ANALYSIS AND DISCUSSION OF THE TREATMENT OF SYDENHAM'S CHOREA

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I

Introduction and History

Osler has defined Sydenham's chorea or chorea minor as " an acute disease of childhood, rarely of adults and of the aged, characterized by irregular, involuntary movements, a variable amount of psychical disturbance, and associated very often with arthritis and endocarditis." (1) It has long been known that chorea is associated with the rheumatic syndrome and has certain special characteristics, but chorea per se evidently is a symptom of a syndrome which can be produced by a variety of etiologic agents. One finds that wherever a series of causative factors is assigned to a disease a corresponding variety of treatments is invoked in the therapy of that disease. This is true of chorea.

In the seventeenth century, Sydenham, in speaking of the relation of the etiology to the therapy of that disease which now bears his name, said

> "As this disorder appears to me to proceed from some humor thrown upon the nerves, which, by its irritation, occasions such preternatural motions, I conceive that the curative indications are to be directed (1) to lessen those humors by bleeding and purging, and (2) to strengthen the nervous system. To answer these ends, I use the following method. First I order seven ounces of blood to be taken away from the arm, or such a quantity, whether more or less, as best suits the age of the patient: next day, I give half or a little more of my purging potion, according to his age, or his being easier or harder to be purged and in the evening the following draught.

" Take of black-cherry water, an ounce; compound piony water, three drams; Venice treacle, a scruple; liquid laudanum, eight drops: mix them together for a draught.

" I order the purge to be repeated thrice, with the interposition of a day between each time of taking it, and the opiate to be given always in the evening after the operation. Afterwards I prescribe bleeding and purging, as before. . ."

(He then prescribes a stomachic electuary, a cephalic infusion, and a cephalic julep.)

" According as the recovery advances, the foot and the hand grow more steady, so that the patient can bring the glass in a straiter line to his mouth, which certainly shows how much better he is. . .

" And, because such as have once had the disease are very subject to a relapse, it is proper to bleed and purge them for some days about the same season next year, or a little earlier than it first began. . ." (2)

It would be interesting to know whether or not this form of prophylactic medicine was very successful.

Osler, noting that mental strain, dietary deficiencies, and a family history of rheumatism, were evidently factors in bringing on attacks of chorea, suggested

1. guarding against mental strain and eye strain in school.
2. maintainence of the nutrition of the child at a maximum with the use of iron and arsenic at the first appearance of anemia,
3. taking special care of children in families subject to rheumatism during the spring months,

avoiding unnecessary exposure to cold and damp. In treating an acute attack of chorea he recommended

1. rest and seclusion,
2. sedation. (In chorea insaniens, chloroform and chloral hydrate were recommended. Potassium bromide was used in combination with the latter, and when the heart became too feeble and there was great prostration, the administration of alcohol was considered proper. Chloroform was also used in the treatment of the chorea of pregnancy.)
3. abundant and nourishing diet,
4. systematic massage, and,
5. arsenic in the form of Fowler's solution (1)

Until comparatively recent years few attempts had been made to treat chorea except in the classic manner which is very similar to Osler's method. This consists of:

1. giving the patient complete physical and mental rest.
2. maintaining the patient's strength by
   a) giving a light, easily digested, nutritious diet,
   b) care of the bowels as required,
   c) promoting sleep by sedation--i.e.

(1) bromides

(2) phenobarbital

(3) scopolamine hydrobromide hypodermically for the maniacal case only

(4) chloral hydrate

(5) veronal

3. salicylates: There has been some disagreement about the value of salicylates in the treatment of chorea. They are used, however, by many, particularly when there is a complicating arthritis or acute endocarditis. Hempelmann thinks that although this class of drugs may be of service in relieving joint pains, and, perhaps, in full dosage, relieving the temperature slightly, the effect on the chorea is usually negligible. (3) Salicylate is generally prescribed in combination with the bicarbonate of soda, both well diluted. Hempelmann recommends initial doses of 5 to 10 grains of sodium salicylate every four hours for a child of about 10 years. Jones noticed that the administration of salicylates had no appreciable effect upon the choreiform movements. His experience with it has been disappointing. He feels that it often masks the symptoms of the disease and gives one a false sense of security. He does not believe that salicylates prevent the development of rheumatic heart disease or shorten

the course of the rheumatic fever. (51)

4. arsenic in the form of Fowler's solution has been used by many clinicians and valued almost as a specific, but Hempelmann and other authors are not convinced of its value except, perhaps, as a general tonic in the later stages of the disease.
5. antipyretics such as antipyrene and acetylsalicylic acid.
6. removal of foci of infection.

Rest has always been a fundamental and most important factor in the treatment of chorea. Drugs have played a secondary part. It is practically impossible to secure complete rest in the patient's own home. And rest, to be effective, must be prolonged. As a result, we have throughout the country large numbers of cases of chorea occupying beds for extensive periods in hospitals supported either by the taxpayer or the voluntary contributor. If a satisfactory method of treatment could be discovered, one that would bring about a quicker cure, it would be a source of great economy as well as of satisfaction to the patient and his parents.

Many forms of treating chorea have been devised, but none of these has ever proved wholly effective. Some of the therapeutic methods that have been used are outlined:

1. By mouth
    a. sodium salicylate
    b. arsenious oxide
    c. mercury
    d. antipyrene
    e. aspirin
    f. chloral
    g. chloretone
    h. trional
    i. bromides
    j. luminal
    k. nirvanal
    l. thyroid
    m. parathyroid
    n. iodine
    o. calcium aspirin
    p. bulbocapnin
    q. calcium gluconate
    r. stramonium
2. Subcutaneously
    a. adrenalin
    b. sodium cacodylate
    c. Rosenow's antiserum (streptococcus)
    d. varieties of antistreptococcal antisera
    e. distilled water
3. Intravenously
    a. novarsenobenzol

b. hypotonic saline

c. Pregl's solution

d. evipan

e. mapharsen

f. epinephrine

g. gentian violet

4. Intramuscularly

a. sulpharsphenamine

b. milk

c. typhoid vaccines

d. typhoid + paratyphoid vaccines, i.e. " TAB"

5. Intrathecally

a. magnesium sulfate

b. colloidal silver

c. gentian violet

d. 1 % phenol

e. atoxyl

f. sodium salicylate

g. horse serum

6. Intraspinally--autoserum

7. Per rectum

a. avertin

b. paraldehyde

8. Diet

a. ketogenic

b. starvation

c. high calorie

9. Bier's hyperemia by band of constriction for the neck.

10. Lumbar puncture

11. Physical Therapy

a. baths

b. massage of nasal ganglion

Dr. Mutch of Guy's Hospital has made the statement that, in its typical form, Sydenham's chorea is not fatal. (4) This is undoubtedly true. Most recorded post-mortem records have been carried out on cases of rheumatic endocarditis and pericarditis complicated by chorea and not on patients succumbing from chorea itself. " If the patient is suitably rested and cared for, the spontaneous recovery rate approaches one hundred per cent, so that the effect of a drug can only be assessed in terms of its ability to lessen the duration or severity of the attack." (4) The classic method of treating chorea, i.e., that based on arsenicals and antipyretics (such as antipyrene), often requires a long period of time in which to produce a cure, whereas some of the newer methods have been reported as capable of quickly ending an attack of chorea. A few of these methods will be discussed, but first let us review the pathology of chorea.

II

Pathology

Very little is known about the pathology of chorea for the reported findings are as variable as are the interpretations of the findings in regard to the mechanism of chorea.

Concerning the postmortem examination of choreic patients, Osler said that " there are no characteristic lesions in fatal cases of chorea. Externally there are frequent bruises and excoriations. In cases of long duration the body is much emaciated, while in acute cases with high fever the appearances are those of a person dead of an infectious disease--the skin is congested, the blood is dark, and the muscles are of a very red color." (1)

Moffet has found that the morbid anatomy in cases dying of chorea " is that of any case dying from extreme emaciation. Endocarditis has been noted in 105 out of 115 autopsies collected by Osler; Sturgis found organic heart disease in 75 out of 80 fatal cases. Usually the mitral valve is affected but other valves may be involved. The heart muscle usually has undergone fatty degeneration and not infrequently a small amount of inflammatory exudation may be seen between the muscle fibers". (36)

In 1890 Dana recorded his findings on the analysis of a series of autopsies and microscopic examinations in

nineteen cases. In sixteen, he found an intense cerebral hyperemia, periarterial exudations, erosions, softened spots, minute hemorrhages, and occasional emboli. These changes were most marked in the deeper part of the motor tract, particularly in the nuclei and the thalami. (5)

Winkelman and Eckel believe that the same infection which produces polyarthritis (i.e. acute rheumatic fever) in the adult may cause chorea in the child and state that the same type of endocardial damage may result from acute chorea as that which results from rheumatic fever. Speaking of " cerebral rheumatism", they remark that the symptoms of this disease may " vary from restlessness, nervousness, and delirium, which may be of a muttering type, to a more severe mental course such as depression or hyperactivity, or may even lead to an actual psychosis. With the infection and toxemia overwhelming the patient, convulsions and coma may occur, terminating in death. Choreic manifestations or meningeal involvement may dominate the picture." (5) These authors made a study of five cases of cerebral rheumatism and concluded that the changes that are present in the brains of patients who have shown neuropsychiatric symptoms during the course of acute rheumatic fever are similar in every way to the changes that occur in any other acute infection, that is: swelling and softness of the brain with vascular injection and occasional small hem-

orrhages. Microscopic examination revealed:

1. areas of endarteritis of the small vessels (the large vessels remained relatively unaffected) which the authors thought to have two causations:
   a. a mechanical factor, edema of the brain. Landis has shown that in the presence of anoxemia there occurs a tissue edema which is proportional to the decrease in oxygen. (7) The resulting alterations in water balance and circulation can be seen microscopically. Winkelman and Eckel believe that the role which edema of the brain plays in the production of cerebral rheumatism has been greatly underestimated.
   b. a toxic irritation through the blood stream

These changes in the small vessels were of two kinds:

a. a recent, acute change, with swelling and proliferation of the lining cells and at times new vessel formation. (This is the same type of change that one sees in the acute stages of syphilis).
b. thickening and hyalinization of the walls. This is, apparently, a later change, and results, according to Hueck, from a colloid

disorganization of the connective tissue that begins with a separation of the intimal vessel layers outside of the endothelium by the tissue fluids and then a coagulation of its albuminous content. This type of vessel change predominates in the relatively long-standing cases, although it may appear within the first week. It is a change characteristic of chronic toxemias, as in tuberculosis (Askavozy) and pellagra (Winkelman) and was seen by Winkelman and Eckel in one case of chorea of pregnancy of six months' duration. (5)

The occurrence of endocarditis may cause a radical change in the encephalopathy; that is, it affords a possibility of embolus. (Purpura of the brain is another factor which may enter into the cerebral pathology, and it may give evidence of its occurrence by similar lesions in the skin.) (5)

2. Areas of "Verodung", or acellular areas. These also occur in other infections and toxemias (" and may form a permanent clinical picture if sufficiently numerous"). (5)

Freeman mentions the presence of small nodules in connection with the vessels which he believes to be "similar

to the Aschoff bodies occurring in the heart and similar cellular nodules in other organs of the body". (7)

He states that there is usually some swelling and vacuolar degeneration of the vascular endothelium with dilatation of the vessel, and later hyalinization without much tendency to necrosis or hemorrhage. " About this is built up a nodule made up for the most part of adventitial cells in the form of undifferentiated polyblasts, and microglial elements. A few lymphocytes and plasma cells are in attendance." (7) These nodules may be few in number and are usually scattered; they have a tendency to occupy the gray matter of the cortex and to a lesser extent the cerebellum. They rarely occur in the brain stem. Of particular interest is their occurrence in the basal ganglia because of the possibility of the production of nervous symptoms through damage to the striated body. In a few cases these nodules have been found in the region of the subthalamic body. It is rare for the white matter to be the seat of such lesions. In these nodules inclusion bodies of uncertain significance have been demonstrated. Winkelman and Eckel, on the other hand, as the result of their detailed studies of these nodules, concluded that they are merely embolic formations; and in their article in Archives of Neurology and Psychiatry (October, 1932) they say, " we have found no Aschoff bodies or the so-called

specific lesion of acute rheumatic fever of the brain". (5)

Acute degenerative changes may be especially severe in the locus niger, neostriatum, and corpus subthalamicum, but the cortical cells are also said to be severely altered in some cases. (5) There is no reaction on the part of the glia according to Freeman; however, in a case of Globus' (which was not an ordinary Sydenham's type, but in which the chorea syndrome was due to diphtheria of the large bowels) severe degeneration of the large and small ganglionated cells of the striated body was found, together with an accumulation of fat substances in the ganglionated cells, and a glial reaction. Also, slight inflammatory phenomena were present in the nerve parenchyma. (8)

No characteristic changes have been met with in the medulla and the spinal cord.

III

Classification of Cases of Sydenham's Chorea

Chorea is grouped by Mutch into the mild, moderate, and severe type of affliction. Under mild he puts that patient in which speech is not definitely affected, and the patient can feed and dress himself with more or less difficulty. Under moderate, the case in which coarse voluntary movements can still be performed, but the patient cannot feed or dress himself. And under severe, the person in whom violent jactitations or ataxic pseudo-paresis prevent all purposeful voluntary motions, and for whom bed boards and other protective measures are required. (4)

Sutton has adopted a somewhat similar grouping in recording a series of 63 cases: (9)

Group	Average Duration	Extremes
1. Mild	35 days	10 - 65 days
2. Moderate	46 days	19 - 120 days
3. Severe	67 days	30 - 180 days

IV

A Review of Proposed Methods of Treating Sydenham's Chorea

Many methods, other than the classical, have been devised for the therapy of chorea. Let us review some of these.

Intravenous gentian violet was used by Visher in a case of chorea with endocarditis and three cases of encephalitis following typhoid fever. His dosage varied from three to ten cubic centimeters of a one per cent solution. Prompt recovery resulted; the author therefore suggested that the drug be given further trial. (48)

Sufrogel injections, according to Freire, have produced constant and excellent results. (17) Improvement was noted in many instances after the first injection, and in some cases following the third to sixth injection. This drug caused slight local pains but never severe secondary effects. Usually a fever of 101° to 104° followed the daily injection. The method is apparently safe and the results are good. It has been considered especially applicable in recurring cases. (15)

Stramonium was used with striking results by Jones in severe chorea, and he advised its use in this type of case. But in the mild to moderately severe case he obtained no appreciable effect even though the drug was pushed

to the symptoms of " atropinization" . (51)

Stephens used distilled water to control the choreiform movements in one of his patients. He described the situation as follows: " A girl of 14 was admitted to the hospital after suffering for a fortnight at home. On admission, she was placed as usual on calcium lactate and parathyroid in the large dose of half a grain of the dried gland. These drugs usually have a good effect. In this case, however, the spasms were so excessive as to prevent sleep as well as the use of her voice. At my suggestion she was then given subcutaneous injections of distilled water, 10 cubic centimeters daily, and two nights later she was able to sleep fairly comfortably. This improvement has been maintained, and at the end of a fortnight, during which she has had altogether eight injections, she was able to sit up in bed and feed herself, using a spoon. My experience of the soothing effects following the use of distilled water has been highly satisfactory, too, in other cases in which the movements have been severe." (53) He ascribed the favorable effect to the injections of distilled water, but we wonder what would have happened if this therapy had not been preceded by the administration of calcium lactate and parathyroid. (He pointed out that distilled water has a high surface tension, and suggested that the introduction of such a liquid modifies the surface tension of all the cells with which it

comes in contact. He felt that the improvement was due to the resulting modification in the metabolism and secretion of these cells.)

Iodine in the form of Pregl solution or Septiiod " Septojod" was employed by Stiefler in 1929. He gave his choreic patients 8 to 10 cc. intravenously every two or three days and diminished the dose as the treatment progressed. This form of therapy was quite effective in the hands of the author, and could easily be tried by the daily practitioner. (20)

Von H. Kuttner (22) claimed to have obtained some interesting results with bulbocapnin (an alkaloid of corydalis cava) which he gave to his choreic patients at the rate of one tablet per day. In a few days he noticed an amelioration of the choreiform movements, the average length of time for obtaining a noticeable effect being from ten to fourteen days.

Heiman investigated the value of magnesium sulphate in the therapy of chorea minor. Meltzer used various routes of administration: intravenous, intraspinal, intramuscular, and subcutaneous. He found that a rapid effect occurred with the intravenous and intramuscular injections, but that it was of short duration; with the intraspinal injections the effect was rapid and of longer duration; and with subcutaneous injections, slow and of still longer duration, with the possibility of a cumulative action.

Heiman treated five cases by means of subcutaneous injections of 25 per cent magnesium sulphate; albuminuria was noted in several instances. He stated that the quantity of solution used, especially at the termination of the treatment was so large that there was a possibility of an inflammatory reaction. In only one of his five patients did the author note marked improvement after the series of injections; in this child, the choreic movements gradually diminished, she became less irritable, and general improvement was noted. The author suggested that the improvement may not have been due directly to the treatment but that it was purely coincidental and the result of natural processes. In his four other cases there was no improvement. He concludes that " subcutaneous injections of magnesium sulphate, though employed in only five cases, did not produce sufficient improvement to justify further trial". (39) Paulian and Dragesco, however, found marked benefit in three cases of recurring chorea and a very severe first case in another child, following the intraspinal injection of 1 cc. of a 25 per cent solution of magnesium sulphate. Three of the cases had previously had neo-arsphenamine without effect. (41) And De Capite reported great improvement in cases of chorea minor, after the subarachnoid injection of 0.10 or 0.15 gms. of a 25 per cent solution of magnesium sulphate. A single injection produced

cure in one of the three cases reported. The other cases required from five to seven injections, given on alternate days. In another series, he gave intramuscular injections of 2 cc. on alternate days until the choreic movements subsided; equally favorable results were obtained by this route. He noted the best effect in two children who had had a little fluid drawn by lumbar puncture beforehand, to reduce the high intracranial pressure; the chorea disappeared after three injections in these cases. The other two cases required from seven to nine injections. In some patients the doses were increased, the maximum being 1.5 gms. intraspinally and 4 cc. intramuscularly. (40)

Hymanson obtained very favorable results by the use of intramuscular injections of boiled milk in six out of seven cases of chorea. (50) He noticed that the duration of the disease was greatly reduced and felt that this therapy should be tried by other workers. (50)

Goodman has reported excellent results following the intraspinal injection of the patient's own serum. After having the child lie in bed for 3 or 4 days or longer without any medication, this worker withdrew from the vein 45 to 50 cc. of blood and rapidly centrifugalized it; the serum was then pipetted off and kept on ice. Lumbar puncture was then performed in the usual manner, the fluid being withdrawn slowly until about 20 cc. were collected. After the serum was heated to body temperature, it was

very slowly injected into the spinal canal. Goodman states that such an injection should take from 10 to 15 minutes, with about 15 to 18 cc. of the serum being used, and that the patient should retain the recumbent position for at least one hour after the injection. Goodman gave from one to four injections, but the interval was not stated. His coworker, Moffett, however, gave this interval as one of five or six days. Furthermore, he added that on the day following the injection there occurred a slight rise in temperature, vomiting, and in some cases a slight stiffness of the neck. These effects all disappeared within a few hours. Some of the patients had slight frontal headaches. On the other hand a certain number of them developed none of these symptoms. (36) This procedure, which is not devoid of danger, has not attained wide use although Goodman's report showed results that seemed very satisfactory from the standpoint of cures, improvements, and the low incidence of recurrences. His results are summarized in the following chart:

Number of Patients	Number of Injections	Cured	Markedly Improved	Slightly Improved	Not Improved
14	1	12	2		
8	2	5	3		
5	3	2	1	1	1
3	4	1	1		1
Total 30		20	7	1	2

Goodman says " To explain our interpretation of the results, cured means absolute cessation of all twitchings within a week. Markedly improved, a cessation of all twitchings within two weeks. Slightly improved, when the twitchings disappear at the end of the third week, and unimproved if the twitchings are still present during the fourth week." (11) Two of the cases had relapses, one after nine months, and the other after eleven months. The rationale of this procedure depended upon the assumption that there may be immune substances in the circulating blood which do not reach the cerebrospinal fluid. In spite of the favorable report of this author (3), his practice has received little support, although Moffett (36) and Faber (37) have recorded good results from its use. Diver also obtained an encouraging effect with autoserum therapy. (38) But a trial of this method carefully conducted in the Children's Medical Division at Bellevue Hospital did not yield similar results. (12) Rohr stated that he found a marked increase in the pressure of the cerebrospinal fluid in five children with chorea, but was unable to produce any beneficial effect by intraspinal injections of the patient's own serum. (45)

Jones reported no benefit from using polyvalent streptococcus vaccine intravenously. (51)

Small passively immunized his chorea patients with the antiserum of the streptococcus cardio-arthritidis in

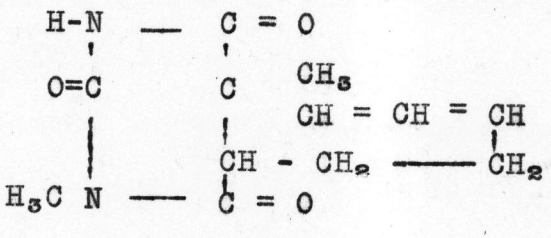
1927. The effect described was that within 24 hours the symptoms present would be favorably influenced. (13) Small said, " In Sydenham's chorea most striking responses appear. These are manifested by the prompt subsidance of the choreic movements, which disappear usually within the week following the administration of the antiserum, that is, before the serum sickness begins. The occurrence of violent serum sickness causes mild choreic twitchings to become noticeable again during the febrile stage of this reaction. The long standing cases show a slower return to complete absence of the choreic movements than do the early ones. Speech defects appear to respond rather more promptly than do the choreic movements in most instances. Incoordination of voluntary movements usually persists for a few days after the choreic movements have ceased. That these responses are not due to the immediate non-specific protein reaction nor to the febrile reactions appearing with the serum disease is shown by the use of normal horse serum in treatment without benefit." (13) This author reported improvement in 24 out of 25 cases who had been treated by his antiserum (14), but Wetchler reported " some improvement in only 13 % of the cases" treated in this manner. (15) Many clinicians have used this serum, but few have reported their results. Disagreeing with Small's theory, Swift believed that this serum caused a non-specific reaction, similar to that obtained with any anti-strepto-

coccic serum. (16) Charney described two cases of chorea, treated with the serum, one with apparently no result, and the other with a reaction that appeared to have led to the death of the patient. (52)

Porter of San Francisco thought that perhaps the effect of Goodman's therapy was due to the fact that the injection of the autogenous serum had set up a sterile meningitis and so had increased the permeability of the choroid to such a degree that antibodies were able to pass from the blood stream into the lymph spaces of the central nervous system. He remarks that several workers have shown that the injection of foreign protein breaks down the defensive power of the choroid and allows substances which ordinarily do not pass to move from the blood into the central nervous system. Because of this fact and the knowledge that horse serum injected in the form of immune antimeningococcus serum is innocuous to children, this author decided to use horse serum for intrathecal injections in the treatment of some cases of chorea minor. Seven patients received such injections. Four of his cases received initial doses of 20 cc. of normal inactivated horse serum half an hour after a half cc. of the same serum had been given subcutaneously in order to test whether the patient was hypersensitive to the serum. Two cases received only 10 cc. for the initial dose; and one case only 5 cc. but this limited dose was followed in twelve hours by half

the normal adult dose of arsphenamine in the vein. Six of the cases showed marked improvement within 3 weeks of the time of the initial dose; in the one case that did not respond the spinal meninges showed no evidence of reacting to the serum by an increased cell count. Two sets of unpleasant reactions followed the use of the horse serum within the spinal canal, an immediate reaction which was evidenced by prostration, headache, and sometimes severe vomiting. The author believed that further investigation was necessary in order to determine the value of serums in the treatment of chorea. (44)

In a single case Slot and Dade administered intravenous sodium evipan (1 cc.) in an infant with chorea minor. A half hour after the child woke up he was quiet. This amelioration endured for a day and a night, and on the next day the disordered movements began again. They injected another cubic centimeter of evipan and the same transitory effect occurred. They repeated these injections four times, finally obtaining an apparent cure of the chorea. (21) The formula for evipan is



Avertin, per rectum, made it possible for one author, Frisch, to save the life of a child with chorea insaniens. The ordinary sedatives (barbital group) and morphine in moderate sized doses were of no value in controlling the violent and rapid choreiform movements from which she was suffering. After five days with no relief from this almost maniac state, avertin was administered per rectum in a dose of 80 mgs. per kilogram of body weight. The resulting rest and sleep permitted subcutaneous injections of glucose and saline which the patient was greatly in need of because of her previous lack of food and fluids. As the effect of the food and fluids began to wear off after about eight hours the sedation was continued by means of 5 cc. of paraldehyde also administered rectally. The child was kept in a semi-stuporous condition for about a week by means of this avertin-paraldehyde combination; and during this time nutrition was maintained by means of hypodermoclysis and transfusions. There was ultimate recovery. (59)

Simple lumbar puncture has been recommended, but it is of doubtful efficacy, (3) although M. M. Casorte, Rayband, and Montus of Marseilles reported three illustrative cases of chorea cured by lumbar puncture. (10)

The ketogenic diet as used for epilepsy, was introduced for the treatment of chorea by Leopold and Rothstein

on a series of twelve cases. They found that the period which elapsed before the development of a definite ketosis required for the disappearance of the choreiform manifestations was approximately nine to twenty-four days. Good results were obtained in nine cases; but in two cases the authors were forced to discontinue the diet after several days before a definite ketosis was even produced because of the development of acute endocarditis and pericarditis in one case, and the contracting of a severe lobar pneumonia in the other. No improvement was noted in one case of severe chorea who had displayed marked symptoms for 7 months prior to her hospitalization. According to these authors the ketogenic diet may apparently be used with success on most cases but not in those complicated by concurrent infection. In some instances the high fat diet was not well tolerated, nausea and vomiting occurring as signs of intolerance without any clinical symptoms of an acidosis developing. According to weekly chemical examinations of the blood, no material or clinically significant changes in the blood or CO_2 figures occurred. The authors have evidently not been convinced of the efficacy of this treatment of chorea for they have reported nothing further since their article of 1929. (18) Mutch has seen no beneficial results from a well controlled and prolonged ketogenic diet. (4)

P. Esau, Wulkan, and Glaser have evidently been convinced that there is something of value in Bier's hyperemia method of treating chorea by placing a constricting banc around the neck of the patient. These authors apply to the base of the child's neck an elastic band of rubber which is tightened from time to time, and which is left on only three or four hours at first, but on the third day of treatment from ten to twenty-four hours. The children, say these authors, become accustomed to this band, which does not hinder feeding, respiration, or play! Rapid results have been obtained by this method in some cases where other treatments have caused no appreciable effect. The improvement was accorded to the hyperemia produced by the stasis of the blood supply. Some of these children became quite calm on the fourth day of treatment and could eat and drink correctly. (21)

Thyroid extract was administered to choreic patients by Lyttle and Sutton after they accidentally discovered that these children had accelerated Kottman reactions (indicating hypothyroidism). They first tried thyroid extract on a boy who had been in Bellevue Hospital for over a month under the usual treatment of isolation and high caloric diet, and who had shown no abatement of symptoms. After the thyroid extract had been given for three days, a marked diminution in the patient's formerly incessant

movements was noted, and within a week he appeared perfectly normal--a fact which was confirmed by several observers. Following this encouraging result, thyroid was given in eight other cases; and equally striking results were obtained in five. (42)

Dr. Tuck treated eight chorea patients with weekly parathyroid extract injections of 1/10 grain--combined with Fowler's solution, 5 to 10 drops t.i.d. With this combination he had very encouraging results, but with parathyroid extract alone his experience was unsatisfactory. (56)

Intravenous injections of dilute solutions of epinephrine were recommended by Duzar (57) for the therapy of chorea minor. Karelitz, however, obtained no benefit in ten out of eleven cases treated by this method and a questionable effect in the eleventh case. (58)

Even injection of the nasal ganglion has been described as being responsible for the cessation of choreiform movements.

"Mc D.T. had been afflicted with chorea and rheumatism involving the left arm and leg for several years. Sometimes the condition was better and sometimes worse, but the patient was hardly ever free from it. When he was tired or excited, the condition was always aggravated. After a hard day, he usually kept some member of the family up a good portion of the night rubbing his leg and ministering to him in various ways, for both the pain and the spasmodic movements would not let him sleep. He was taken to one physician after another who made exhaustive studies to determine the cause of the trouble, and who instituted standard methods of treatment: but all were without avail.

" A year previously, I had cocainized the left nasal ganglion of the patient's sister and had caused arrest in a case of sciatica. I had followed this up with nasal treatment and the sciatica had completely disappeared. For this reason the patient was brought to me.

" When he was presented, his left arm and hand had already begun to show the angularity, the unshapeliness, and awkwardness that come from disuse and from disturbed muscular behavior. His left leg was in poor control, so that walking was accomplished with varying degrees of difficulty.

" On February 10, the patient was taken in charge. Results of a general physical examination were negative. The tonsils were not large but cryptic, general rhinitis was present; the teeth were good and the ears and eyes were normal.

" The left nasal ganglion was cocainized. As soon as the cocaine was applied to the ganglion, the limbs became agitated, the patient being unable to control either the arm or the leg. Within two or three minutes this disturbance passed away, and the limbs came within control--not merely the usual control, which, at best, was crippled, but in good control; except for the awkwardness, normality was restored.

" On February 17, the right ganglion was cocainized, but without perceptible effect. Then the left ganglion was cocainized, with a duplication of the former experience. On February 20, both ganglions again were cocainized with the same results as before, namely, that the right gave a negative result, and the left, a positive.

" On February 27, and on March 3, the procedure was repeated, with the same results. On March 7, the right ganglion was injected with alcohol. This was done for control purposes. Good results were not expected and none occurred. On March 20, the left ganglion was cocainized--with the same results as before.

" On March 25, the left ganglion was injected with 0.5 cc. of 0.5 per cent alcohol with 5 per cent phenol. The injection was made under local anaesthesia. The symptoms at this time were active, but the cocaine relieved them. This was followed by the injection of the alcohol. For nearly three years, the patient has not

had a trace of chorea. He is now more than 6 ft. tall, and during the last school year has won honors in basketball." (55)

It would be interesting to see this method used on another case. Possibly suggestion was a significant factor in both etiology and treatment of this particular instance.

Copeman treated forty-four cases of long-standing chorea without drugs but by means of somewhat prolonged immersion in baths at "neutral" temperatures and general (light) massage. All these cases responded well after periods of treatment varying from eight to twelve weeks in the milder cases to five months or more in the severe ones. A small control series he treated with varying drugs, including nirvanol. He found that the latter group responded more quickly, but that relapses were more common than in the bath group. He suggests that a combination of his method (bath and massage) and drug therapy would prove a more successful measure than either separately. (23)

Grossman has discussed the re-education of chorea patients; he approved the relaxation exercises given by Maloney and described them in detail:

" The diaphragmatic breathing is of great aid in inducing relaxation in the muscles. The patient is asked to take a deep breath using his diaphragm, restricting his thoracic movements, and at the height of inspiration to pause, then slowly and evenly expire, and again pause; this breathing soon tires the patient if continued too long, so after ten or twelve of these deep respirations have been taken, the depth of inspiration and

the pause are shortened until the patient is breathing, without effort, as in sleep.

" To relax the muscles, passive movements in which the muscles are alternately lengthened and shortened are employed. The muscles of the forehead, cheek and jaw are thus manipulated until wrinkling of the forehead, and blinking of the eyelids disappears and the muscular spasm is eliminated. Next a shoulder is relaxed, then an arm; each in turn must be passively moved until all traces of muscular tension vanish and the part lies motionless and flaccid, and falls limply from any unsupported position. Then the leg on the same side should next be taken. After a part is relaxed, those parts previously treated should be briefly dealt with again, in the order in which they were first relaxed. This linking of parts previously relaxed to parts newly relaxed is helpful in bringing the entire body into a state of relaxation. During the passive movements, the operator should continually direct the patient's attention to the control of the choreic twitchings; gradually this requires less and less effort, and soon complete and perfect relaxation is possible.

" After the temperature and pulse rate have reached normal and remained so for several days, and the child has mastered the rest exercises well enough to allow her limbs to be freely moved passively in all directions without exciting either rigidity or spasm, active movements may be begun. At first simple movements, flexion, extension, adduction and abduction at the joints should be used. These movements should be guided along the normal planes; rhythm rate and force of the movements should be regulated by counting or using a metronome. Next the patient resists the movement, in order to increase her ability to maintain tonic contraction; and finally the movement is done against the resistance of the operator. (This resistance tends to overcome the loss of power in the muscles due to lack of control.) When the patient is able, in a recumbent position, to perform all movements in proper time and rate to the normal extent and with normal force, reeducation in maintaining the normal attitude may be begun. Creeping on the hands and knees is first taught; next balancing and creeping on the knees are attempted; and finally maintaining an erect attitude and progression are taught. The changes should be made gradually and the patient must avoid all fatigue. By alternating the rest exercises with active work several hours a day can be used for reeducation,

without fatiguing the patient.

" Precision of movement can be regained by the use of toys and games which at the same time will interest and amuse the patients. Building blocks, fishing games, jig saw puzzles consisting of pictures cut into small pieces, irregular in shape to be fitted one against the other to form a complete picture; for older children dominoes, pegs to be fixed in the holes in a backgammon board and innumerable other toys found in the kindergarten.

" The aim of these exercises is to encourage freedom as well as precision of movement; any incoordination present is corrected and if continued for a sufficient length of time it promotes continued concentration with increased mental stability." (43)

Burnet (46) also recommends massage.

Arsenic has been used in the treatment of chorea for over a century with results which are generally considered to have established its usefulness. Yet, its effect has been variable. Burnet, in 1923, objected to the use of arsenic in the form of Fowler's solution for he believed that the large doses of the drug that are needed in order to produce a cure do this by inducing a mild form of neuritis which paralyzes the peripheral nerves. (46) He also stated that the results are rarely permanent, that the arsenic exercises no influence over the complications and sequelae of chorea, and that it in no way benefits the rheumatic constitution of the patient. Jones and his coworkers used Fowler's solution on a number of cases to the point of arsenic intoxication, and they found that it had no noticeable effect on the chorea. (51) The chief value

of Fowler's solution is its effect as a tonic in keeping up the general metabolism of the patient while he is receiving bromides or other sedatives. Graham treated fifteen chorea cases with sodium salicylate, fifteen with liquor arsenicalis, and fifteen with intravenous neo-kharsivan (an arsenical preparation). He found that those cases which were treated intravenously had to be given relatively larger amounts of arsenic and took longer to clear up than those receiving the arsenic by the oral route; as a result he voiced some doubt as to the verity of the statement that improvement in chorea is proportionate to the amount of arsenic that is given. Furthermore, he noted that those cases receiving arsenic by mouth took just as long to subside as those cases receiving the sodium salicylate. He concludes that the course of chorea is not influenced by treatment with arsenic. (54)

The treatment of chorea with intravenous injections of salvarsan and neosalvarsan was first advocated because of the supposed favorable action of arsenic in this disease. However it was not long before it was used in the belief that chorea is a manifestation of syphilis. (43) Herrera, however, reported the Wasserman test as being negative in the nine cases of chorea which he cured by from one to seven injections of arsphenamine as suggested by v. Bokay in 1923; in these cases the chorea was from

a few weeks up to six years standing. There was nothing to indicate syphilis in any of the families except a positive Wasserman in one of the mothers. (49) In 1924 Moffett and Smith treated nine cases of chorea by intravenous injections of 10 mgs. sulpharsphenamine per each kilo of body weight; the dose was in most cases repeated at intervals of five days until three doses had been given. Five of these cases showed definite clinical involvement. (47)

In 1929 Bokay used novarsenobenzol (a brand of neoarsphenamine (neosalvarsan)) in the treatment of chorea. (19) He recommended this for the grave case of chorea. His method consists of giving 0.1 to 0.3 gms. of the drug at intervals of 5 to 7 days, the total dose being 1 to 2 gms. One must wait for three to five weeks before any effect of the treatment is evident. The author said that this form of treatment produced improvement more rapidly than the oral administration of arsenic. He said that one must begin this therapy as early in the disease as possible in order to have rapid and lasting results.

A new form of arsenic has been used at the Wisconsin General Hospital. This is mapharsen which is given intravenously. The first dose varies from 15 to 25 mgms. and the following doses from 15 to 30 mgms. Four to five day intervals are allowed between the injections which are continued until improvement is noted; this is generally within 5 to 8 weeks.

V

Nirvanol, Fever Therapy, and Calcium Therapy in Chorea Minor

None of the methods of treating chorea mentioned in the preceding chapter has proved entirely satisfactory, and one finds that references to their use are few in number.

The drug nirvanol (phenyl-ethyl hydantoin) was first introduced as a hypnotic but was soon discredited because of its tendency to produce skin eruption. In 1919 it was reintroduced by Roeder of Germany as a specific remedy for chorea and as a remedy which shortens the course of the disease in a large number of cases. (16) The dose consists of 25 to 45 centigrams of the drug per day (given in 3 to 4 doses) for approximately 14 days. About the tenth or fourteenth day there is produced in these patients a series of signs bearing witness to the efficacy of the medicine: these signs consist of a generalized, scarlatiniform or morbiliform eruption, with fever, and a rather marked eosinophilia (10-20 % and more) (21) The degree of intensity of the exanthema varies. There is occasionally observed a slight irritation of the conjunctivae. Once in a while, shortly before the appearance of the reaction, a slight exaggeration of the choreiform twitchings may be observed. (16) The drug should be discontinued at the onset of the rise of temperature or the event of the appearance of an exanthema. If neither event occurs the drug

should be discarded at the end of 14 days for the exanthema will not occur if it has not manifested itself by that time.

The fever, which is not always very significant, and the other symptoms of nirvanol intoxication disappear in a few days; and the sickness is ameliorated or cured in about twenty days. (21)

Concerning the biologic character of " nirvanol disease" it may be stated that it has some resemblance to an anaphylactic reaction: the incubation time of from 9 to 12 days may be considered as the time necessary for the development of amboceptors; the clinical picture is identical with that of serum disease; and the metabolic-chemical changes are similar to those observed in serum disease. Shortly before the appearance of the reaction an alkalotic change develops in the organs, a " pre-anaphylactic tetany" similar to that observed in serum disease, and a galvanic hyperirritability of the peripheral nerves also develops. But a change in metabolism in the direction of acidosis occurs as the exanthema develops. Siegel believes that the effect of the drug is due to the rash or the " metabolic shock" or upset (i.e. the change from alkalosis to acidosis) which precedes the rash; and Rietschel reported in 1920 that the drug exanthema was essential for the production of the therapeutic effect

of nirvanol; (16) but M. Schacter says, " Often it is not necessary to have all the nirvanol manifestations in order to get consecutive sedation and cure. Everything can be ascribed to a little fever, and to the eosinophilia, without an eruption. . . This hypothesis is sustained by the authors, who with H. Flesch (Budapest) have seen in all the cases treated with nirvanol, the undisputed existence of an eosinophilia, where they have not been able to note the other modifications". (21) Husler believes that nirvanol modifies " strio-pallidal lesions caused by the choreic virus". (21)

Pratt and Bender treated twenty-six cases with nirvanol; fourteen of which had some rheumatic symptoms at various times. In sixteen of their cases there were heart lesions ranging from mild cases of mitral regurgitation to several cases of endocarditis. In the latter cases treatment was begun after the endocarditis had cleared up, and in not one of the cases was the heart condition made worse. And a re-examination nine months later showed the hearts to be the same or improved. (62)

Nirvanol therapy often produces a dramatic cure within two to three weeks, but not infrequently its effect is rather drastic and not at all free from risk. In fact, fatalities have been attributed to its use. Blood dyscrasias such as leukopoenia, thrombocytopoenia or purpura

hemorrhagica, may occur. There may be multiple mucosal hemorrhages, jaundice, and pulmonary or renal complications. (24) Rusleer observed a case with a severe recurring exanthema, severe stomatitis, balanitis, and a very high fever; and Joloicz a case of transitory intestinal paralysis with a high degree of tympanities following excessive doses. (16)

Because of these associated risks, nirvanol should be employed only in a hospital where the patient can be carefully watched. Goebel has recourse to this drug only in cases resistant to other common treatments, in serious cases, and then only when thorough clinical examinations reveal the patient to be a fairly good " risk" . (21)

Silber and Epstein studied 28 cases of chorea treated with phenyl-ethyl hydantoin. They concluded that the drug is <u>not</u> a specific cure for chorea; that it does not prevent the occurrence of cardiac complications, but that there is no deleterious effect on already existing heart disease; and that the number of recurrences in cases of chorea treated with phenyl-ethyl hydantoin are no less than with the recurrences in cases treated by other methods. They noted marked improvement in 40 % of their cases, slight improvement in about 35 %, and no improvement in 25 % of their cases. They believed that the therapeutic effect of nirvanol is best in severe cases of chorea and that it is of no value in mild cases. (25)

Mutch says of nirvanol, " the biochemical trauma produced by this drug is more impressive than its efficacy in controlling the chorea". (4)

One of the most recent developments in the treatment of chorea is fever therapy. It was Osler who noted that fever in chorea is rare, except in the severe maniacal form. (1) Fever therapy for its own sake was first used in the treatment of Sydenham's chorea by Mas de Ayala in 1930 who used the Treponema hispanicum to produce relapsing fever in a boy with chorea of two years' duration. Improvement began after four febrile attacks and continued until the boy was cured. (26)

Prior to this, Von Kern (27) had noted improvement in choreic patients as the result of intramuscular injections of milk, but he did not attribute the improvement to the resulting fever. Likewise, Horton (28) failed to give credit to the febrile reaction when he observed improvement in two patients with chorea after intravenous injections of a pure protein prepared from ox-blood fibrin. And in 1928 Small (13) reported improvement in 24 out of 25 patients with chorea who had been treated with his Streptococcus cardioarthritidis antiserum, but he considered that the cure was due to the specific serum and not to a non-specific protein reaction associated with fever. Pilcher and Geratenberger, in 1913 noted that those patients

who were benefited by treatment with phenyl-ethyl hydantoin (nirvanol) were the ones who reacted to the drug by developing a rash and a fever. (29)

It was Tarnovaki, a Roumanian physician, who first noticed that any fever occurring during the course of chorea would often alleviate and sometimes even end the attack. (21)

However, it is to Sutton (1931) that the merit goes for having used typhoid vaccine with the express intention of producing the fever in order to cure chorea. She had noted improvement in a patient who had received phenobarbital to the point of toxicity and who had developed a rash and a fever. She thought that the fever was the beneficial agent in this case and in those cases reported as having been aided by phenyl-ethyl-hydantoin so decided to use typhoid-paratyphoid vaccine intravenously to produce fever. Her instructions are outlined:

"Aims:

1. To shorten the duration of the chorea, and therefore treatment is begun as soon after admission as possible.
2. To get a daily temperature rise of 104°, or over, and to maintain it for as many hours as possible. Treatment being given daily until all signs of chorea have cleared. A day when the temperature does not reach 104° is a wasted day!
3. To make the children as comfortable as they can be made during treatment.

Method:

1. Use New York City triple typhoid vaccine (containing 1,000 million B. typhosus, 750 million each

of Para A and B per c.c.) a tuberculin syringe, and 24 G 3/4" needle.

2. The vaccine should be boiled for three minutes before the first time it is used, and always kept in the ice box between treatments.

3. First dose 0.05 c.c. TTV, undiluted, intravenously.

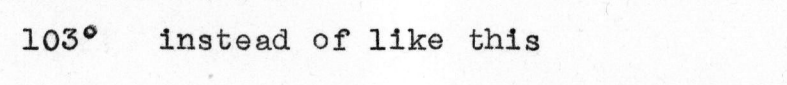
4. Second dose is governed by the reaction of the child to the first dose: for instance if the temperature the first day goes to 106° or over, repeat 0.05 c.c. the second day: if it goes to 105° ± then give 0.075 c.c., and if to only about 104° then give 0.1 c.c. TTV.

5. Subsequent doses are determined entirely by the reaction of the child. In general increase the dose of vaccine by a larger amount each day. The average case may take: first day, 0.05 c.c.; second day, 0.075 c.c.; third day, 0.15 c.c.; fourth day, 0.25 c.c.; fifth day, 0.4 c.c.; sixth day, 0.6 c.c.; seventh day, 0.85 c.c.

However, this routine cannot be counted on to obtain adequate temperature elevation. A much larger increase may be necessary or:

6. Second doses on the same day may have to be given. If the temperature does not reach 103°, or only one or two readings in the neighborhood of 103° are obtained, then a second dose on the same day should be given. This second dose is usually one-third to one-half the original dose of the day. For instance if the first dose of the day was 0.6 c.c. and at the end of two hours the temperature is 103.2° and fifteen minutes later is 102.8°, than 0.2 c.c. TTV should be given at this time. If the temperature has dropped below 102°, then 0.3 c.c. should be given.

Note: In giving the second dose it is necessary to get it in as soon as possible after the temperature becomes stationary or begins to fall, otherwise a temperature curve like this



may be obtained. When it becomes obvious that a second dose may be necessary, have temperatures taken more frequently than one q hour, so that it will be known almost as soon as it begins to fall.

7. Keep the child well covered during the whole of the temperature reaction. If the child becomes uncovered, temperatures do not stay up so well.

8. Treatment should be given daily unless condition of patient indicates need of a rest (severe vomiting, poor fluid intake, etc.) or unless the ward situation makes it impossible. Never give first dose on a visiting day. (The child may be taken out by the parents

with a temperature of 104° if you do.)

9. Treatment should be given until all signs of chorea have disappeared. This is generally easy to tell in the mild and moderate cases, but may be more difficult in the severe ones. If there is much weakness and pseudo-paresis present, there may be incoordination due to this weakness and to the prolonged treatment, after all signs of true chorea have cleared. When in doubt try massage and occupational therapy. The mild and moderate cases take on an average of 5-7 treatments and the severe cases 10-15.

10. Urines should be examined by the interne daily during treatment, for albumin and red cells. In our series we have not seen anything more than a transient albuminuria, and occasional red cells. However, hematuria has been reported to us. Therefore if the urine shows more than an occasional red cell, stop treatment until the hematuria clears.

11. Occasionally, especially in severe cases, a second course of vaccine may be necessary after an interval of several days or longer. In this case we have found that the size of the first dose of the second series depends on the interval. The following is a rough guide for dosage.

Interval of 1-3 days--Proceed as though there had been no interval.

Interval of 4-7 days--Give the same dose as that given on the last day of the first series.

Interval of 8-9 days--It is probably best to give a somewhat smaller dose than that given at the end of the first series, although if the reaction to that dose was poor, then the same dose may be repeated.

Interval of 10-20 days--We have had no patients who have fallen into this group. To be safe the dose should probably be decreased to about one-half the previous dose at 14 days and to one-quarter at 16 days.

Interval of 20 days--Series should be started over again at 0.1 c.c.

Care of patient during reaction:

1. Protein shock, with chill, severe headache, vomiting, etc., generally occurs 20-50 minutes after the vaccine is given. The children are more comfortable if already hot; therefore extra blankets and hot water bottles should be given as soon as the vaccine has been given.

2. Codeine in maximum doses (1/4 to 3/4 gr. according to size of patient) relieves the headache to some extent. This should be given about 20 minutes after the

first and second days of treatment, and should be given by hypodermic in thigh (to avoid a sore arm on which a tourniquet will be put the next day). After the first two days' treatment, the codeine may not be necessary, and it may therefore be left as an S. O. S. order, which may be given by mouth if the child is not vomiting.

3. Vomiting usually occurs during the first two or three reactions. Therefore lunch is omitted on these days. After this, vaccine may be given immediately after the noon meal. If for any reason the vaccine is to be given at another time during the day, see that provision is made for adequate food intake at some time during the day.

4. We have found that large drinks of fluids are likely to bring the temperature precipitously down, and therefore fluids should be limited during treatment. Small sips of water or fruit juice, however, make the children much more comfortable.

Treatment of hyperpyrexia:

1. Aspirin gr. 5, ice-cap to head, and a drink of water are usually given if two readings above 106 at fifteen-minute intervals are obtained. This should be done routinely if there is no doctor on the ward. However, some of the children have surprisingly little discomfort at high temperatures, and unless the temperature is going dangerously high, these procedures may be omitted, if the interne is present to assume responsibility for it.

2. For very high temperatures, 107° or more, all coverings should be taken off immediately and the child given a tepid sponge. Aspirin gr. 10 should be given by mouth unless the patient is vomiting or is unconscious, in which case give a double dose 15-20 gr. by rectum. Take the temperature every ten or fifteen minutes. If it continues to go up the child may be placed in a tub of water at 100°, the water then being gradually cooled. Sedatives and stimulants should be given as indicated.

Note: these very high temperatures seldom occur, and when they do usually they respond readily to the above treatment. They are not so terrifying as they look!

Routine orders usually written on the chart:

Vaccine given at 12 P.M. Take the temperature stat. and q 1 hr. until it returns to 99.6° (q 1/2 hr. when above 104° on the way up).

Extra blankets and hot water bottles stat.

Codeine gr. 1/2 (h. in thigh) at 12:20, and repeat after hrs. 3 if necessary.

Limit fluids to small sips of water, lemon, or orange juice.

Aspirin gr. 5 and ice-cap to head for temperature over 106°.

Daily urine to laboratory during treatment.
Do not be afraid of high temperatures-- they are necessary to cure the chorea.
Do not be afraid of large doses of vaccine.
Care of the patient during convalescence:
1. Children are kept in bed at least one week after completion of fever therapy--longer if the chorea has been severe, or if there has been any evidence of active carditis.
2. High caloric diet to make up for the loss in weight which usually occurs during treatment.
3. Occupational therapy (basket weaving, coarse sewing, etc.).
4. Transfusion if indicated for anemia.
5. Children are sent to a convalescent home from the hospital if possible. Treatment of subsequent attacks by TTV.
There is apparently no increased sensitivity to the vaccine. In general we have found that more vaccine is required to obtain the desired temperature reaction when a child is being treated a second time with vaccine, than was required during the first course of treatment." (30)

An outline of the exact dosage for producing fever cannot be given, Sutton states, for individuals react differently to the vaccine. The dose on any one day, after the first one, depends on how the patient reacted to the previous dose. The treatment is continued daily until the chorea is over unless the child seems to be exhausted and in need of a day off.

In the Journal of Pediatrics for June, 1933 Sutton compared the results of 150 cases of chorea treated without fever prior to 1930 with 150 cases treated with fever after 1930. There was a marked reduction in the duration of the disease in all fever treated cases compared with those not so treated. Similar effects were reported by

her in Medical Clinics of North America for November, 1935. (31) Very striking results were obtained at Bellevue in those cases treated early in their first attack. But Kapper and Bauer feel that the treatment has proved of most value in the long-standing cases. In Sutton's group of patients the mild cases were stopped in the shortest time, the moderately severe cases took slightly longer, and the severe cases longer yet.

In 1933 Huxley Fish " tentatively" suggested the following types of chorea as being suitable for treatment by induced pyrexia:

" 1. Cases with no signs of cardiac rheumatism which show little improvement after four weeks in bed in an institution.

2. Cases with slight cardiac rheumatism in which a period of rest longer than four weeks in proportion to the severity of the heart disease has produced little improvement.

3. Cases of choreic relapse in which the previous attack or attacks have been of long duration (the heart again being only slightly affected)." (32).

He stated that the treatment " would appear to be unsuitable for cases with extensive valvular disease, especially if active rheumatic carditis or any degree of

cardiac failure be present". (32)

On April, 1935 Sutton and Dodge reported on the effect of fever therapy in rheumatic carditis associated with chorea. They presented sixteen patients in which the diagnosis of active rheumatic carditis was justified. These cases were given artificial fever therapy produced by the intravenous injection of triple typhoid vaccine. In nine of these patients all the clinical signs of activity had subsided by the end of treatment, and in the others the signs were gone in from a week to ten days following the end of treatment. (Furthermore, they treated two cases of subacute rheumatic carditis without chorea; these children were given artificial fever therapy produced by radiant energy. In one patient the signs of rheumatic activity cleared immediately following one treatment but recurred again to a much lesser degree eight weeks later. After receiving a second fever treatment she has shown no clinical evidence of activity. The second child showed improvement following one treatment, but the signs of activity did not completely subside until after a second treatment two weeks after the first. Because of these encouraging results these authors feel that the presence of a subacute carditis or inactive rheumatic heart disease is not necessarily a contraindication to the use of fever therapy in the treatment of chorea, and they

believe that fever therapy actually has a beneficial influence on the course of the carditis. (60)

On the other hand Ash and Einhorn noted no effect in three out of five chorea patients with active carditis treated by means of fever therapy; in fact, there was steady progress in the activity of the rheumatic process during the period of administration of the vaccine, and one of the children subsequently died. These men further noticed that during the febrile reaction following intravenous injections of typhoid vaccine there is a depression of the granulocytes; in one of their cases leukopenia persisted to such a degree that it was deemed advisable to discontinue the injections of vaccine. They therefore advise frequent check-up of the white blood cell count. (61)

The disadvantages of this form of treatment according to Sutton are: first, the unpleasantness to the patient of the foreign protein shock, and second, the fact that the fever is not really controllable, i.e., a good febrile response is not always obtained and the temperature stays high for only a short time. Thirdly, minor complications may develop: about one-third of her patients developed herpes labialis; two showed slight temporary jaundice and enlargement of the liver, and one had urticaria. But no bad effects appeared in those who had

either active or inactive heart disease. (31)

Possible advantages of typhoid-paratyphoid vaccine over phenyl-ethyl hydantoin therapy seem to be that: " 1.) The febrile reaction can be induced immediately without the necessity of waiting for a period up to two weeks for intoxication to develop. 2.) All cases respond to TAB with a fever whereas not all cases show intoxication with phenyl-ethyl hydantoin, even when it is given over prolonged periods. 3.) TAB does not cause complications, such as severe skin eruptions, agranulocytosis, broncho-pneumonia and nephritis, which have been described with phenyl-ethyl hydantoin. 4.) By increasing the dose of TAB, or when giving it again after a course of injections, fever can always be produced. But a second course of treatment with phenyl-ethyl hydantoin, even when intoxication has been produced before, fails to produce the desired reaction. (9)

Several cases of Sydenham's chorea were treated with nirvanol at the Wisconsin General Hospital, but the systemic reactions were so severe that the administration of the drug was discontinued, and typhoid injections were used in preference to it.

Montfort attempted to clarify the present status of the treatment of chorea by making a comparative study of 49 patients, 24 of whom were treated with phenyl-ethyl hydantoin and 25 with typhoid paratyphoid vaccine. He

noted spectacular benefits from phenyl-ethyl hydantoin in some cases, but in most the average duration of the disease was 24 days; in eight cases the condition was not improved; and in one the drug caused a fatality. Thus we see that this method is of questionable value. On the other hand, results of the treatment with typhoid, paratyphoid vaccine showed this form of therapy not dangerous, although it produced discomfort; also, the period of treatment was shorter by eight days than with the phenyl-ethyl hydantoin. And no recurrences occurred in patients treated with vaccine, or did valvular heart lesions occur in this group. These factors would make treatment with typhoid paratyphoid vaccine seem preferable. (33)

There are several other ways of inducing fever which are better from the point of view of abili ty to raise the temperature to the desired level and to maintain it there for as long as is necessary: radiotheramy, diathermy, and radiant energy will all do this. With the first two methods the practical difficulties of the expense of the apparatus and the danger of burning the patient present themselves. (31) Stafford Warren (34) and his associates of Rochester, N.Y., found that radiant energy obtained from carbon filament bulbs will raise the temperature just as well. The apparatus can be made by any skilled carpenter and electrician, it is inexpensive, and there

is little danger of burning.

Schnabel and Fetter have treated several cases of chorea by inducing fever by physical means. The present technique of Schnabel and Fetter is to give the patient three hour sessions at 105° to 106° F. twice weekly in the Kettering hypotherm. (14) This apparatus was developed by the late Walter M. Simpson of the Miami Valley Hospital at Dayton, Ohio, Mr. C. F. Kettering, Director of the Division of Research of General Motors Corporation, and Mr. Edwin C. Sittler, engineer of the same organization; in this apparatus the patient lies free in an air conditioned cabinet, surrounded by a moving current of heated and humidified air, by means of which the temperature is raised. No electrodes are in contact with the patient, and no high frequency currents are used. The patient's temperature and pulse rate can be taken every fifteen minutes or oftener. The temperature reaches the desired level in from 60 to 90 minutes. As many treatments as needed are given. Three to five have generally been sufficient. These men have completed treatments on eleven children affected with Sydenham's chorea. Three of these had severe choreiform movements (one was so active as to require constant restraint); six had moderately severe chorea; and in the remaining two the condition was relatively mild. The age of the patients ranged from

4 to 15 years; and the duration of the disease before treatment was given varied from three and one-half weeks to two years (this last was one of the mild cases). Seven of the eleven patients had had their choreic symptoms for less than six weeks. Four treatments was the average number given, each treatment consisting of three hours of elevated temperature. Six of the eleven children had an associated mitral valvulitis; the other five had no evidence of heart disease. In most cases a striking diminution of the choreiform movements was noted after the first treatment. Children with generalized movements improved more rapidly than those in whom the movements were localized. In general, the degree of improvement was proportional to the severity of the process, that is, those children with the most marked choreiform movements showed the most rapid improvement.

Of the eleven cases that were treated, nine were cured, and so far (from one to six and one-half months afterwards) have not shown any recurrence. The other two (who were among the earlier subjects on whom the lower temperatures were used: 103° - 104° F. for three hours and repeated at weekly intervals) did not show complete cessation of their symptoms. The authors believe that higher temperatures would have caused complete cessation of the choreiform movements, but " further treatment seemed the counsel

of perfection. In those cases in which there had been previous attacks of chorea the family physician or the parents said the improvement was much more rapid with the fever therapy than without." (14) One case, which was not included in the eleven mentioned above was fatal; concerning this patient the authors say,

" This was a boy of 12 years with moderately severe chorea of three weeks' duration, and with no history of previous rheumatic infection. His heart was normal on physical examination, and his electrocardiogram was normal. After being in the cabinet for only one and a half hours, he suddenly went into collapse with a fall of blood pressure to zero, marked cyanosis, and a cardiac rate of over 180. He was immediately removed from the cabinet and given treatment for shock. His temperature rose to 108° F. (rectal), but it responded to sponges and other fever reducing measures. His condition improved gradually but steadily for nine hours after being removed from the cabinet. His temperature dropped to 101° F. (rectal), his cyanosis diminished markedly and he was entirely conscious and responded normally. His cardiac rate remained at 160 but was regular. His clinical condition at this time seemed quite satisfactory. Subsequently, however, his temperature and cardiac rate rose again and the cyanosis returned. This time efforts at stimulation and reduction of the temperature were without effect. He died 17 hours after his initial collapse.

" At autopsy the chief gross changes were in the brain. These consisted of intense edema and venous congestion. Grossly, the heart was entirely normal. The adrenals showed mild parenchymal degeneration and the thymus slight hyperplasia. There was acute passive congestion of the lungs, spleen, liver, kidneys, and gastrointestinal tract. Thus it seems apparent that death was due to a cerebral disturbance and particularly a disturbance in heat regulating mechanism.

" It is clear that the death was a direct result of the fever treatment, but it should be stressed that this boy was treated under exactly the same conditions as the many patients we have successfully treated and that he seemed

in every way an excellent subject. Such a death is perhaps comparable to the unforeseen deaths under anesthesia and should be viewed in the same light. Only time and a compilation of facts will tell whether such accidents are to be so frequent as to counterbalance the favorable results of fever therapy or whether, as in the case of anesthesia, they will be but an unfortunate but relatively small item in a desirable and beneficial whole. We hope and believe the latter will be the case." (14)

Thus we see that pyrogenetic methods, whether based on the use of a drug, a vaccine, or a mechanical apparatus, appear to cut short attacks of Sydenham's chorea in an effective manner. These methods, however, must be classified as drastic forms of therapy. All of these treatments must be given in a hospital where the patient is in the hands of a competent nurse and where the work is under the constant supervision of a physician who has been especially trained in fever therapy. These patients, according to Mutch, (4) are " decidedly exhausted and aenemic afterwards, and require a considerable period for convalesence" . It is clearly desirable, therefore, to find some simpler method of therapy if possible. It would seem that the etiologic factors--infectious diseases, commonly polyarthritis, nervous strain, and calcium deficiency should suggest a more gentle type of therapeutic approach.

In 1927 the Medical Research Council reported that general poverty was the only environmental factor which appeared to be operative in the production of the rheumatic

troubles of childhood; and the incidence of rheumatic fever in the history of choreic patients is 26 per cent according to investigations published in 1887 and 1896 respectively, and these figures still represent the situation. Owen (4) has reported that the topographical distribution of chorea seems to follow that of rickets. For some time it has been known that a lack of calcium leads to increased muscular excitability, manifesting itself in spontaneous twitchings, rhythmical contraction, and increased sensitiveness to electrical stimuli. The excitability of the motor cortex also rises as the concentration of calcium falls. In man a fall in the calcium content of the blood serum leads to increased electrical excitability of the muscles ending in tetany. Carter-Braine, Spurrell, and Warner (35) recently demonstrated an increased response of the muscles to galvanic stimulation in chorea, and Warner succeeded in correlating this with a deficiency of calcium in the serum and cerebro-spinal fluid. In his series of carefully controlled cases of active chorea he found that there was always a calcium deficit, and that this was greater in the severe cases than in the mild ones; and that this deficit no longer exists at the end of an attack. He notes further that the ionic calcium appears to be more affected so that the percentage fall is more conspicuous in the

cerebro-spinal fluid than in the blood.

Mutch noted that the oral administration of calcium-aspirin produced a rise in the calcium content of the blood. This author treated nineteen cases of Sydenham's chorea with calcium-aspirin, the daily dose varying between 25 to 60 grains, which was given orally after being dissolved in water. (Calcium chloride is present in this stabilized preparation to an extent approximating to the formula: $(C_6H_4(OCOCH_3)CO_2)_2\ Ca\ 4H_2O + 1/3\ CaCl_2)$. The average duration of the nineteen cases (mild 5, moderate 11, severe 3) so treated was 17 days, whereas the average duration of sixty-three undrugged cases recorded by Sutton (33 mild, 46 moderate, and 67 severe) was 47 days. The drug diminished the discomforts of the patients during all stages of the treatment, without producing any of that mental depression which accompanies the use of chloretone and certain other hypnotics. No undue drowsiness or digestive derangement occurred, nor was there any relapse or secondary exhaustion when the drug was finally withdrawn. It would seem, from this report, that calcium aspirin affords a method of treating chorea minor which does not occasion discomfort, exhaustion, or risk to the patient. The drug is less toxic than acetyl-salicylic acid itself, and is free from the irritating action which the parent substance has on the stomach and bladder. Fur-

thermore, it is freely soluble, almost tasteless, and rapidly absorbed. It has a triple action in that it is an antirheumatic, a corrector of calcium deficiency, and a sedative to the brain.

Calcium-aspirin is not the only therapeutic method which results in a chemical change in the blood. When typhoid-paratyphoid vaccine is introduced into the body chemical changes occur during the resulting febrile period: there is a change in the acid base equilibrium, and invariably a low carbon dioxide content of the blood during the fever, with a low level of chlorides, a moderate raising of the calcium, and a lowering of the phosphorus. In three of Montfort's cases (33) the pH of the blood was slightly increased and there was a coincident lowering of the carbon dioxide content and chloride level. (The bases are not lost in these cases but are bound to the proteins because of the increase in pH). There is a question as to whether the improvement noted in these cases should be accorded to this sudden shift in the acid-base equilibrium, or to the increase in calcium during the febrile period.

Another method of improving the deficient calcium content of the blood serum of choreic patients has been studied at the Wisconsin General Hospital during the past year. This consists in giving the patient calcium glucon-

ate, dram 1/4 to 1 mixed with aspirin, grains 5 (and dissolved in water) three times a day until relief from the choreic symptoms is obtained. Very good results were obtained in the following two cases by the use of this therapy:

F.M., white male, age 13, was admitted to the Wisconsin General Hospital on 7 - 16 - 36 with a chief complaint of " shaking of the right hand". The patient stated that he was well until three weeks ago. At that time his right hand began to shake one morning while he was in bed. He then noted that it became markedly clumsy when he attempted to do any of the chores about the farm, and he was unable to feed himself or milk the cows with his right hand. More recently there appeared a tremor and clumsiness of the right leg, and a tremor of the head.

History by systems revealed occasional poor vision, otitis media when nine years old, occasional tinnitus, infrequent vertigo, pain in the right ankle upon running, a recent weight loss of unknown amount. Past medical history disclosed the fact that there had been frequent tonsillitis until tonsils were removed at the age of nine years. Social and family histories were uninformative except for the information that patient lives on a farm.

The pertinent physical findings were purposeless choreiform movements which were most marked in the right arm and hand, but which were also present in the feet and head. However the patient was able to feed himself with his right hand. The face was flushed, and the skin warm and moist. The right pupil was slightly irregular and larger than the left with sluggish reaction to light and accomodation and retinal pallor. The anterior and posterior cervical glands were slightly enlarged and tender. There was no cardiac enlargement, but there was a loud harsh systolic murmur, maximum in the second interspace and transmitted toward the axilla; also, there was a short mid-diastolic rumble just inside the apex. P_2 was accentuated and considerably louder than A_2. On one occasion a pericardial friction rub was heard. The pulse was 90, regular, and with extra systoles. Blood pressure was 114 systolic and 76 diastolic. The neurological examination was essentially negative except for slight

weakness of the right hand and arm, and hypoactive reflexes on the right side.

Laboratory examinations included urinalysis which showed the urine to be essentially normal except for the presence of a few white blood cells. The blood cell count revealed a hemoglobin of 72; color index .7; red blood cells 4,600,000; white blood cells 8,3000; neutrophiles 62, small lymphocytes 32. Blood chemistry examinations revealed a sugar of 86, a N.P.N. of 31, and a blood calcium of 13.6, phosphorous 4.84. The blood Wasserman was negative. The spinal fluid revealed a gold sol of 0122110000, a negative Wasserman; the Ross Jones and Noguchi were faintly positive; there were no cells. The sedimentation rate was within normal limits. The electrocardiogram studies were consistent with slight myocardial changes. Orthodiascopic examination revealed slight enlargement of the left auricle and changes in the cardiac area consistent with early mitral stenosis.

A diagnosis of Sydenham's chorea with rheumatic heart disease and subacute cervical adenitis was made.

Therapy consisted of aspirin, grains V t.i.d. and calcium gluconate, drams I t.i.d. orally. Sedation was provided for by means of luminal and amytal p.r.n. Under this regimen the patient made a rapid improvement as far as the choreiform movements were concerned, the movements being less marked on the third day of hospitalization.

The pulse rate, temperature, and respiratory rate were within normal limits (97°-99°) throughout his stay at the hospital. (This would seem to indicate that the production of a fever is not always necessary in the treatment of chorea.) The patient was kept at complete bed rest, and given a nutritious high caloric high vitamin diet. Fluids were forced. And a cardiac check-up was made. Iron ammonium citrate, grains XV, q.i.d. was started, and there was gradual improvement in the heart condition. The patient was discharged on 8-23-35 with instructions to remain at complete bed rest until about 9-15-35 or until his clinical condition permitted him to start taking graduated exercise. He and his family were instructed that his diet should be nutritious and that he should be given cod liver oil and other vitamin containing substances. Furthermore, the patient was instructed to return to the hospital after several months for a check-up.

Summary: mild case of Sydenham's chorea treated by rest and sedation, aspirin, and calcium gluconate. Choreiform movements ceased within 35 days; patient discharged within 38 days.

The second case was that of A.M.R., white female, age 12, was admitted to the Wisconsin General Hospital, on 3-6-35 with a chief complaint of nervousness. She stated that she was well until November, 1934 when she developed a stiff neck, swollen glands in the neck, and a loss of appetite. About December 1, 1934 she developed scarlet fever and was confined to bed for two weeks. During that time her joints and back ached for three days, and she resented being moved. She became somewhat run down, and three weeks prior to admission, it was noticed that she would laugh easily and not act like herself in that she seemed to be quite nervous. She had lost her ambition and pep. A week prior to admission the right ankle had swollen. And five days prior to admission it was noticed that the right fist had a tendency to remain closed; and during the three days before she entered the hospital she was unable to feed herself. She talked all right until five days before admission when her speech was so affected that she could only say a few words. Her mind seemed to remain clear. She had difficulty in walking and this had been getting steadily worse; she was unable to gauge her distance and so would bump into objects. She was never still for a second.

History by systems revealed that since she had been breathing a good part of the time with her mouth open. Also, that she had had several mild nose bleeds when she had scarlet fever.

Past medical history revealed that in addition to scarlet fever the patient had had measles, mumps, and chicken pox. Social history gave no relevant facts. Family history informed one that the patient had four sisters and three brothers all living and well. One grandmother had cancer of the stomach.

Physical examination showed a well developed, fairly well nourished 12 year old girl who evidenced purposeless, patternless, continuous, bizarre movements of the face, tongue, neck, limbs, and trunk. At times her movements were athetotic. There was marked dysarthria, the eyes were constantly moving. The fundi seemed normal. She had a subsiding right otitis media. There were a few carious teeth; the gums bled easily; and pus was present at the

base of the upper first pre-molar. The tonsils were extremely large and red, and the submaxillary glands were large and firm. Respiratory movements were irregular and cog wheel in type; the lungs were clear. The heart was not enlarged, but there was a rough apical and precordial systolic murmur in recumbency, slightly transmitted toward the axilla; also a sinus arrythmia. The blood pressure was 130 systolic and 75 diastolic. The gait was decidedly ataxic in all movements; all modalities of sensation were intact.

Laboratory examinations revealed the complete blood count to be normal except for a leukocytosis of 16,850 with 79 % neutrophiles. The blood Wasserman was negative. Blood chemistry examinations showed the blood sugar to be 92, N.P.N. 35, calcium 9.9, phosphorus 4.5. Repeated urinanalyses were normal. The spinal fluid Wasserman was negative; the gold sol 0122210000; the Ross Jones and Noguchi faintly positive; there were no cells found in the spinal fluid.

A diagnosis of Sydenham's chorea with active rheumatic heart disease, mitral stenosis, and chronic tonsillitis was made.

Therapy consisted of absolute bed rest; aspirin Gr. V and calcium gluconate Gr. XV t.i.d., in addition to other supportive measures. (The tonsils were removed after their infection had been controlled--on 5-7-35). There was steady improvement. She became much less restless, and the abnormal movements of the tongue and limbs became less manifest by the fourth day of hospitalization. By the ninth day the choreic movements had decreased to such an extent they appeared only on volition. By the twenty-second day of hospitalization she was able to feed herself. Cardiac examination, however, on 4-13-35 showed slightly accentuated systolic apical sounds; and a soft blowing systolic murmur along the left sternal border and at the apex which was transmitted faintly toward the axilla; and a continuous murmur in the second left intercostal space resembling a venous hum which varied considerably with respiration. There were no diastolic murmurs. The patient's activities were gradually increased after her pulse had stabilized and on 5-7-35 a tonsillectomy was performed from which she recovered satisfactorily. She was discharged on 5-12-35 at which time her leukocyte count was normal. Because of her cardiac involvement her physician was instructed to restrict her activities

considerably. And she was told to rest at home as much as possible, and to be careful not to exercise to the point of tiring. It was suggested that she continue taking aspirin Gr. V-X. per day for a period of two or three months.

Summary: a severe case of chorea treated by rest, sedation; aspirin and calcium gluconate. (Also tonsillectomy). Movements began to decrease within four days, markedly decreased within nine days--so that they were absent unless patient attempted voluntary movement. By the twenty-second day the patient was able to feed herself. Dismissed after sixty-seven days.

VI

Summary and Conclusions

A review of the various forms of therapy which have been proposed for treating cases of Sydenham's chorea is given, preceded by a discussion of the pathology of the disease. Two forms of classification are noted.

The rapid termination of the purposeless movements and the avoidance of complications are two objects of concern in these cases. It is generally agreed that chorea, at all times, even in its mildest form, is sufficiently serious to demand careful handling. The victim of this disease should be kept at bed rest during the acute stage in order to minimize the liability of serious complications. This is better carried out at the hospital than at home. All mental activities and intellectual efforts should be avoided, and emotional influences disturbing to the patient should be shunned. Good nursing care is essential.

Non-specific measures consist of promoting sedation by means of the barbiturates and bromides, or by the more powerful avertin or paraldehyde in cases of chorea insaniens; of treating concurrent rheumatic involvement by means of the salicylates; of giving the patient an abundant and nourishing diet; and of relieving constipation promptly whenever it occurs. Fowler's solution is still used by many physicians but its value as a specific has

undoubtedly been overestimated. However, it serves to keep the general metabolism of the patient at a normal level while he is receiving sedatives of various forms. And the value of many other forms of arsenicals is still a matter of debate. This is true also of various forms of sera.

Foci of infection must be searched for and eradicated, this not necessarily, however, during the acute stage of the disease. Following this stage of the disease, and for several years after convalescence, the patient should undergo a periodic physical examination in order that any rheumatic cardiac lesion such as mitral insufficiency may be detected early.

Physical therapy in the form of baths and light massage is undoubtedly beneficial. Re-education of the muscles by relaxation exercises, and passive and active motion all help the patient to regain normal precision of movement.

As for specific drugs, many have been tried, but none have been proved to be entirely satisfactory. Measures which influence the underlying pathological physiology of the disease seem to be most beneficial. That is, the uncomplicated case of Sydenham's chorea is unaccompanied by fever; and the production of fever by means of typhoid-paratyphoid vaccine or by some form of radiant energy has

been found to greatly shorten the duration of purposeless movements. Furthermore, certain workers have noted that there is a calcium deficiency in the blood of many chorea patients; this has been found to be less evident than a similar deficiency in the spinal fluid. The administration of this element in the form of calcium-aspirin or calcium-gluconate has proved of definite value in cases of chorea minor. Likewise those remedies which produce a change in the pH of the blood serum, a change toward the alkaline side, have been beneficial; nirvanol and typhoid-paratyphoid vaccine both do this during the temporary febrile state which they induce. Of these two remedies, typhoid-paratyphoid has proved of greater value because of its relative harmlessness, shorter time required for cure, ease of administration, and significant lack of sequelae. However, because the pyrogenetic methods are more drastic than the oral administration of calcium, the latter form of therapy would appear more desirable, especially for the patient that must be treated at home where it would be impossible to control the type of temperature variations produced by vaccine administration. Whether or not the calcium acts more quickly than the induced fever and whether or not its effect will be more permanent (as judged by the frequency of recurrences) are factors which can be determined only by a protracted study of a considerable number of patients. It would be interesting in such a group

of cases to ascertain the calcium content of the blood and spinal fluid both before treatment and at various stages during treatment. Parathyroid extract has been used (in combination with Fowler's solution; and calcium lactate) in chorea therapy with a fair amount of success; because of its relation to calcium metabolism, its significance in chorea should be considered. It is of interest that Sutton and Lyttle had reason to believe that a considerable number of their patients had deficient thyroid activity, and that improvement in their chorea followed the administration of thyroid extract.

In conclusion: many remedies have been suggested for treating chorea. Most of these have been used in such a small number of cases that their value has neither been proved or disproved. Furthermore, the evaluation of any method of treating a disease like chorea, which has several grades of severity, and which, when untreated,has such a variable duration, is difficult. The induction of fever and the administration of calcium have both recently been proved to have a definite beneficial effect; the latter form of therapy is less drastic than the former and can easily be used at home when it is impossible to hospitalize the patient.

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