summarizing his work from 1899 to 1908, showed the antagonistic action of the monovalent alkaline earth salts to the divalent alkaline earth salts in regard to their physiological action upon muscle. He expressed this in the ratio $\frac{Na^+ + K^+}{Ca^{++} + Mg^{++}}$. He states:

"We are, therefore, indebted to the calcium concentration of our blood that our muscles do not constantly twitch."

No doubt stimulated by Ringer's experiments and Loeb's early papers, Sabbatoni (21), in 1902, found that a solution of calcium applied to the brain diminishes its irritability and that oxalates would increase the irritability. Then, as early as 1905, the subject of calcium deficiency was introduced into the pathogenesis of spasmophilia by Quest (22), who reported a diminution in percentage of calcium in brain tissue of infants suffering from spasmophilia.

Perhaps the greatest advances in this field were made by MacCallum and Voegtlin in a series of experiments begun in 1909. They found, in 1909, (23), that the administration of calcium relieved the symptoms of experimental tetany. In 1911 (24) they demonstrated a decrease of calcium in the blood in experimental tetany and inclined to the belief that an evil product of metabolism produced the fall in calcium. However, in 1913, (25), after further work, they make the statement that:

"In spite of our efforts to shake it, the theory of calcium disturbance in parathyroid tetany is supported by stronger evidence than any other idea."

Paton and Findlay (26), accepting the work of Yanase (18), began a series of experiments in 1912 working on experimental tetany. They were much impressed by the

fact that bleeding and perfusing dogs with physiological saline solution relieved the symptoms of tetany. They believed this was an indication tetany was due to an intoxication.

It has been known, since 1876, that guanidine will produce muscle spasms (27) and when Koch (28) demonstrated the occurrence of methyl guanidine in the urine in experimental tetany, Paton and Findlay believed they had found the solution to their intoxication theory. Koch, himself, accounted for the methyl guanidine by the fact that the parathyroidectomized dog passed little urine in the hours preceding death and that the kidneys showed considerable pathology. At any rate, Paton and Findlay, in 1916, came to the conclusion that the parathyroids controlled the metabolism of guanidine or like substance, rendering it atoxic, thus accounting for infantile tetany, or spasmophilia, by saying that it is due to an accumulation of guanidine substances due to a defective parathyroid action.

Under the stimulating effect of the controversy between the Glasgow school advocating the intoxication theory, Yanase in Escherich's clinic advocating an endocrine explanation, and American and Italian workers supporting the calcium privation theory, the literature on spasmophilia, calcium metabolism and experimental tetany began to increase and to become very complex. The analogy between parathyroid tetany and spasmophilia became doubtful as pathologists failed (29) to substantiate Yanase's data.

Calcium privation as an explanation for the spasmophilic manifestations was not the whole story, for Greenwald (30), in 1913, showed there was an increase of the acid soluble phosphorus in the blood following parathyroidectomy in dogs and Binger (31), in 1918, produced tetany in dogs by the injection of alkaline phosphates. He demonstrated a fall of calcium with the rise of phosphorus but could not get tetany with acid phosphates. He concluded the phosphate ion at a certain Ph exerted a toxic action.

Uhlenhuth (32), in 1918, submitted his experiments on feeding salamanders thymus. He concludes there is an antagonism between the thymus and the parathyroid, the tetany toxin being produced by the thymus.

At this time Howland and Marriott (33), after an accurate method of determining the calcium of the blood had been devised, unquestionably showed that in spasmophilia there is a reduction of the calcium content of the blood serum from ten milligrams per hundred cubic centimeters, which they call normal, to seven milligrams or less per hundred cubic centimeters. In those cases below ten milligrams per hundred cubic centimeters, but above seven, they found the condition of latent spasmophilia. This work was quickly confirmed by others (34), (35), (36).

Kramer and Tisdall (34) found no disturbance of the sodium, potassium or magnesium content of the blood serum. They, therefore, account for the spasms of spasm-

philia on the basis of a decreased calcium, using Loeb's ratio $\frac{Na^+ + K^+}{Ca^{++} + Mg^{++}}$. Greenwald (37) disagreed with Binger (31) on the toxicity of the phosphate ion mentioned above and explains the spasms by an increase in the sodium in Loeb's ratio. However, as MacCallum (38) pointed out:

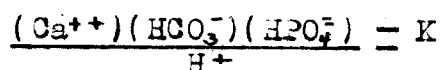
"Conditions are so complicated by the various anions concerned and by the varying rates of excretion of the alkaline kations, that it is not always easy to refer the results of experiments directly to changes in the relation of sodium and potassium to calcium and magnesium."

A simple lowering of calcium, however, is not the whole story in spasmophilia as Anderson and Graham (39) point out. Low calcium content of the blood may exist without signs of tetany in conditions of acidosis from starvation and nephritis. Binger (31), it will be remembered, could only produce tetany with alkaline phosphates. Freudenberg and Gyorgy (40) report that ammonium chloride relieved infants of their symptoms of tetany and Haldane (41) found calcium chloride or ammonium chloride relieved the tetany by alternating the acid base balance in the acid direction without necessarily a coincident rise in calcium value. Grant and Goldman (42) report cases of typical tetany by hypernea, which, as they interpret, is caused by a resultant alkalosis of the blood. Gamble and Ross (43) showed that hydrochloric acid not only relieved the symptoms of spasmophilia but raised the calcium level and Hess (29) found hydrochloric acid milk

tends to intensify rickets as judged by the roentgenological picture which suggests that acid-producing foods tend to mobilize calcium from body depots. It has long been known that tetany will follow excessive vomiting (44).

Elias (45) does not think the therapeutic influence of acid or alkali proves the etiology of any disease. In spasmophilia, disturbances in acid alkali metabolism are not essential. He attributes the symptoms of tetany to the increase of phosphorus in the blood of spasmophiliacs. At this stage, one must conclude that there may be several types of tetany, experimental tetany, gastric tetany, tetany from forced respiration, tetany from alkalosis and the so-called idiopathic infantile tetany, or spasmophilia.

An excellent theory explaining many things was developed by Freudenberg and Gyorgy and summarized in a paper in 1925 (46). They consider changes in ionization of calcium as the main factor in the pathogenesis of tetany. They say a lowering of the calcium ion level (not necessarily calcium content) may be due to changes in the H⁺ ion concentration (respiratory tetany), bicarbonate concentration (gastric tetany or administration of alkali), or concentration of phosphate ions (as in spasmophilia, according to Gyorgy). This conception may be expressed by a modification of the Rona Takahashi formula as --



All this admits, as its underlying idea, the essential importance of calcium ion on its effect upon the excitability of nerves or muscles, all of which is not incompatible to the still more fundamental possibility that it is the relative proportion of sodium, potassium, calcium and magnesium ions that finally effect the excitability characteristic of spasmophilia even though calcium ions are the only ones affected. Thus it may be seen in the above formula why an increase of phosphate with an increase in H^+ should not reduce the Ca^+ value such as occurs in nephritis with acidosis, and why, as Freudenberg Gyorgy insist, spasmophilia is due to a coincident alkalosis and rise in phosphorus. In treatment, they say, acids cause a phosphate diuresis, alkalosis is relieved and the spasmophilia is cured.

Freudenberg and Gyorgy's formula, although very plausible and useful, has its critics. Drucker and Faber (47) do not find a condition of alkalosis in spasmophilia to account for a difference in Ca^+ as calculated by the Rona Takahashi formula, and further, in conditions of acidosis, the blood is not saturated with calcium and the formula only applies to saturated solutions. Hale (48) also criticised the validity of Gyorgy's mathematics and does not find the formula applicable to blood serum. However, Irving (49) finds that the blood serum either has some soluble calcium salt not understood or that the serum is supersaturated. Rohmer and Woringen (50), in their re-

search upon twenty-five infants with spasmophilia, find a marked reduction of the alkali reserve in most cases which is less pronounced in latent spasmophilia.

With the literature from 1918 until 1926 flooded with work on disturbances of calcium, we may wonder what has become of the guanidine theory. Paton and Sharpe (51), in 1926, re-assert the parathyroids control the metabolism of the guanidine in the body and thus regulate the tonus of muscle. Forner and Klinger (52), in an attempt to reconcile the toxic theory with that of calcium depletion, believe the function of the parathyroids, owing to the chemical affinity between the protoplasm of their cells and toxic bases (guanidine and methyl-guanidine, which normally occur in the blood and are eliminated through the urine), attract the latter from the blood and neutralize their effects. Calcium chloride forms an insoluble precipitate with guanidine carbonate explaining its beneficial effect. However, Greenwald (53), who has done considerable work on the parathyroids, states:

"There are two, and only two, well-authenticated metabolic changes after parathyroidectomy. One is lowered calcium in the serum; the other is diminished excretion of phosphorus in the urine."

Behrendt (54) observed progressing phosphorus content in the muscles of parathyroidectomized dogs while in guanidine poisoning the phosphorus remains the same. Collip and Clark (55) put the guanidine theory to a severe test.

by following the urea and non-protein nitrogen curves of the blood in untreated parathyroidectomized dogs and dogs poisoned with guanidine. There was no change in the former and a considerable rise in the latter. It is their opinion that the results are opposed to the guanidine theory. It is Greenwald's belief (56) that the parathyroid hormone is a substance that keeps $\text{Ca}_3(\text{PO}_4)_2$ in solution, not merely retarding its deposition, but actually dissolving it. He warns against the use of parathyroid hormone in spasmophilia. Dragstedt, Phillips and Sudan (57) are unable to find a marked fall of calcium after guanidine intoxication and no characteristic symptoms of tetany could be seen objectively. MacCallum (38) discusses the question thusly:

"Through the literature there runs the idea that there must be a toxin responsible for the tetany though no one has ever been able to demonstrate it. The arguments in favor of methylguanidine are based on the feeling of a need of a toxic substance. Guanidine found in the blood or urine extracted by very complicated chemical procedures has an air of artificiality.

Graham (44) describes the methods of estimating the toxin as cumbersome and inaccurate.

Recent work by Minot and Cutler (58) and Ellsworth (59) would seem to associate guanidine increase with injury to the liver. A point of significance is the fact that parathyroid extract and guanidine do not exhibit the reciprocal control over each other which we should expect if the function of the former were the neutralization of the toxic effect of the latter as Collip and Clark have

shown (60).

The symptoms of spasmophilia seem, at the present time, to be explained by most writers as due to a fall in Ca^{++} (Lesne and Turpin (61), Woringer (2), Gersteinberger (62), MacCallum (38), Drucker (63)). It is impossible to determine the Ca^{++} value and have done with the question because, at the present time, there is no way of doing this with any degree of accuracy. It is quite probable that the Rona Takahoshi formula, or some modification of it, gives a fairly accurate conception of what effects the availability of calcium. It must be remembered that the calcium is present in the blood in three forms-- non-diffusible organic 45%, un-ionized diffusible inorganic 35% and ionized 20% (64) and very little is known of the factors that govern the equilibrium between these three forms and the calcium reserves of the body. All in all, until we have further information, it would seem the part of wisdom to emphasize the importance of the lowered calcium concentration in the pathogenesis of infant tetany, and tentatively, to accept the point of view that this decrease is accompanied by a diminution in ionization.

It may be recognized from the above that tetany is not an entity from the pathogenetic view. It is merely a symptom-complex resulting from an increased irritability of nerve or muscle which may be caused by a number of factors. Loeb's quotient $\frac{Na^+ + K^+}{Ca^{++} + Mg^{++}}$ may be regarded as the

fundamental framework with the more explanatory formula $\frac{(Ca^{++})(HCO_3^-)(HPO_4^{2-})}{H^+} = K$ showing the immediate influences acting upon the available calcium. Thus, hyperventilation tetany is accompanied by a fall in alveolar CO_2 tension with an alkalosis and decreased availability of calcium. The same may be said of bicarbonate tetany with, perhaps, the additional action of the introduced Na ion. Gastric tetany involves a disturbance of the acid base level with an increase of bicarbonate ions, both of which decrease the Ca^{++} . Parathyroid tetany is not as easily explained but, as it does not appear to be a factor in infant tetany, will not be discussed. Work on experimental tetany, however, has been useful in understanding many things.

And now, most interesting of all, what is the mechanism that causes the development of "idiopathic" infantile tetany for which it would seem preferable to reserve the name "spasmophilia"? It has long been recognized that there is an intimate relationship between infantile rickets and spasmophilia (8). From a clinical point of view, it may be considered practically all infants with signs of tetany have rickets to some degree (29), (38), (62). The points of similarity are striking in relation to etiology and both are cured by the same measures. Huldrchinsky (65), in 1920, associated treatment of rickets with the development of spasmophilia. Shiply, Park and their colleagues (35) refer to spasmophilia as

the low calcium form of rickets, while Hess, Calvin and co-workers (36) feel rickets and spasmophilia represent two phases of the same disorder rather than two distant types and this disorder may be affected by extraneous factors such as activity or healing of the process. They believe spasmophilia represents an approach to the healing point of rickets. Hummel (66) finds the gravest cases of rickets are not spasmophilic because there are so many acid proteins in the osteod tissue. A spasmophilic condition is already a step toward the cure of rickets. Falkenheim and Gyorgy (67) found the mercury quartz lamp aggravated spasmophilia. Greenwald (37) says--

"It is curious that healing rickets should frequently be associated with tetany. It would seem as if, in such cases, the process making for calcium deposition were stimulated so as to over-power the parathyroid or calcium dissolving power."

It seems peculiar that, with all this evidence pointing toward the connection between rickets and the pathogenesis of spasmophilia, it has only been in the past two or three years that any work has been done to produce spasmophilia in a rachitic laboratory animal. Hamilton, Bengl (68) and associates produced the characteristic low phosphorus rickets of infancy in animals by standard methods and found that if the phosphorus in the food were raised to normal, or if cod liver oil was given, that a temporary drop in calcium occurred with symptoms of tetany.

They also observed the same phenomena in spontaneously healing rickets, due, no doubt, to endogenous liberation of phosphorus. They suggest the factors governing the solubility of calcium in low-phosphorus rickets are adjusted differently than in normal serum. The abrupt increase of phosphorus, as occurs in the initial steps in the cure of rickets, would then precede the re-adjustment of the solubility factors, and, hence, the initial effect of the increase in phosphorus would be a depression of available calcium. According to the formula

$$K = \frac{(\text{Ca}^{++})(\text{HCO}_3^-)(\text{HPO}_4^-)}{\text{H}^+}$$
 this would suggest, in rickets, a compensatory shift of H^+ , HCO_3^- , and HPO_4^- , resulting in a relative increase of H^+ with decreases of HCO_3^- and HPO_4^- . In other words, an acidosis, which, indeed, is borne out by earlier workers (66), (46). Shahl and Brown (69) produced this work, essentially the same, in rats while the last and most significant advances were made in 1931 by Hess, Weinstock and Gross (70), who induced tetany in rachitic rats by means of a normal diet. They found that if rachitic rats are given a normal diet, the calcium in the serum of rachitic rats falls and inorganic phosphorus rises with the production of tetany in some of the animals in which healing of the rickets occurred at the same time and this, in spite of the fact that the diet may contain more calcium than phosphorus. The only necessity for the development of spasmophilia was well-developed rickets and a sudden change

in diet. This recalls the statement made in textbooks that signs of spasmophilia often develop within a few days of the time when cow's milk is first given after the infant has been taken off the breast. The rat spasmophilia was not due to relatively high phosphorus in the diet nor to absolute increase but to a sudden fall in the Ca/P ratio in going from the rachitic diet to the normal. Whether or not this change disturbs the calcium-phosphorus balance because of a compensatory mechanism already established in rickets as mentioned above, of course, is not known. But, without question, the ability to produce experimental spasmophilia will soon lead to a far more perfect understanding of the mode of origin of spasmophilia.

In conclusion, one thing may be said about the impressions received from reviewing the literature concerned with spasmophilia. It would be interesting to know whether the spasms of the various muscles of the spasmophilic are myogenic or neurogenic or both. It does not seem, as yet, permissible for any writer to dogmatically assert the symptoms are due to either as so many have done. The understanding of the pathogenesis of spasmophilia will only progress with the progression of biochemistry and physiology. The study of each ion soon becomes linked with the behavior of other ions so that it seems there is no limit to the problems that arise.

Herein will be presented six case reports of children in the University Hospital at various times with the diagnosis of spasmophilia or tetany. It was surprising to discover only one case in the history of the hospital with enough work done on it to justify the diagnosis of spasmophilia. As will be seen, most of the cases lack sufficient data, and, hence, the relation they have to the pathogenesis of spasmophilia will be, in the main, conjecture.

CASE I

Robert Scott, age thirteen months, entered the hospital April 21st, 1928, with the complaint of convulsions, spasms of hands and feet, vomiting and catching of breath.

Onset and Development-

The child had a normal delivery and nursed until four months of age. He was then put on cow's milk for a month, then Eagle Brand milk, and, finally, upon Borden's Malted Milk, upon which he was living at time of entry. At nine months of age he had "intestinal flu" with which he was sick for two weeks. During this time his hands and feet would cramp. Since that time, has had convulsions. He does not jerk during them. He has not had orange juice or cod liver oil.

Physical Exam.-

Weight 20½ lbs. His general nutrition appears

good. There is beading of the ribs, bowed legs and strabismus. He has four teeth.

Progress-

4/24/28 - Crowing inspiration noticed.

4/27/28 - Blood calcium found to be 5.6 mg. per 100 c.c. Chevostek's sign present. Now given Ca lactate gr. x each four hr. with cod liver oil $\frac{1}{2}$ oz. t.i.d.

5/4/28 - Dismissed. No convulsions since institution of calcium lactate. Weight 21 lbs. Temperature curve flat after first two days.

Laboratory-

Blood count essentially negative. Erb's sign not absolutely positive.

The first thing we may note is the time of the year the baby showed his symptoms apparently first appearing in January or February. Gersteinberger (62), in a recent paper, discusses the seasonal aspects of spasmodophilia and its relation to pathogenesis. The trend of recent work is not to explain this phenomena as the result of the "spring hormonal crisis" of Behrendt and Freudenberg (71) and Moro (72), but rather to irregular therapeutic effect of sunlight in early spring as shown by Brown (73) with subsequent partial cure of rickets, the following mechanism of which is discussed above. The change of diets, according to the work of Hess (70), no doubt, had its influence. The infection also, no doubt, played its part as Gyorgy (74) is of the belief that

children easily tend to an alkalosis with increased irritability of the respiratory center because of fever. The vomiting also tends to cause a decreased H^+ . All of these many factors have been shown to decrease calcium ion concentration. It is worthy of note the child showed moderate to severe rickets which also, as discussed in the thesis, plays its part.

CASE II

Babé Williamson, five months, entered the hospital September 17th, 1920, with the complaints of loss of weight and vomiting.

Onset and Development-

Babe had normal delivery, breast-fed for a few weeks with satisfactory progress. Then he was removed from the breast and fed other food, the nature of which is not known. Soon after this change, the baby began to lose weight, acquired a diarrhea and a persistent vomiting.

Physical Examination-

The child has a leaden hue, his face resembles and old man. There is marked emaciation. The hands are flexed in spasm, the thumb under the fingers. Weight 7 lbs. 2 oz., temperature 103.

Progress-

Baby died September 18th, 1920, Autopsy showed fatty degeneration of the liver.

This case, because of persistent vomiting and dehydration, probably had a considerable upset of the acid

base equilibrium with the production of the so-called gastric tetany, the vomiting causing a decrease of the acid-forming chlorides with a drop in the H^+ ion concentration of the blood. In such cases as this, it is probable the HPO_4^- ion is retained at a high concentration to compensate for the lost chlorides. The available calcium here would be depressed from two causes- depressed H^+ and increased HPO_4^- and, again, as calcium, no doubt, acts as a base in the blood equilibrium, it is possible it would tend to be excreted faster than the HPO_4^- ion with a decrease of the actual Ca/P ratio still further depressing the available calcium. While the Rona Takahashi formula, as used to explain the varying Ca^{++} ion, has not been accepted by all workers as applying to spasmophilia. Most of them do not hesitate in a frank, uncompensated alkalosis such as in gastric tetany to ascribe the manifestations to a decreased Ca^{++} brought about in a manner at least similar to the mechanism implied in the Rona Takahashi formula.

In this case, however, there is no proof of the condition discussed above, Indeed, we have a very good reason for thinking the spasms of the hands are due to guanidine intoxication. Dodd, Minot, et al, (75), in January of this year, demonstrated an abnormal amount of guanidine in the blood of children suffering from severe diarrhea and malnutrition. It will be recalled that increased guanidine is found in liver damage (58) (59), and in this case, as in most cases of severe malnutrition,

fatty degeneration of the liver was demonstrated.

CASE III

Babe Malcolm, Hosp. No. 20550, age two months, was admitted to the hospital August 16th, 1926, with complaints of convulsions, diarrhea and skin lesions on right finger and back of neck.

Onset and Development-

Birth was normal. Baby was breast-feeder until two days ago when he had six greenish stools. The next he had five and formula changed to protein milk. The following day he had a convulsion and was admitted to the hospital.

Physical Examination-

Weight $8\frac{1}{2}$ pounds. Babe appears fairly well-nourished. Two erythematous macular lesions upon the neck, a weeping exfoliating skin lesion extending over the distal half of one finger.

Progress-

On the day of the entry a convulsion occurred. The babe was put upon CaCl_2 gr. V each three hrs. with protein milk and ammoniated mercury 3% upon skin lesions.

Patient dismissed the 28th improved, weighing ten pounds, temperature curve varied from 99 - 100.

About the only connection that can be made between this case and the pathogenesis of tetany is the presence of infection with an increased irritability of the respiratory center because of fever resulting in hy-

pernia. Also it may be seen that the convulsion occurred about a day after the conversion to protein milk, again reminding us of Hess' conclusions (70) that sudden dietary changes are very prone to cause temporary tetanic symptoms.

CASE IV

This case, although meager in information, is interesting from the pathogenetic viewpoint and, incidentally, from the therapeutic standpoint.

Babe Nelson, hospital No. .2490, age three months, admitted December 9th, 1923, with the complaint of diarrhea.

Onset and Development-

Babe had normal delivery, nursed three weeks, then took cold, developed a diarrhea and has continued with this until entry into hospital.

Physical Examination-

No weight recorded. The child is emaciated, eyes sunken, breathing jerky with an expiratory grunt, temperature 102, pulse 112. The arms and legs are flexed, the thumb of the hand under the flexed fingers.

Progress-

12-13 - Physiological salt solution given intraperitoneally in the morning. In the afternoon the babe had what appears as a convulsion.

12-15 - Babe is vomiting continually with an increase of spasticity.

12-16 - Babe is given calcium lactate, which re-

lieved the spasm somewhat.

12-18 - Exodus.

Aside from the comments made before that will apply to this case, we note a convulsion followed the use of salt solution, most probably increasing the Na in the ratio $\frac{Na^+ + K^+}{Ca^{++} + Mg^{++}}$ causing the increased susceptibility to spasm and convulsion over and above the factors already present. This might suggest the use of some of the various solutions containing calcium. It counteracts the monovalent salt sodium and also renders guanidine, if that is present, as in cases of severe toxemia there is reason to believe, atoxic.

CASE V

Jacqueline Lainback, hospital number 12478, age six months, admitted December 7th, 1925, with complaint of vomiting and diarrhea.

Onset and Development-

Babe was taken off the breast four and a half months ago. Since then has had persistent diarrhea and vomiting. Delivery was normal.

Physical Examination-

Baby crying weakly. In very poor state of nutrition. The right ear is draining.

Progress-

Distinct improvement of symptoms with gain of weight until the right ear flared up when the vomiting and diarrhea re-occurred.

1-21 - Baby develops an inspiration similar to

laryngospasm.

1-27 - Marked evidence of tetany follow intra-peritonealy injection of Ringer's solution.

1-28 - Exodus.

This case is much similar to the preceding case, especially with the convulsions occurring after injection of fluid, this time, however, with Ringer's solution. Although Ringer's solution contains calcium and has the advantage of supplying some of the mineral matter lost from the body, it has the disadvantage of containing a higher concentration of NaCl than that of the blood. With anhydremia, associated with oliguria and chloride retention, it may cause a further increase in the blood chloride and a corresponding fall in blood carbonate, the chloride retention playing its part in the ratio $\frac{Na^+ + K^+}{Ca^{++} + Mg^{++}}$.

CASE VI

Babe Hubbard, hospital No. 16287, seven months, admitted March 24, 1925, with complaint of convulsions.

Onset and Development-

Baby breast fed - no other information.

Physical Examination-

Weight 11 lbs. 5 oz. The baby is small and does not appear markedly undernourished. There is head sweating. The anterior fontanelle is 2 cm. in diameter.

Diagnosis-

Rickets, malnutrition and spasmophilia.

4-10 - Dismissed - No laboratory work done.

This case is probably a spasmophilia following rickets as the age and season indicate. There is no history of infection or change of feeding. The active factor here is probably exposure to sunlight with partial deposition of $\text{Ca}_3(\text{PO}_4)_2$ as bone - an increase in phosphorus retention and a decreased calcium of the blood. The intermittent sunlight causing a fluctuating serum calcium and subsequent spasmophilia.

B I B L I O G R A P H Y

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