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Polyneuritis in pregnancy

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POLYNEURITIS IN PREGNANCY

By

HAROLD F. FRIESEN

SENIOR THESIS PRESENTED TO

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DEFINITION AND INTRODUCTION

The recognized serious conditions which may complicate pregnancy are designated as the toxemias, including eclampsia and pre-eclamptic toxemia, nephritic toxemia, pernicious vomiting, and the like. In addition to this more or less well defined group, there is still another group of cases which are much less frequently seen and even less well understood, which are usually classed as presumable toxemias. Under this category may be included certain psychoses, excessive salivation, the noncontagious skin lesion impetigo gestationis, and certain examples of multiple neuritis or polyneuritis. Peripheral neuritis, polyneuritis, and toxic myelitis are all the same as toxic neuronitis.

Polyneuritis of pregnancy is a more or less simultaneous involvement of many peripheral nerves, and is quite distinct from the more frequently seen traumatic and infectious types.

The aim of this thesis is to suggest B complex avitaminosis as an etiologic factor in polyneuritis of pregnancy.
INCIDENCE AND OCCURRENCE

Polyneuritis is far more common than was formerly thought. The frequency cannot be estimated. Many cases of so-called late toxic vomiting of pregnancy should be placed in this category. Cases where there may be a suspicion of hysteria because of the character of the subjective complaints and the almost complete absence of evidence of visceral disease should be placed in this group. In any doubtful case, careful neurologic examination is demanded, since it is only in this way that polyneuritis can be diagnosed.

In 1938 Schultze (46) reported sixty cases which he gathered from the German literature in one year.

The disease occurs more commonly in those pregnant for the first or second time, although women with a greater number of previous gestations are not exempt. There is no age relationship. Patients who have previously exhibited evidences of mental instability may be more susceptible. The condition occurs most frequently between 21 and 35 years of age, the period when the incidence of pregnancy is the greatest.
HISTORY

Among the earliest references to polyneuritis is a paper by Churchill (8), published in 1854, in which he reports a case of paralysis following delivery observed by himself, and collected 33 other examples of various types. Only few of these apparently fall into the group caused by peripheral lesions of the nerves, many of the others being of the hemiplegic type. Churchill suspected the possible toxic nature of the condition on account of the association of albuminuria at times.

Moebius (39) in 1887, reported seven cases of peripheral neuritis, all occurring in the puerperium, and with no associated general disturbances. None of these were due to trauma, and all recovered. He subsequently reported several other cases of a similar nature. Apparently, the earliest recorded case associated with severe vomiting and a profound general disturbance is that of Whitfield (60) reported in 1889. He ascribed the neuritis, and the resulting paralysis to the persistent vomiting. This was undoubtedly one of the severe toxic types. The patient recovered. Lindemann (34), in a fatal case reported by Solovieff (48), found at autopsy in addition to lesions of various peripheral
nerves, a fatty degeneration of the liver with cloudy swelling, and degenerative changes in the kidneys. Similar lesions were found in the liver and kidneys of the fetus. He did not regard these lesions as specific. During the illness of this patient, Solovieff recorded the interesting observation that the stomach contents contained no hydrochloric acid, this being ascribed at the time to the fact that she had been taking "soda water." This patient also presented marked mental disturbances during her illness.

Von Hoesslin (21) in 1905, wrote an excellent review of the subject and collected 94 cases from the literature, including several observed by himself. His series included all types, in some only a single nerve being involved, in others groups of nerves, while still others were of the severe type with progressive general-paralysis, and associated severe vomiting and mental disturbances. In those patients presenting a generalized paralysis, he found the mortality to be 20 per cent.

Von Hoesslin did not feel that interruption of the pregnancy was necessarily indicated in this condition, even in the severe form. He based this statement on the fact that many patients improved without having the pregnancy interrupted, and also on the fact that
termination of the pregnancy was not necessarily fol-
lowed by improvement. Furthermore in not a few patients,
the first symptoms appear in the puerperium, several
days or even more after the pregnancy has come to an
end. In the presence of a vital indication or devel-
oping blindness, however, he conceded that pregnancy
should be interrupted. Other observers felt that preg-
nancy should be interrupted in those instances where
improvement failed to occur following palliative treat-
ment.

Among the series reported is that of Albeck (1),
who presented 9 cases of the severe type with severe
vomiting, psychoses, and progressive paralysis. In
7 of them pregnancy was interrupted, all apparently
recovered, though the convalescence was prolonged, and
months elapsed before normal muscular function was
restored.

Korsakow (32) reported a case of paralysis re-
sulting from peripheral neuritis, in which the child
died several days before delivery. Death of the child
did not bring about immediate improvement, the con-
valescence being long drawn out, and some permanent
paralysis persisting. Korsakow and Serbski (30) ob-
served an example of the condition associated with
advanced extrauterine pregnancy and dead fetus.
ETIOLOGY

It has been commonly assumed that polyneuritis is the direct result of the action of a toxin which is elaborated by the product of conception and which has an especial affinity for certain parts of the nervous system. No evidence is available to support the hypothesis, which moreover is rendered improbable by the fact that termination of the pregnancy frequently fails to arrest the progress of the disease.

In 1859 Churchill (8) offered anemia, uremia, rheumatism, and hysteria as possible causes of the paralysis. Jaccoud (27), in 1886, made a highly theoretical suggestion that the paralysis was due to exhaustion of the nervous system by prolonged and continued excitement of the cord, and that the impulses were transmitted by the uterine nerves, exhausting the excitability of that particular segment of the cord, closing the avenues by which motor impulses pass. Later Jolly (30) ascribed the paralysis to hysteria, while Moebius (39) in 1887, was one of the first to suggest a theory of autointoxication. He believed that some "morbid condition of the blood" of the pregnant woman was the causative factor. Tuillant (55)
noticing that severe vomiting preceded the neuritis, suggested that the lack of nourishment was the probable cause. To refute this theory, Lindemann (34) undertook a series of observations on dogs, and his results showed that malnutrition alone, however extreme, failed to show any microscopic degenerative changes in nerves. Polyneuritis resulting from starvation has been reported by Schlesinger (45) and others, but histopathological studies have been largely neglected. Since 50 per cent of pregnant women had nausea and vomiting in the early part of pregnancy, Bouchard (5) concluded that all pregnant women suffered to a greater or less extent from auto-intoxication. Viet (57) held that all disturbances of pregnancy resulted from cytolytic processes following the entrance of fetal ectoderm into the maternal circulation. Ewing (14) maintained that vomiting of pregnancy, yellow atrophy of the liver, and eclampsia were all manifestations of disturbed metabolism and should be grouped together under a common heading of toxemia of pregnancy.

In 1897, Reynolds (43) gathered from the literature 49 cases of polyneuritis in pregnancy. He observed that the disease was more common in multiparas. In 12 cases
the onset occurred during pregnancy. Of the cases commencing after delivery, 16 cases developed symptoms within the first week, 7 developed symptoms during the second week, 6 cases during the third and fourth weeks, and 2 cases within the second month. In the 5 remaining cases the details are not available. In 15 cases out of the total of 49, there was a distinct history of some form of sepsis with shivering and fever. In 11 cases there was marked and incessant vomiting of pregnancy, so great in some instances that abortion had to be procured. In 2 of these cases the symptoms of neuritis did not come on until about three weeks afterwards. In 4 cases there was a distinct alcoholic history, and as in many instances there was marked tenderness on deep pressure of the muscles. The question arose as to whether more of the cases were not due to alcohol. Reynolds (43) stated that during pregnancy and in the puerperium not a few women take alcohol. After a careful study of the symptomatology of puerperal neuritis, he concluded that alcohol was not the cause since alcoholic neuritis is practically never associated with paralyses of the cranial nerves. He considered sepsis and incessant vomiting as the most potent factors in producing the condition. He suggest-
ed that possibly the incessant vomiting set up a condition of acetonaemia, and that the acetone or some allied body in the blood produced the neuritis.

Elder (13) observed excessive vomiting during pregnancy in some of his cases of polyneuritis. Some of his patients did not have excessive vomiting and yet developed polyneuritis. He suggested the possibility of vomiting being only a concomitant symptom. Most of his puerperal polyneuritis cases gave a distinct history of fever during the puerperium so that they were really cases of septicemia neuritis.

Berkwitz and Lufkin (4) studied their cases of polyneuritis very carefully and concluded that polyneuritis of pregnancy presented a distinct picture, both clinically and pathologically, from the other complications which result from toxic conditions in pregnancy.

In 1930 Theobald (53) suggested that the cases of pregnancy neuritis seen in this country might be a form of beriberi, and for three reasons: (1) the incidence of the neuritic form of beriberi in Bangkok was much higher in pregnant than in non-pregnant women, indicating that an increased intake of vitamin
B was necessary during pregnancy, (2) the neuritic symptoms of beriberi were indistinguishable from those of the polyneuritis of pregnancy, and (3) it was his opinion that all the toxemias of pregnancy were interrelated and due to dietetic deficiencies and considered that the increased incidence of beriberi during pregnancy supported that hypothesis.

In 1932 McGoogan (36) stated that polyneuritis was possibly of a toxic origin, although the nature of the toxin was unknown. There is a distinct clinical and pathological picture accompanying the disease, differing somewhat from the other complications which result from the other toxic conditions in pregnancy. McGoogan also states that it must have some relationship to hyperemesis gravidarum, as all cases have their onset in pernicious vomiting. It is well known that certain cases of pernicious vomiting are of toxic origin. Toxic neuronitis may bear the same relationship to pernicious vomiting that eclampsia bears to pre-eclampsia.

It has been customary to refer to any and all pathologic conditions developing during pregnancy as manifestations of some occult toxemia, relief from which may be secured by terminating the gravid state.
In 1933 Strausz and McDonald (52) related that not one of the "toxins" allegedly responsible for the anemias of pregnancy, for the polyneuritis, for hyperemesis gravidarum, or for eclampsia had been identified, isolated or recovered in any form. It is not many years since pernicious anemia, pellagra and beriberi were commonly considered disorders due to the action of hypothetic toxins. To this day, in fact, adherents of the toxic theory are still endeavoring to overcome the evidence that these conditions are dietary deficiency diseases either due directly to faulty diet or indirectly arising from some gastro-intestinal factor.

The anemias of pregnancy have frequently been considered toxic manifestations of the gravid state. Investigations have not only failed to reveal any evidence of toxemia but show that dietary deficiencies, especially of iron, vitamin B₂ and related substances, can account for both the hypochromic and the macrocytic anemias of pregnancy. In some cases a direct lack of these substances in the diet can be held responsible, but in most instances the deficiency can be explained as due to gastric secretory and related defects. Pregnancy normally produces marked reduction in gastric secretion and since the fetus is able to drain the
maternal organism to supply its needs, the pregnant state is indeed one that readily enhances the development of dietary deficiency disorders. Patients with anemia of pregnancy, if treated on a quantitative basis by supplying the materials that are lacking, recover.

Forman (16) reported a case of polyneuritis of the beriberi type with mild hypochromic anemia. The former is known to be due to vitamin B₁ deficiency. His patient had pernicious vomiting for two months which he considers ample time for the development of deficiencies in all essential food materials. This case responded to adequate dietary regime.

According to the work of Schultze (46), there is a greater need for all the vitamins during pregnancy. The vitamins concerned are mainly the fat soluble A, D, and E, and the water soluble B and C. Vitamin B₁ is concerned with carbohydrate metabolism and the function of the peripheral nerves. The greater the sugar metabolism of the body is, the greater is the need for vitamin B. Experimental work has shown that beriberi can result from the taking of to great amounts of sugar over a long period of time. Chronic vomiting results in a disturbance in absorption and vitamin B
Is not obtained in sufficient quantities. Schultze (46) noticed that most of their patients with polyneuritis came in at Christmas time or soon after. He thinks this is due to the high carbohydrate diet used during the Christmas season.

Vandel (56) reported a group of cases of polyneuritis which occurred among Italian women in St. Louis. The patients treated at his clinic lived under very poor hygienic and dietary conditions. He has observed this disease more frequently during the three years preceding 1933 as a result of a poorly balanced ration directly due to the then present economic crisis.

Wechsler (59) wrote about his observations on polyneuritis in 1930. In looking over the records at the Montefiore Hospital, he found several cases of polyneuritis which were of interest. What seemed most striking was that in practically all of them there was a history either of vomiting or gastro-intestinal disturbance or restriction in diet. The question then arose whether he was not dealing with instances of food deficiency, possibly an avitaminosis, which was the result of direct privation or poor digestion and absorption of food. Further observation and investigation only served to confirm the suspicion and therapeutic efforts
to supply the deficiency by means of diets rich in vitamins lent additional color to the view as to the etiology.

Polyneuritis progresses to a fatal termination very frequently regardless of whether the uterus is emptied or not. Berkowitz and Lufkin (4) suggest abortion as soon as neurologic symptoms appear. A study of the cases reported in the literature shows that if the nervous element of the disease is advanced, abortion is of no avail. This definitely indicates that some concomitant etiologic factor exists in addition to the pregnancy, or that some complication develops as a sequela of the disease or from some shortcoming in the treatment during the pernicious vomiting of pregnancy.

Luikart (35) reported a very good case to support the avitaminosis theory. During the illness of this patient her system was flooded with large quantities of water and glucose, which of course are vitamin free. She showed a temporary improvement followed immediately by an exaggeration of her symptoms unless vitamin containing nutrition was administered with the water and glucose. This observation is in close keeping with Cowgill's work in which he has pointed out that the expression "toxemia" is drawn into service at present.
as an explanation for a variety of manifestations of disease for which no clear interpretation is available. Startling cures that occur following the administration of vitamins to so-called polyneuritic pigeons, in which nerve degeneration can be demonstrated so readily, can hardly be explained as due to sudden correction of the degenerative changes in nerves. This had led many of the investigators to favor the idea of toxemia from toxins injected with food or from faulty metabolism. One of the methods supposed to relieve such a condition consists in "washing out" the system by liberal intake of water and producing a vigorous diuresis. This process is sometimes accelerated by the parenteral administration of fluids. The plan has been put to the test in the laboratories of Yale Physiological Chemistry Department by Cowgill (11) and his collaborators, in the case of animals deprived of their optimal intake of vitamin B complex by a selected regime. When they were given large amounts of water it was found that the time required for the appearance of the anorexia characteristic of the dietary essential was markedly shortened. Instead of being protected, the animal was rendered more susceptible to the deficiency of the vitamins. Cowgill (11)
pointed out that this result was not in harmony with the hypothesis that the symptoms of deficiency of vitamin B complex are essentially those of toxemia. The urge to eat was restored by undifferentiated vitamin B complex. His explanation of the results of the forced fluids was a temporary relief of the anorexia and anhydremia, but the diuresis probably was actually detrimental in that it washed the vitamin B complex from an already partially depleted body. Certainly sufficient evidence was at hand, he concluded, that trials of the administration of some potent source of vitamin B complex are warranted. In any event the vague assumption of an existing toxemia may no longer be entirely sufficient to the clinician.

Cowgill (11) also pointed out the well-known fact that the capacity for storage of vitamin B complex in the body is rather limited. Increased exercise definitely decreased the period required for the development of anorexia characteristic of lack of vitamin B complex. These observations are considered to be supported by the fact that vigorous exercise increases voluntary food intake. Furthermore, the vitamin B complex intake requirement of an animal is significantly increased when the metabolic rate is increased by thyroid administration.
Baer (3), in 1921, gave a report on 44 normal cases in late pregnancy in which the basal metabolic rate averaged 33 to 35 per cent above the normal for non-pregnant women. This fact, in view of Cowgill's observations, would make logical the assumption that the vitamin B complex is endangered even during normal pregnancy.

Spinal cord and peripheral nerve lesions may occur in animals fed on a diet rich in the vitamin B complex. These lesions may be prevented by the addition of vitamin A to the diet. Beriberi is usually attributed to a deficiency of vitamin B1 in the diet, but in 1934 Mellenby (38) suggested that the nerve lesions associated with this disease, as well as those occurring in pellogra, were due to vitamin A deficiency. He asserted that he was unaware of any evidence which proved that neuritis involving demyelination of nerve fibers could be produced in animals by diets deficient only in the anti-neuritic vitamin B and doubted whether the condition once produced could be cured by the exhibition of this vitamin alone. The apparently conflicting laboratory results appear to be due to two main facts: 1) in order to produce lesions in animals it is often necessary to feed them with diets to which they are not
accustomed and which may be deficient in other substances, organic and inorganic, as well as the vitamin concerned; 2) once nerve lesions have been produced a long period of time may be necessary for their recovery even when the diet is adequate, and it is difficult if not impossible to be sure of early lesions in animals.

Wilson and Garvey (64) reported three cases of polyneuritis in 1932. Each of these cases also showed profound mental disturbance, and at the onset of the illness had severe and persistent vomiting. They felt that they had satisfactorily excluded such toxic agents as alcohol and lead, and also infection as possible etiologic factors. They felt justified therefore in ascribing the origin to a toxemic process associated with pregnancy.

In the 52 cases collected by Berkwitz and Lufkin (4), improvement did not occur during pregnancy in any of the cases. Even after removal of the fetus they reported a mortality of 25 per cent. Against this rather hopeless outlook, Strausz and McDonald (52) presented certain facts and observations indicating the curability of the condition. First, and of most importance, is the fact that severe vomiting almost
always occurs recurrently for many weeks before the onset of polyneuritis. This prevents the patient from ingesting and absorbing the proper food. Secondly, it has been shown that abnormalities of the gastro-intestinal tract can play an important role in the causation of deficiency diseases, and in pregnancy there is ordinarily a marked decrease of gastric secretory function. Thirdly, in pregnancy the fetus takes all sorts of materials from the maternal organism, no matter what depletion may result to the mother. Fourthly, the clinical and pathologic examination in polyneuritis of pregnancy is identical with that of beriberi and alcoholic polyneuritis and is unlike the more strictly motor nerve involvement due to lead, and triorthocresyl phosphate polyneuritis.

The modern American diet has been regarded as deficient in many respects, due in part to faulty dietary habits and food selections based largely on appearance or taste, often leading to a high carbohydrate intake and an excess of fat. Again, economic status plays a part and, in an effort to provide sufficient calories in energy foods at low cost, a carbohydrate diet prevails. Organic or functional disease may interfere with both absorption and utilization and bring
to light latent deficiency conditions.

The international unit of vitamin B₁ has been defined as the anti-neuritic activity of 3 micrograms of the international standard preparation of crystalline vitamin B₁ hydrochloride. One milligram of thiamin chloride is equivalent to 333 international units of vitamin B₁.

Staehler (49), in 1938, studied the effect of vitamin B₁ on four non-pregnant women, four normal pregnant women, and one woman with polyneuritis of pregnancy. He found that the pregnant women excreted 30 per cent less vitamin B₁ in their urine than the non-pregnant women, the pregnant women needing from 7 to 8 mg. of vitamin B₁ in 24 hours, while the non-pregnant used from 5 to 6 mg. in 24 hours. He also found that the placenta was very permeable to vitamin B₁.

In 1939 Jolliffe and his associates (29) experimentally produced the symptoms and signs of vitamin B₁ deficiency in normal subjects. The vitamin B₁ poor diet used was probably adequate for normal man except in vitamin B₁. The experimental observations on each of five subjects were divided into three periods: control, deficiency and recovery. The thiamin excretion
in the urine was also determined during these periods.

Deficiency of vitamin B₁ was initiated by placing five subjects on the vitamin B₁ poor diet. The first few days of the deficiency period were symptom free. On the third and fourth day the subjects began to complain of the monotony of the diet. The symptom common to all subjects was fatigue. Four subjects complained of anorexia. It occurred as early as the fourth day in one patient. Symptoms referable to the cardiovascular system occurred in three subjects. The symptoms were dyspnea on slight exertion in two subjects and precordial pain in three subjects, and palpitation in one subject. The precordial pain occurred on effort, lasted for 2 to 3 hours, was aching in character, precordial and substernal in location, and did not radiate to the shoulders, neck or arms. The dyspnea and fatigue in one subject was so severe that he was unable on the eighth day of his deficiency period to walk up a flight of stairs without resting or to continue his duties as house physician.

Neurologic symptoms were observed in three subjects, all of whom complained of burning of the feet especially at night. This symptom was first noted on the fifth day by one subject and on the eighth day by
the other two subjects. Cramps in the calf and feet muscles occurred in two subjects by the seventh and eighth days respectively. Paresthesias were not noted by any subject.

The addition of thiamin to the vitamin B₁ poor diet, which marked the beginning of the recovery period, was followed by the prompt disappearance of all symptoms, in that no subject had any abnormal complaints after the third day of the recovery period. By this time anorexia had given way to hunger. The fatigue and lassitude which had been obvious to all who observed these subjects, was replaced by a feeling of well-being; burning of the feet, muscle cramps, precordial pain, dyspnea and palpitation were no longer present. The relief of symptoms occurred without the subjects being aware, except from the change in their own subjective feelings, that thiamin had been added to the hydrochloric acid supplement. The amount of thiamin added to the vitamin B₁ poor diet was 3.36 mg. daily.

Objective signs of vitamin B₁ deficiency occurred in four subjects and were limited to hyperesthesia, calf tenderness, and changes in the electrocardiogram. Definite hyperesthesia was limited to the plantar
surface of the feet in all these subjects except in one, in whom by the twelfth day it extended to the mid-calf of both legs in a sock distribution. Calf muscle tenderness was elicited in only one subject. When thiamin was added in the recovery period, the objective signs disappeared in the reverse order of their occurrence.

They found that the urinary excretion of thiamin was roughly proportional to the dietary intake of vitamin B₁. It was also evident that the urinary excretion reflects, as a rule within 24 hours and always within 48 hours, changes in vitamin B₁ intake of the magnitude used in their study. This was true whether vitamin B₁ was added or removed from the diet.

In addition, it was noted that during the deficiency period subjective symptoms did not occur unless the excretion of thiamin fell below 100 micrograms daily, and in one subject subjective symptoms did not occur until a level of about 30 micrograms was reached. During the recovery period, the symptoms and signs noted above did not promptly disappear when the urinary excretion of thiamin exceeded 100 micrograms daily.

The average thiamin excretion during the control period varied from 319 micrograms to 676 micrograms,
accounting for 13.1 to 25.7% of the estimated intake. During the deficiency period the average thiamin excretion varied from 35 micrograms to 108 micrograms accounting for 7.4 to 23% of the estimated intake. In the recovery period, the average thiamin excretion varied from 339 micrograms to 806 micrograms, accounting for 11.7 to 21.1% of the estimated intake.

That signs and symptoms may develop as rapidly as seen in this study with diets only moderately restricted (43 to 62% adequate) has many clinical implications. It suggests the possibility of a high prevalence of mild thiamin deficiency in the general population.

Williams, Mason and Smith (62) reported controlled observations on induced thiamin deficiency in human beings in December of 1939. In that study, 4 young women for twenty-one weeks received a diet which was more deficient in thiamin than commonly is reported in association with the syndrome of beriberi. This diet was made adequate in vitamin A, ascorbic acid, proteins and minerals and in addition was supplemented with crystalline preparations of riboflavin and nicotinic acid. The period of restricted intake of thiamine extended from December 12, 1939 to March 9, 1940.
The time of onset of signs and symptoms varied. In general, the more active subjects were the first to experience symptoms. The abnormalities ultimately noted in all of the subjects who were deprived of thiamin for periods of several weeks were: depressed mental states, generalized weakness, dizziness, backache, soreness of muscles, palpitation, dyspnea and precordial distress on exertion, insomnia, anorexia, nausea, vomiting, loss of weight, atony of muscles, very slight roughness of the skin, faint heart sounds, lowered blood pressure and bradycardia when at rest, with tachycardia and sinus arrhythmia on exertion. In all cases physical activity greatly decreased. Less regularly there were observed states of apathy, re-awakening of psychotic trends, difficulty of thought and memory, photophobia, headache, abdominal distention, sensations of cold and heat, burning of the soles of the feet, numbness of the legs, fatigue of the ocular muscles, tenderness of the muscles of the calves and depressed tendon reflexes. Changes in the size of the heart were not detectable in any case. Edema was not apparent in any case. The concentration of plasma proteins remained within normal limits in all cases. The values of serum calcium and serum phosphorus re-
mained normal. Anemia did not develop.

In all cases the capacity for work, was measured
with a calibrated chest weight exercising machine, fell
progressively during the period of restricted intake
of thiamin. In 3 of the 4 subjects the blood sugar
time curves became diabetic in type.

The period of restricted intake of thiamin was
terminated after eighty-eight days by giving a sub-
cutaneous injection of 1 mg. of thiamin hydrochloride,
(March 9, 1940). The diet low in vitamin B1 was con-
tinued until March 26, 1940. During the interval from
March 9 to March 15, daily injections of small doses
of thiamin hydrochloride were made, and the amount of
thiamin contained in the urine was determined daily.

Subjective improvement was observable in every
case within a few hours after the initial injection
of 1 mg. of thiamin hydrochloride. Nausea and vomit-
ing ceased; food which previously had been revolting
to the patient was eaten without urging; fatigue dis-
appeared; activity was resumed, and apathy was replaced
by lively interest in ward work and current events.

During the eighteen days (March 9 to 26 inclusive) in
which administration of thiamin hydrochloride repres-
ented the only change made, all signs and symptoms
incident to the period of restriction of thiamin disappeared. The electrocardiograms became normal; the previously diabetic type of sugar tolerance curve was replaced by a normal curve; and the previously sluggish motility of the intestinal tract was replaced by normal activity.

Two of the six subjects placed on the diet restricted in thiamin were given thiamin hydrochloride orally. This was done without their knowledge. The basal diet contained 0.15 mg. of thiamin. The initial dose of thiamin hydrochloride was 0.5 mg. It was given eleven days after starting the diet, at a time when the urinary content of thiamin had fallen to very low levels. Thereafter a daily dose of thiamin hydrochloride was administered in gradually increasing doses up to 2 mg. a day. A substantial increase of thiamin in the urine did not occur until the intake of the vitamin had reached 0.95 mg. Marked improvement in the clinical state of the subject was accompanied with an increased capacity for work. On March 27, when the daily level of intake was lowered from 2 mg. to 0.75 mg., the capacity for work again fell, and when more thiamin was given, on April 10. The capacity for work again increased.
In both of these subjects an intake of less than 0.95 mg. of thiamin daily was associated with fatigue, irritability, poor appetite, insomnia, soreness of muscles and constipation. On the other hand, a feeling of unusual well-being associated with unusual stamina and enterprise accompanied the period (March 7 to 26) in which the intake of thiamin was at the level of 2 mg. daily. This was followed by a letdown when the intake of thiamin was lowered by substituting the routine hospital diet for the basal diet which had been supplemented with thiamin hydrochloride. The change at this time was so striking that one subject begged to be returned to the basal diet. This constitutes strong evidence that the hospital diet, which by calculation contained approximately 0.6 to 0.8 mg. of thiamin daily, provided less than an optimal allowance of thiamin. They determined the basal diet was 0.95 mg. of thiamin daily. The observations indicate that institutional diets in general provide less thiamin than is desirable.

These observers also suggested that the isolated withdrawal of thiamin from the diet does not produce beriberi symptoms. They were led to question whether thiamin is the vitamin the lack of which is responsible
for the classic features of beriberi and to suggest that deficiency of factors of the vitamin B complex other than thiamin may be more important in the production of such features than thiamin itself.

Williams and his associated (62) were impressed by the degree of debility induced by the isolated withdrawal of thiamin. Fatigue, lassitude and loss of interest in food developed early and increased progressively as the period of deficiency extended, to the point of intolerance for food. So great was this intolerance that uncontrollable vomiting, even after tube feeding and parenteral injection of solutions of sodium chloride and dextrose, automatically brought the observations to a close. They noticed that patients needed less thiamin in the summer months.

The disease induced by restricting the intake of thiamin differed from classic beriberi in that the edema, cardiac dilatation and peripheral pain were absent. The early stage of the disease induced closely resembles neurasthenia; the later simulates anorexia nervosa.

In 1938, Sidall (47) advanced the theory, based upon his observations on prenatal cases afflicted with beriberi in China, that normal function of the pit-
uitary gland is possible only when an adequate supply of vitamin B₁ is available. He believes that in the pregnant woman a deficiency leads to an over-compensation or malignant hyperfunction of the gland. This in time produces the various symptoms of toxemia; disturbed carbohydrate metabolism, edema, elevated blood pressure, nausea and vomiting, and an increase in prolactin and decrease in estrin.

Williams and his associates, (61) in their studies of the food records, showed that one-third of a group of 91 pregnant women were not receiving an adequate amount of vitamin B₁. This was calculated on a ratio of 15 international units per 100 calories. Practically two-thirds of this group were receiving less than 500 units of vitamin B₁. They found some positive correlation between the inadequacy of the intake and deficiency symptoms, such as excessive nausea and vomiting, fatigue and paresthesias.

Following the chemical identification of thiamin and its successful synthesis by Williams and Cline (63) in 1936, the term vitamin B₁ has been generally regarded as synonymous with thiamin. Before that date, however, it was generally used by clinicians to mean no more than the hypothetical anti-beriberi vitamin.
this reason, any writings prior to 1936 in which specific claims were made for the etiologic relation of vitamin B₁ deficiency to nutritional polyneuritis cannot with justification be quoted as expressions of the opinion that thiamin as now known was the factor concerned (37).

Since the earliest differentiation of the vitamin B complex into the heat-labile (B₁) and heat-stable (B₂ or G) fractions, the former has been thought of as having two outstanding characteristics: first, that its deficiency in animals results in the signs of opisthotonus and inco-ordination (erroneously supposed to be evidence of anatomic polyneuritis); and secondly, that its deficiency in man results in the neurologic and cardiovascular manifestations of beri-beri. The pure substance thiamin, which cures the nervous signs in animals, has now been isolated; but it does not necessarily follow that thiamin is capable of filling the role of the hypothetical "anti-beri-beri vitamin."

Meiklejohn (37), basing his beliefs on experimental work and a review of the literature, states that there is no proof at present that thiamin deficiency produces in animals the anatomic changes of
a true peripheral neuritis, and certainly no evidence that thiamin will cure the peripheral neuritis produced in animals by other deficiencies.

The exact deficiency responsible for nutritional neuritis remains obscure. Quite probably it is a multiple deficiency involving several dietary factors of which thiamin may be one. But there is still a possibility that the true anti-neuritic vitamin has yet to be discovered.
PATHOLOGY

Berkwitz and Lufkin (4), in reviewing the literature up to 1932, were able to find reports of only six cases in which gross and microscopic examinations were made postmortem. These cases were reported by Kast (31), Lindemann (34), Polk (42), allmann (2), Dustin (12), and Job (28). Lindemann described the pathological findings of Solowieff's (48) cases. Berkwitz and Lufkin have made postmortem examinations on three of their cases. The absence of gross anatomical changes was striking. They found the thoracic and abdominal viscera normal or showed only cloudy swelling and mild fatty changes in the liver and kidney. They found the brain, spinal cord, and peripheral nerves were normal. Kast found an area of yellowish softening of the lower cervical portion of the spinal cord which microscopically showed great swelling of the axis cylinders. Dustin found a decrease in size of the larger nerve trunks.

Careful microscopic examination of the nervous system has nearly always revealed definite lesions; but even these lesions were less conspicuous than the severity of the clinical symptoms would lead one to expect. The peripheral nerves were examined in the
cases of Dustin, Lindemann, Job and Berkowitz and Lufkin. The latter investigators demonstrated nerve degeneration on their three cases. Almost invariably degenerative changes were found in the anterior horn cells of the spinal cord. The changes are most marked in the lumbar portion of the cord and consist of loss of Nissl substance, swelling of the cells, eccentricity of the nuclei, and occasionally cell necrosis. These changes were present to some degree in all three cases autopsied by Berkowitz and Lufkin and also reported by Dustin, Job, and Kast. The anterior horn cells were normal in the cases of Allmann and Polk. In Linde­mann’s cases, the spinal cord was not examined.

Petechial hemorrhages formed a rather prominent part of the pathological picture in the Berkowitz and Lufkin cases. These lesions were found in the spinal cord in one case and in the brain in the third case. In case two the brain showed evidences of old petechial hemorrhages. These lesions had not been noticed previously because the brain and spinal cord were not ex­amined.

Theobald (53) commented on the similarity of histological changes in the tissues of the nervous system in patients dying from beriberi, scurvy, and
polyneuritis of pregnancy.

Wechsler (59) reviewed the whole subject of polyneuritis in 1930. He thought sufficient evidence had been adduced to show that what was previously regarded as a peripheral nerve inflammation was in reality a spinal cord involvement. In his estimation, the excessive vomiting in cases of pregnancy could bring about a nerve degeneration due to some deficiency. It is difficult to say why such a change should occur in some cases and not in others.

In 1932 McGoogan (36) reported postmortem findings on several of his cases. Again the remarkable fact was the lack of gross pathological changes. Microscopic studies of the parenchymatous organs showed cloudy swelling. Those of the brain showed small petechial hemorrhages, while degenerative changes were present in the peripheral nerves and anterior horn cells of the spinal cord.

The pathology can probably be summarised as follows: Grossly, the brain, spinal cord and peripheral nerves usually appear normal, although petechial hemorrhages may be detected, especially in the cerebrum and the meninges. Visceral lesions are usually confined to mild degenerative changes in the various organs as, kidney
heart, liver, suprarenals and the like. Microscopically, the peripheral nerves show degenerative changes, while in the spinal cord, particularly in the anterior horn cells, there may be swelling of the cells with loss of the Nissl substance and occasionally a definite necrosis. Cerebral lesions are usually limited to petechiae. The involved muscles show marked degenerative changes.
SYMPTOMS - SIGNS - DIAGNOSIS

Gestational polyneuritis, of the type under consideration, almost invariably develops late in the course of, or following an attack of hyperemesis gravidarum. It makes its appearance from twelve to twenty weeks after conception.

According to Reynolds (43), in 1897, the great majority of cases of polyneuritis begin with sensory disturbances, especially in those which are afterwards affected with paralysis of motion. These consist of numbness, tingling, hyperesthesia, paresthesia, or severe shooting pains. He found well-marked tenderness on deep pressure of the muscles, and great tenderness on pressure of the nerve trunks in not a few cases. The sensory symptoms were followed very soon by motor troubles, and in some cases the motor came on simultaneously with the sensory disturbances, and progressed very rapidly over the whole body, running a course not unlike that seen in Landry's, and ending in speedy death from respiratory failure. Reynolds (43) gave a report on 49 cases of polyneuritis. Bulbar symptoms were present in 5 cases, and showed themselves either as difficulty of swallowing, alternation of voice or actual aphonia, pains in the fifth cranial nerve, or paralysis of the
third, sixth, seventh or twelfth cranial nerves. In one case there was an atrophy of the optic nerves with blindness in addition to a severe multiple neuritis. In 23 cases there were general signs of paralysis attacking both legs and arms. The loss of power was as a rule first noticed in the legs, and more or less rapidly extended to the arms, sometimes only one arm being affected, but more generally both. In many of these cases the trunk muscles were affected with some involvement of the respiratory muscles and very rarely some affection of the bladder and rectum. In all cases the paralysis was of an atrophic character, often with well-marked reaction of degeneration.

In 15 cases the symptoms were confined to the arms, in 10 of these being limited to one side. In 7 the sensory and motor disturbances affected the median and ulnar nerves only, the paralysis being as usual of the atrophic type. In one case there was a complete diffuse atrophy of all the muscles of the right arm, in another atrophic paralysis of the upper arm and shoulder muscles on both sides, and in a third a unilateral paralysis of the same region; in 2 cases the ulnar nerve only was affected, and in 2 others the median only.

In 10 cases the muscles of the legs only were
affected, in 8 of these the symptoms being on both sides. The muscles most generally involved were those of the anterior tibial and perineal groups, less commonly those with paralysis of the quadriceps extensor, and in 3 cases all the muscles of the legs. The position of the legs was almost exactly like that seen in alcoholic paralysis with talipes equino-varus and flexion of the toes with absent knee-jerks. In very many of the cases of generalized paralysis there was a marked edema, especially of the legs.

In 1924, Cline (9) described a case of multiple neuritis with a Korsakoff syndrome following hyperemesis gravidarum. The salient features of a Korsakoff's psychosis are impairment of immediate memory, mild mental clouding, confusion, and fabrication. This condition was first described by Korsakoff (9) in 1887. He found it to be a very frequent complication of alcoholic multiple neuritis. Von Hoesslin (21) states that the Korsakoff syndrome was observed in the multiple neuritis following toxemias of pregnancy long before Korsakoff placed this syndrome before the scientific world. Von Hoesslin also observed that the incidence of this syndrome was greater in gestational toxemia than in alcoholic neuritis.
Berkwitz and Lufkin (4) reviewed the literature in 1932 and collected 52 undoubted cases of this disease. Severe pernicious vomiting was present in 40 of 41 patients in whom note was made as to this condition. The vomiting usually has its onset in the first two months of pregnancy, which is the same time the so-called morning sickness makes its appearance. It is generally mild at the onset and is indistinguishable from the ordinary type of vomiting which occurs in about 50 per cent of pregnant women. Gradually it becomes more severe and assumes the pernicious form. However, not all forms of pernicious vomiting are followed by nerve changes, although their appearance is identical. Berkwitz and Lufkin (4) state that the vomiting in this condition rarely responds to the usual form of treatment but ceases abruptly when symptoms of paralysis first appear. The patient is generally dehydrated and emaciated from vomiting. The blood pressure and temperature are not changed, but the pulse rate may be accelerated to 120 or more.

It is in the third and fourth month that the first symptom of paralysis usually occurs. The early complaints frequently are weakness, numbness, and increased muscle pain generally in the lower extremities. Very
often the complaining woman is unjustly thought to be hysterical or malingering in this stage when she is really ill. The abdominal muscles, diaphragm, thorax, upper extremities, and in some cases the cranial nerves are involved as the condition progresses. In some cases the neurological symptoms are confined to the peripheral nerves, producing the stocking-glove type of anesthesia, while in others the cord is involved producing such symptoms as sphincter disturbances. Optic neuritis has been reported by some writers rather frequently.

In 1932 Hoffman (22) gave the following signs and symptoms: tachycardia, muscular weakness, absence of knee, biceps, and tendon of achilles reflexes, stupor, loss of appetite, loss of memory, blurring of vision, and not infrequently optic neuritis.

Not infrequently women are seen who in the latter weeks of pregnancy complain of numbness and tingling in the hands and arms with possibly more or less severe radiating pains in the shoulders and arms or possibly of the lower extremities. These symptoms may give rise to considerable discomfort, but the general health is ordinarily not affected except possibly from loss of sleep. Wilson and Garvey (64)
regard these patients as suffering from a mild form of peripheral neuritis of possibly toxic origin. They recommend the application of heat, massage, and mild sedatives to relieve the condition. These symptoms ordinarily subside entirely in the puerperium.

At times a more severe type is observed in which the injury to one or more nerves is so extensive as to cause an actual paralysis of the muscles which they supply. This may occur during the course of pregnancy or may even originate during the puerperium. In this type there is usually numbness and tingling in the affected parts, followed by pain, and this in turn succeeded by weakness and paralysis. There may be no disturbance of general health. The prognosis as far as life is concerned is usually good in this group, although the vagus and phrenic nerves might become involved in degenerative processes. After a rather prolonged convalescence the paralysis may clear up entirely, though in some instances there may be a permanent residual disability, and atrophy of the affected muscles. One or more of the cranial nerves may be affected.

In a third group of patients a much more serious state of affairs is encountered. The patients appear
Profoundly ill. There is persistent vomiting with rapid and progressive loss of weight. There may be quite profound mental disturbances and progressive involvement of various nerves with paralysis of the corresponding muscles. The mortality in this group is very high.

Vorhous, Williams, and Waterman (58) have given this clinical method of differentiating the various stages of B1 avitaminosis:

Group 1. The state of total deficiency of vitamin B1 that is known clinically as beriberi is well recognized. It is characterized by weakness, pains in the extremities followed by paralysis of the legs, fever, anorexia, diarrhea or constipation, signs of myocardial insufficiency, secondary anemia, and at times marked edema (dry or wet form). If untreated, it usually results in death, frequently sudden (acute cardiac type).

Group 2. The next most advanced stage, that of severe deficiency of vitamin B1 is also recognizable clinically as a state of avitaminosis. Its symptoms are weakness, severe persistent pain in the extremities, paresthesia, anorexia and mild signs of myocardial insufficiency. Sometimes it is associated with edema of the legs and a history of dietary restriction.
(nutritional edema). In the tropics it is frequently diagnosed as rudimentary beriberi. It may develop into typical beriberi or subside spontaneously.

Group 3. The third stage, continuing in the direction of diminishing severity, is the advanced deficiency of vitamin B₁, recognized clinically as polyneuritis. Here the principal symptoms are weakness, anorexia, and severe pain in one or more of the extremities or elsewhere in the body. This type is sometimes classified as alcoholic polyneuritis or toxic neuritis. It may be associated with bacterial infections, alcoholism, gastro-intestinal disease or deranged carbohydrate metabolism. In some cases it is possible that the deficiency is due less to an insufficient supply of the vitamin than to inadequate absorption.

Group 4. The state of moderate deficiency of vitamin B₁ is usually unrecognized, clinically. The symptoms include localized, persistent pain, usually in an extremity or in the back, and anorexia. Paresthesia is frequently present. There is little or no weakness. This condition is usually associated with obesity and a disturbed carbohydrate metabolism. It is frequently classified as diabetic or metabolic neuritis.

Group 5. The least severe stage, mild deficiency
of vitamin B₁ also goes unrecognized. There are vague pains, usually elicited only by pressure over the nerve roots, general malaise, anorexia, and constipation. Small amounts of sugar may be present in the urine, without hyperglycemia. There is usually a large carbohydrate intake, often associated with a tendency to obesity. These cases are frequently classified as potential diabetes.

The diagnosis of polyneuritis depends on relatively few chief symptoms and signs. General weakness usually first appears in the lower extremities and may be limited to them. Ordinarily, the extensor muscles are more involved than the flexors, although the distribution is not uniform. The ankles and wrists may be less affected than the knees and elbows, or the paralysis may be more clearly of the ascending type. With the increasing weakness there is evident atrophy of the muscles, which become soft and flabby. Hyperesthesia in the affected parts is extremely variable. Occasionally the skin is hypersensitive, but more commonly increased tenderness is elicited only by pressure deep into the muscles or over the nerve trunks. Placing the nerves on tension, as by forceful flexion at the ankles or raising the straight leg on the abdomen, produces ex-
quise pain.

Tachycardia is almost uniformly present and may be among the earliest changes to attract attention. The cardiac rate is not altered by physiologic doses of atropine, a fact that suggests actual involvement of the vagus. Electrocardiograms give no evidence of abnormal cardiac action other than the increased heart rate.

Absence of the tendon reflexes in the affected extremities points to involvement of the lower neurons. As a rule, the knee jerks and achilles reflexes are lost first, while the biceps and triceps jerks may merely weakened or may disappear relatively late in the disease. Plantar stimulation and tibial pressure may evoke no response or one that cannot be easily interpreted.

Korsakoff's psychosis, with loss of recent memory, disorientation as to time and place, and a tendency toward confabulation, denotes cerebral involvement. It may appear late and, in mild cases, may disappear within a week or two. On the other hand, it usually persists for some months and may be permanent particularly as regards the loss of recent memory.

There are many less characteristic and more variable
symptoms and signs which occur in polyneuritis. Ocular nystagmus, lateral and vertical, ocular squint, more commonly divergent, and diplopia may result from involvement of the oculomotor muscles. Optic neuritis may be indicated by indistinct, raised disk margins and slightly enlarged veins and may result in dimness of vision. Ophthalmoscopic examinations may be negative and yet the dimness of vision may be attributable to an optic neuritis. Retinal hemorrhages of the "flame" variety have been rather commonly reported.

Central deafness is occasionally evident. There is good evidence that the actual auditory apparatus is adequate, as shown by the prompt turning of the head in the direction of an unusual sound, but that the receptivity of the cerebrum is disturbed, so that response to questions is greatly delayed. In other instances there is evidence of nerve deafness, pointing to involvement of the auditory nerve. Auditory hallucinations have also been observed.

Delirium or drowsiness may develop in association with the psychosis, or quite independent of the mental alterations characteristic of the Korsakoff syndrome.

Choreiform movements of the head and face are uncommon.
Dysphagia may result from paralysis of the muscles of deglutition; dysphonia, from the involvement of the laryngeal and pharyngeal apparatus, while dyspnea may be due to paralysis of the diaphragm or the intercostals.

Pain in the involved extremities, independent of motion or pressure, is rarely prominent but may occasionally demand attention. Loss of positional sense is usually present as a manifestation of the ataxia of the extremities.

Involuntary urination and defecation have been noted rather frequently but appear more commonly late in the disease. In other instances there may be difficulty in urinating, and catheterization may be necessary.

Jaundice has been described but is not common. Even in the patients who become icteric there is usually no marked necrosis of the hepatic cells.

Numbness is occasionally a prominent symptom, even when there are no other evidences of sensory disturbances.
LABORATORY

The blood chemistry in this condition is usually normal. Laboratory tests for the retention of toxic products are very crude measures and are of little value. Cloudy swelling found at a necropsy is a finer index of the retention of toxic products than any known laboratory test. The urine shows no albumin and the specific gravity is normal.

In the cases observed by McGoogan (36) the spinal fluid pressure was usually under normal. Its cytology and chemistry are usually within normal limits, although there may be an occasional increase in the number of cells present.

In two of the three cases reported by Wilson and Garvey (64), there was a profound disturbance of the general metabolism, characterized particularly by a high carbon dioxide combining power and low blood chlorides. The findings were those of an alkalosis, yet inasmuch as the Ph in each instance fell within normal limits, they regarded the condition present as a compensated alkalosis. None of these women had had any alkaline mediation during their illness.

In the last year a very simple test has been devised to detect thiamine excretion in the urine.
TREATMENT

Titus (54), in 1925, treated his patients with intravenous injections of glucose and carbohydrate feedings. He gave 5 per cent glucose intravenously because the liver is involved in the toxemias. Pregnancy depletes the glucose and renders the liver more liable to the action of toxins. He reported 328 cases of hyperemesis gravidarum which were treated in above manner with favorable results.

In 1930 Cowgill, Rosenberg, and Rogoff (11) published some results on their studies in the physiology of vitamins. The experimental work was done to determine the effect of administration of large amounts of water on the time required for development of the anorexia characteristic of a deficiency of the vitamin B complex. Their results showed clearly that the onset of a loss of appetite in dogs on a diet lacking undifferentiated vitamin B may be greatly hastened by forcing fluids by mouth. This experimental work was done on dogs.

Pregnant women with hyperemesis should be repeatedly examined neurologically. Berkwitz and Lufkin (4) believe artificial induction of labor should be considered if neurological symptoms appear. Although the maj-
ority of patients improve after abortion, some continue to grow worse the following week or two. They believe this is probably due to the fact that toxins still exist in the circulation and continue to affect the nervous system, persisting in the same manner as the toxins from alcoholic poisoning. For that reason the physician must act quickly rather than wait until the patient's condition grows critical before intervention is resorted to. Abortion is frequently deferred too long because it is usually unnecessary in most cases of hyperemesis.

Complete recovery from the paralysis does not always occur because the nerve cells are frequently destroyed. If the paralyzed extremities are not properly treated, contractures frequently develop. As soon as muscle tenderness disappears, active and passive movements should be instituted.

In view of a vitamin B1 deficiency, Strausz and McDonald (52) suggest that rational therapy should avoid operative intervention with pregnancy, and be directed to supplying suitable material to meet the deficiency. In cases in which suitable material cannot be retained by the stomach, the use of intramuscular therapy seems indicated.
It has been observed that certain cases of macrocytic anemia of pregnancy lack not merely a dietary factor associated with vitamin B₂, but also in an unidentified factor like the one absent in Addisonian pernicious anemia, and which is present in normal human gastric juice. Strausz and McDonald suggest the possibility that a similar dual mechanism may be at work in certain cases of polyneuritis of pregnancy. For this reason they suggest the use of liver and liver extracts, both by mouth and by injection, in cases not responding to simple preparations of vitamin B₁ and B₂. They also recommend prophylactic use of vitamin B in all patients with pernicious vomiting.

Vandel (56) reported three cases of polyneuritis which were successfully treated with high vitamin diet, including orange juice, raw liver, yeast tablets and two drams of iron and ammonium citrate per day. His first patient suffered from an anemia as well as a polyneuritis which followed a period of vomiting. Improvement in general condition followed when suitable diet was retained. The symptoms returned subsequent to another period of vomiting and again disappeared after the vitamin diet was instituted. This patient delivered a full-term baby after a labor of
ten hours. The other two patients also had normal deliveries.

Fouts, Gustafson, and Zerfas (17) reported successful treatment of a case of polyneuritis of pregnancy in 1934. The medication received by the patient was as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/5/33 to 10/20/33</td>
<td>Cod liver oil, drams 2 o.d.</td>
</tr>
<tr>
<td>5/5/33 to 7/6/33</td>
<td>Vegex (autolyzed yeast prep.), 12 gm.</td>
</tr>
<tr>
<td>5/6/33 to 6/5/33</td>
<td>Liver extract, vials 3 per day.</td>
</tr>
<tr>
<td>5/5/33 to 10/20/33</td>
<td>Liver extract, vials 6 per day.</td>
</tr>
<tr>
<td>5/17/33 to 6/14/33</td>
<td>Iron and ammonium citrate, 30 gr. t.i.d.a.c.</td>
</tr>
<tr>
<td>6/14/33 to 10/20/33</td>
<td>Reduced iron, 10 gr. per day.</td>
</tr>
<tr>
<td>6/12/33 to 7/3/33</td>
<td>Liquid vitamin B1 concentrate (rice polishings), 3 c.c. o.d. (1 c.c. being equal to 500 units vitamin B1)</td>
</tr>
<tr>
<td>7/3/33 to --------</td>
<td>Vitamin B1 capsules (concentrated extract of rice polishings), capsules 8 per day (1 capsule equals 200 units vitamin B1).</td>
</tr>
<tr>
<td>5/25/33 to 7/7/33</td>
<td>Weekly intravenous injections (20cc.) of liver extract derived from 100 gm. of whole liver.</td>
</tr>
<tr>
<td>7/7/33 to --------</td>
<td>Weekly intramuscular injections (6 c.c.) of concentrated liver extr. derived from 200 gm. of whole liver.</td>
</tr>
</tbody>
</table>

As soon as the patient was started on the above medication and a high vitamin diet there was no advancement in signs or symptoms of the disease. The improvement in the mental condition was one of the first signs noted.

This patient presented the typical findings of a polyneuritis of pregnancy which had developed following
pernicious vomiting and the treatment for the vomiting. The condition of the patient was critical when the vitamin B therapy was instituted. However, her condition showed definite improvement soon after the onset of therapy and she was carried to term. The marked improvement of the neurologic signs and symptoms before delivery, although the nausea and vomiting persisted until after the delivery, suggests that polyneuritis of pregnancy is not the result of a toxemia but that it is due to dietary deficiency. This would indicate that vitamin B should be administered parenterally to all patients with hyperemesis gravidarum as a prophylaxis against the development of polyneuritis. The fact that the most marked improvement of the neurologic symptoms followed the administration of the large doses of vitamin B₁ (as a concentrated extract of rice polishings) strongly indicates that relatively large quantities of the vitamin should be administered to all cases. The liver extract was administered by mouth not only because of its high vitamin B (mainly B₂) content, but also because it was thought that the active principle of the liver extract might be of some benefit to the patient. The liver extract supplied the vitamin B after the Vegex was discontinued, as the extract of
rice polishings has little or no vitamin B₂, although it had a very high concentration of vitamin B₁. The patient received weekly injections of liver extract because this type of therapy has been shown to be the most successful in the treatment of neurologic involvement of pernicious anemia. It is difficult to determine just what benefit was derived from the injections by this patient. However, in patients who continue to have severe vomiting, or for any other reason are unable to absorb the vitamin B complex from the gastro-intestinal tract, this therapy should be of great benefit. Previous work has shown that patients having pernicious anemia or pellagra not responding to oral liver therapy will respond to liver extract administered parenterally. It is reasonable to assume that similar results would be obtained in cases of polyneuritis not able to absorb the vitamin B complex of the liver extract or a concentrated vitamin B complex preparation were administered parenterally as was suggested by Strausz and McDonald (52).

Bryant (7) suggests that modern methods of treatment of pernicious vomiting of pregnancy tends to wash out whatever vitamins may be stored in the body, and at the same time restricts further intake.
According to Vorhaus, Williams, and Waterman (58) the normal adult human intake of vitamin B₁ is about one mg. daily, the richest sources being the bran coats of grains, leguminous seeds and lean pork. Diminished carbohydrate tolerance is most consistent and marked in B₁ avitaminosis. Diabetic patients with neuritis when treated with vitamin B₁ are rendered symptom free.

It is recognized that large doses of iron will improve secondary anemias associated with a large variety of causes such as malnutrition, infection, metabolic diseases and even malignancy. Why cannot it be assumed that adequate amounts of B₁ may stimulate reparative processes in the neuraxon, resulting in progress toward the normal state, even in the absence of a B₁ deficiency and regardless of the continued presence of neurotoxins?

In 1935 Cook (10) reported his successful treatment of a patient suffering from polyneuritis gravidarum. The patient was first treated with a high carbohydrate diet and liberal vitamins, especially B with a sedative alkaline mixture. The patient left the hospital only to return several weeks later. At this time splinting was instituted and combined with massage. "Marmite" and yeast were pushed to toleration point.
Open air sleeping and general hygienic measures were adopted, as well as a generous sun tanning, hoping that the tanning would augment the vitamin intake. This same patient was in a different hospital between her two visits described above. At that hospital the patient received one ounce of glucose combined with ten units of insulin three times daily. The patient refused this treatment when she entered the first hospital the second time. She had a normal delivery with a labor which lasted three hours. The baby weighed ten pounds. The patient went home in eight days and in two months was doing her own housework and breast feeding her baby.

Hildebrandt and Otto (20) published some dramatic results in 1938 with the use of vitamin B in polyneuritis. In one instance they gave 1,782 mg. of vitamin B1 during a pregnancy complicated by a severe polyneuritis. There was no toxic reaction to the drug, and no excretion of the vitamin in the urine up to the time of delivery. Evidently the demand did not permit saturation even with so large an intake.

Kramm (33) also reported a case of polyneuritis successfully treated with vitamin B. In the same year, Schultze (46) reported sixty cases which he gathered
from the literature in one year. These patients were treated with Betabion (Merck) and Betaxin (Bayer) which were supplied by the companies free of charge. The dosage was as follows: First day injection of 20 to 30 mg. Then in from three to six days, 6 mg. were given in tablet form. After this there was usually a marked improvement. Then the second series of doses was given. This consisted of injection of 10 to 20 mg. and 3 mg. in tablet form by mouth. The third series of injections were given to one-third of the patients only. Some of the severe cases were given medication by injection only. This consisted of three doses of 20 mg. each in two days. No undesirable reaction occurred from the injections. One patient was given 100 mg. of vitamin B in 48 hours without any undesirable reaction. The tablets were used only in mild cases and only recommended for prophylactic use. Of these sixty cases, 37 recovered completely, 16 showed some improvement, and 7 were not improved.

In 1939, Hildebrandt (19) published his results with vitamin therapy in polyneuritis. In spite of the large doses of vitamin B1 given, his patient had normal labor pains. Vitamin B and C helped the low gastric acidity, and even caused the liver symptoms to
change. The blood sugar remained normal in cases treated with vitamin B, while before the blood sugar had to be controlled with insulin.

It is of paramount importance that the treatment of polyneuritis of pregnancy should include an ample and nutritious diet, together with the administration of such preparations as yeast and crude liver extract to ensure an adequate supply of the entire vitamin B complex. Additional thiamin is beneficial, particularly in the relief of the muscular pain and weakness.
PROGNOSIS

According to Reynolds (43), the prognosis as regards complete recovery is worst in the generalized forms, and is best in the partial cases, especially where the arms only are affected. Years may elapse before an absolute recovery takes place and treatment by massage should be kept up for long periods.

Berkwitz and Lufkin (4) give a mortality figure of 25 per cent. They state that this figure can be reduced considerably if the toxemia is recognized early, and if pregnancy is interrupted. The mortality in their cases was very high. They reasoned that this was probably due to the failure to recognize the presence of the toxemia early. In all of these cases the diagnosis was considered as being of functional origin, and the patients were treated with the usual symptomatic treatment such as rest, sedatives, and restriction in the diet. The weakness of these patients was attributed by their physicians to the lack of nourishment rather than to actual nerve involvement.

McGoogan (36), in 1932, gave a mortality rate of 40 per cent. In his article, to be published in 1941, are reported 144 cases of polyneuritis in pregnancy. In these cases there were 39 deaths or a mortality
rate of 26 per cent. In the series of 39 cases treated with B complex there were 3 deaths or 7.6 per cent. In 105 cases with no treatment, the number of deaths was 35 or a percentage of 33.3.
SUMMARY

The earliest references to polyneuritis were published in 1854. Many theories have been advanced as to the cause of the polyneuritis. Clinical and experimental studies in the last ten years have shown that polyneuritis of pregnancy is unquestionable due to nutritional deficiency, and is in every way similar to the polyneuritis of Oriental beriberi. The exact deficiency responsible for the condition remains obscure. Quite probably it is a multiple deficiency involving several dietary factors. The vitamin B complex appears to be the main cause. Vitamin B1 has been called the anti-neuritic vitamin, but this is probably not limited to B1. Also, recent investigators have questioned the assumption that vitamin B1 is composed of thiamin alone. There is the possibility that the true anti-neuritic vitamin has yet to be discovered.

The pathology is rather limited in this condition. Grossly, the brain, spinal cord and peripheral nerves usually appear normal, although petechial hemorrhages may be detected in the cerebrum and the meninges. Visceral lesions are usually confined to mild degenerative changes in the various organs. Microscopically, the peripheral nerves show degenerative changes, while in
the anterior horn cells of the spinal cord, there
may be swelling of the cells with loss of the Nissl
substance. The involved muscles show marked degen-
erative changes.

The diagnosis of polyneuritis depends on relat-
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usually first appears in the lower extremities and
may be limited to them. With the increasing weakness
there is evident atrophy of the muscles, which become
soft and flabby. Very often the complaining woman is
unjustly thought to be hysterical or malingering in
the early part of the disease. Polyneuritis is always
preceded by pernicious vomiting.

The laboratory has become a great aid in deter-
mining the amount of urinary excretion of vitamin B₁.

The treatment of polyneuritis of pregnancy should
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