MD Theses

5-1-1941

Polyneuritis in pregnancy

Harold H. Friesen
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

POLYNEURITIS IN PREGNANCY

By

HAROLD F. FRIESEN

SENIOR THESIS PRESENTED TO

THE COLLEGE OF MEDICINE,

UNIVERSITY OF NEBRASKA,

OMAHA, 1941.

TABLE OF CONTENTS

DEFINITION AND INTRODUCTION

The recognized serious conditions which may comp-
licate pregnancy are designated as the toxemias, in-
cluding eclampsia and pre-eclamptic toxemia, nephritic
toxemia, pernicous vomiting, and the like. In addit-
ion to this more or less well defined group, there is
still another group of cases which are much less freq-
uently 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 sim-
ultaneous involvement of many peripheral nerves, and
is quite distinct from the more frequently seen traum-
atic 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 similiar 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 Solowieff (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, Solowieff 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 dis-
turbances during her illness.

Von Hoesslin (21) in 1905, wrote an excellent re-
view of the subject and collected 94 cases from the lit-
erature, 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 general-
ized 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

-4-

termination of the pregnancy was not necessarily followed 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 developing blindness, however, he conceded that pregnancy should be interrupted. Other observers felt that pregnancy should be interrupted in those instances where improvement failed to occur following palliative treatment.

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 resulting from peripheral neuritis, in which the child died several days before delivery. Death of the child did not bring about immediate improvement, the convalescence being long drawn out, and some permanent paralysis persisting. Korsakow and Serbski (30) observed 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)

-7-

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 histo-pathological studied 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 metalolism 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 multiparae. In 12 cases

the onset occurred during pregnancy. Of the cases com-
mencing after delivery, 16 cases developed symptoms with-
in the first week, 7 developed symptoms during the sec-
ond week, 6 cases during the third and fourth weeks,
and 2 cases within the second month. In the 5 remain-
ing 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 quest-
ion 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 puer-
peral 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-

-9-

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

-10-

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 inter-
related and due to dietetic deficiencies and considered
that the increased incidence of beriberi during preg-
nancy 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 relation-
ship 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 relation-
ship 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 secrued 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, pellogra 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 condtions are dietary defic-
iency 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 B_2 and related substances,
can accou nt for bothe 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. Preg-
nancy 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 B_1 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 B_1 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 poly-
neuritis 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 poly-
neuritis 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 dist-
urbance or restriction in diet. The question then arose
whether he was not dealing with instances of food def-
iciency, 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

-14-

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. Berkwitz 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)

-16-

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 warrented. 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 excerise 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.

-17-

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 B_1 in the diet, but in 1934 Mellanby (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 sub-
stances, organic and inorganic, as well as the vita-
min concerned; 2) once nerve lesions have been prod-
uced 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 les-
ions 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 on-
set of polyneuritis. This prevents the patient from
ingesting and absorbing the proper food. Secondly, it
has been shown that abnormalities of the gastro-intest-
inal tract can play an important role in the causation
of deficiency diseases, and in pregnancy there is or-
dinarily a marked decrease of gastric secretory funct-
ion. 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 diet-
ary habits and food selections based largely on appear-
ance or taste, often leading to a high carbohydrate in-
take 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 in-
terfere with both absorption and utilization and bring

to light latent deficiency conditions.

The international unit of vitamin B_1 has been defined as the anti-neuritic activity of 3 micrograms of the international standard preparation of crystalline vitamin B_1 hydrochloride. One milligram of thiamin chloride is equivalent to 333 international units of vitamin B_1.

Staehler (49), in 1938, studied the effect of vitamin B_1 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 B_1 in their urine than the non-pregnant women, the pregnant women needing from 7 to 8 mg. of vitamin B_1 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 B_1.

In 1939 Jolliffe and his associates (29) experimentally produced the symptoms and signs of vitamin B_1 deficiency in normal subjects. The vitamin B_1 poor diet used was probably adequate for normal man except in vitamin B_1. 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 B_1 was initiated by placing five subjects on the vitamin B_1 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 B_1 poor
diet, which marked the beginning of the recovery per-
iod, was followed by the prompt disappearance of all
symptoms, in that no subject had any abnormal com-
plaints 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 feel-
ing 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 B_1 poor diet was 3.36 mg.
daily.

Objective signs of vitamin B_1 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 B_1. It was also evident that the urinary excretion reflects, as a rule within 24 hours and always within 48 hours, changes in vitamin B_1 intake of the magnitude used in their study. This was true whether vitamin B_1 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,

-24-

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, account-
ing 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 vitamin B_1 deficiency in the gen-
eral 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 vitamin B_1 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 nico-
tinic acid. The period of restricted intake of thi-
amine extended from December 12, 1939 to March 9, 1940.

-25-

The time of onset of signs and symptoms varied. In
general, the more active subjects were the first to
experience symptoms. The abnormalities ultimat&ly
noted in all of the subjects who were deprived of
thiamin for periods of several weeks were: depress-
ed mental states, generalized weakness, dizziness,
backache, soreness of muscles, palpitation, dyspnea
and precordial distress on exertion, insomnia, anor-
exia, nausea, vomiting, loss of weight, atony of mus-
cles, 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 de-
creased. 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 subcutanious injection of 1 mg. of thiamin hydrochloride, (March 9, 1940). The diet low in vitamin B_1 was continued 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 vomiting ceased; food which previously had been revolting to the patient was eaten without urging; fatigue disappeared; 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 represented the only change made, all signs and symptoms

-27-

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 re-
stricted in thiamin were given thiamin hydrochloride
orally. This was done without their knowledge. The
basal diet contained 0.15 mg. of thiamin. The init-
ial 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 thi-
amin hydrochloride was administered in gradually in-
creasing doses up to 2 mg. a day. A substantial in-
crease 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 mus-
cles 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 con-
stitutes 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 al-
lowance 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 pro-
duction 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 sol-
utions 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 close-
ly resembles neurasthenia; the later simulates anor-
exia 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 B_1 is available. He believes that in the
pregnant woman a deficiency leads to an over-compen-
sation 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 prolan 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 B_1. 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 B_1. They found some positive correl-
ation between the inadequacy of the intake and defici-
ency 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 B_1 has been generally regard-
ed as synonymous with thiamin. Before that date, how-
ever, it was generally used by clinicians to mean no
more than the hypothetical anti-beriberi vitamin. For

-31-

this reason, any writings prior to 1936 in which
specific claims were made for the etiologic relation
of vitamin B_1 deficiency to nutritional polyneuritis
cannot with justification be quoted as expressions
of the opinion that thiamin as now known was the fac-
tor concerned (37).

Since the earliest differentiation of the vit-
amin B complex into the heat-labile (B_1) and heat-
stable (B_2 or G) fractions, the former has been thou-
ght 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 ner-
vous 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 exper-
imental work and a review of the literature, states
that there is no proof at present that thiamin def-
iciency 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 on to expect. The peripheral nerves were examined in the

-34-

cases of Dustin, Lindemann, Job and Berkwitz 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 Berkwitz and Lufkin and also reported by
Dustin, Job, and Kast. The anterior horn cells were
normal in the cases of Allmann and Polk. In Linde-
mann's cases, The spinal cord was not examined.

Petechial hemorrhages formed a rather prominent
part of the pathological picture in the Berkwitz 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 prev-
iously because the brain and spinal cord were not ex-
amined.

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

-35-

polyneuritis of pregnancy.

Wechsler (59) reviewed the whole subject of poly-
neuritis 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 swell-
ing. Those of the brain showed small petechial hemorr-
hages, 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 men-
ings. 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 nec-
rosis. Cerebral lesions are usually limited to petech-
iae. 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 senory symptoms were followed very soon by motor troubles, and in some cases the motor come 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 at-
tacking 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 tht 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 genrally 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 ner-
ves 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 sphinter 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 af-
fected parts, followed by pain, and this in turn suc-
ceeded 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 B_1 avitaminisis:

Group 1. The state of total deficiency of vitamin B_1 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 B_1 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.

-44-

(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 B_1, 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 B_1 is usually unrecognized, clinically. The symptoms include localized, perisitent 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 B_1 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-

-46-

quisite 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 be 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 invol-
vement 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 recept-
ivity 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 un-
common.

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 mediaction during their illness.

In the last year a very simple test has been devised to detect thiamin 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 ex-
ist in the circulation and continue to affect the ner-
vous system, persisting in the same manner as the tox-
ins from alcoholic poisoning. For that reason the phy-
sician must act quickly rather than wait until the pat-
ient's condition grows critical before intervention is
resorted to. Abortion is frequently deferred too long
because it is usually unnecessary in most cases of hyper-
emesis.

Complete recovery from the paralysis does not al-
ways occur because the nerve cells are frequently de-
stroyed. If the paralyzed extremities are not properly
treated, contractures frequently develop. As soon as
muscle tenderness disappears, active and passive move-
ments should be instituted.

In view of a vitamin B_1 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 can-
not be retained by the stomach, the use of intramuscul-
ar therapy seems indicated.

It has been observed that certain cases of macro-
cytic anemia of pregnancy lack not merely a dietary
factor associated with vitamin B_2, but also in an un-
identified factor like the one absent in Addisonian
pernicious anemia, and which is present in normal hum-
an gastric juice. Strausz and McDonald suggest the pos-
sibility 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 B_1
and B_2. They also recommend prophylactic use of vit-
amin B in all patients with pernicious vomiting.

Vandel (56) reported three cases of polyneuritis
which were sucessfully 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 suit-
able diet was retained. The symptoms returned sub-
sequent to another period of vomiting and again disap-
peared 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 suc-

cessful treatment of a case of polyneuritis of preg-

nancy in 1934. The medication received by the patient

was as follows:-

Date	Medication
5/ 5/33 to 10/20/33	Cod liver oil, drams 2 o.d.
5/ 5/33 to 7/ 6/33	Vegex (autolyzed yeast prep.), 12 gm.
5/ 6/33 to 6/ 5/33	Liver extract, vials 3 per day.
6/ 5/33 to 10/20/33	Liver extract, vials 6 per day.
5/17/33 to 6/14/33	Iron and ammonium citrate, 30 gr. t.i.d.a.c.
6/14/33 to 10/20/33	Reduced iron, 10 gr. per day.
6/12/33 to 7/ 3/33	Liquid vitamin B_1 concentrate (rice polishings), 3 c.c. o.d. (1 c.c. being equal to 500 units vitamin B_1)
7/ 3/33 to -------	Vitamin B_1 capsules (concentrated extract of rice polishings), capsules 8 per day (1 capsule equals 200 units vitamin B_1).
5/25/33 to 7/ 7/33	Weekly intravenous injections (20cc.) of liver extract derived from 100 gm. of whole liver.
7/ 7/33 to -------	Weekly intramuscular injections (6 c.c.) of concentrated liver extr. derived from 200 gm. of whole liver.

As soon as the patient was started on the above

medication and a high vitamin diet there was no advance-

ment in signs or symptoms of the disease. The improve-

ment 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 vit-
amin B therapy was instituted. However, her condit-
ion 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 prophy-
laxis 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 B_1 (as a concentrated extract of rice pol-
ishings) strongly indicates that relatively large quant-
ities 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 B_2) 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

-55-

rice polishings has little or no vitamin B_2, although it had a very high concentration of vitamin B_1. 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 B_1 is about
one mg. daily, the richest sources being the bran coats
of grains, leguminous seeds and lean pork. Diminished
carbohydrate tolerance is most consistant and marked
in B_1 avitaminosis. Diabetic patients with neuritis
when treated with vitamin B_1 are rendered symptom free.

It is recognized that large doses of iron will
improve secondary anemias associated with a large var-
iety of causes such as malnutrition, infection, met-
abolic diseases and even malignancy. Why cannot it be
assumed that adequate amounts of B_1 may stimulate re-
parative processes in the neuraxon, resulting in prog-
ress toward the normal state, even in the absence of
a B_1 deficiency and regardless of the continued presence
of neurotoxins?

In 1935 Cook (10) reported his successful treat-
ment of a patient suffering from polyneuritis gravid-
arum. The patient was first treated with a high carbo-
hydrate diet and liberal vitamins, especially B with
a sedative alkaline mixture. The patient left the hosp-
ital 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 be-
tween her two visits described above. At that hosp-
ital the patient received one ounce of glucose com-
bined 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 house-
work and breast feeding her baby.

Hildebrandt and Otto (20) published some dramatic
results in 1938 with the use of vitamin B in polyneur-
itis. In one instance they gave 1,782 mg. of vitamin
B_1 during a pregnancy complicated by a severe poly-
neuritis. 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 per-
mit 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 undesireable reaction occured 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 B_1 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

Accoring 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 ahould 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 pres-
ence 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 symptom-
atic treatment such as rest, sedatives, and restriction
in the diet. The weakness of these patients was attrib-
uted 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 B_1 has been called the anti-neuritic vitamin, but this is probably not limited to B_1. Also, recent investigators have questioned the assumption that vitamin B_1 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 degenerative changes.

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. 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 determining the amount of urinary excretion of vitamin B_1.

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.

BIBLIOGRAPHY

1. Albeck.: Vier Faelle von Polyneuritis Gravidarum, Monatschr. f. Geburtsh. u. Gynaek, 44:351-356, 1916.

2. Allmann, J.: Zur Frage der Gravidtaetesmyelitis, Inaugural Disseration, Kiel, 1909. Cited from Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy, Surgery, Gynecology and Obstet. 54:743-757, 1932.

3. Baer, J. L.: Basal Metabolism in Pregnancy, Am Journal Obst. 2:249-255, 1921.

4. Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy, Surgery, Gynecology and Obst. 54:743-757, 1932.

5. Bouchard.: Lecons sur l'autointoxication, Paris, 1887. Cited from Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy, Surg. Gynec. and Obst. 54:743-757, 1932.

6. Brockman, J. M.: Polyneuritis Case, Memphis Med. J. 14:130-131, (July) 1939.

7. Bryant, R. D.: Polyneuritis of Pregnancy with a Case Report, The Journal of Medicine. 16:348-352, 1935.

8. Churchill, F.: On Paralysis Occurring During Gestation and in Childbed, Dublin J. M. Sc. 17:257, 1854.

9. Cline, C. A.: Case of Multiple Neuritis with Korsakoff Syndrome Following Hyperemesis Gravidarum, Med. Clin. N. America 8:416-420, 1924-1926.

10. Cook, B. A.: Polyneuritis, M. J. Australia 2:319 (Sept. 7) 1935.

11. Cowgill, G. R., Rosenberg, H. A., and Rogoff, J.: Studies In the Physiology of Vitamins, Am. J. Physiol. 95:537-541, 1930.

12. Dustin, A P.: La Polyneurite Gravidique Nouv.
        incomog. de la Salpetriere, 4:349, 1909.
        Cited from Berkwitz, N. J., and Lufkin,
        N. H.: Toxic Neuronitis of Pregnancy, Surg.
        Gynec. and Obstet. 54:743-757, 1932.

13. Elder, George.: Peripheral Neuritis in Pregnancy,
        Lancet 2:232, 1896.

14. Ewing, J.: The Pathological Anatomy and Patho-
        genesis of the Toxemia of Pregnancy, Am. J.
        Obstet. 1:145, 1905. Cited from Berkwitz,
        N. J. and Lufkin, N. H.: Toxic Neuronitis
        of Pregnancy, Surg. Gynec. and Obstet.
        54:743-757, 1932.

15. Ford, R. K.: Polyneuritis, J. Obst. and Gynec.
        Brit. Emp. 42:641-645 (Aug.) 1935.

16. Forman, G. W.: Polyneuritis; Treatment with
        Vitamin B, J. Missouri M. A. 34:197-199,
        (June) 1937.

17. Fouts, J. P., Gustafson, G. W., and Zerfas, L. G.:
        Successful Treatment of a Case of Polyneur-
        itis of Pregnancy, Am. J. of Obstetrics
        28:902, 1934.

18. Funk.: Ueber Schwangershaftslaehmungen der Muetter,
        Deutsche Med. Wchnschr. 34:1702, 1908.

19. Hildebrandt, A.: Polyneuritis and Its Therapy,
        Zentralbl. f. Gynaek. 63:306-310, 1939.

20. Hildebrandt, A., and Otto, Hans.: Ueber Schwanger-
        schafts Polyneuritis und Ihre Beziehung zum
        Vitamin B$_1$, Muenchener Med. Woch. 85:1619-
        1622, 1938.

21. Hoesslin, Von R.: Die Schwangerschaftslaehmungen
        der Muetter, Arch. f. Psychiat. 38:730-861,
        1903, und 40:445, 1905.

22. Hoffman, L. O.: Presumable Toxemias, Nebr. State
        Med. Journal :422-424 (Oct.) 1932.

23.   Hofman, J. A.: Beriberi in Chinese Women And
            Its Relation to Childbearing, China Med.
            Jour. :987 (Dec.) 1924. Cited from Plasz,
            E. D., and Mengert, W. F.: Gestational
            Polyneuritis, J. A. M. A. 101:2020 (Dec. 23)
            1933.

24.   Hornstein, M.: Rarer Forms of Toxemia of Pregnancy,
            Am. J. Obst. 74:270, 1916.

25.   Hornung, R., and Creutzfeldt, H. G.: Laehmungen
            vom Landryschen typ in der Schwangerschaft,
            Deut. Med. Wochensch. 56:35, 1930.

26.   Horwitz, O., and Farley, D. L.: Vitamin B$_1$ Def-
            iciency in Pregnancy as Indicated by Test
            For OBT Principle, Surg. Gynec. and Obst.
            71:313-316, 1940.

27.   Jaccoud.: Traite' des paraplegies, Paris, 1864.
            Cited from Hoesslin, Von R.: Die Schwanger-
            schaftslaehmungen der Muetter, Arch. f.
            Psychiat. 38:730-861, 1903.

28.   Job, L.: Contribution a' l'etude de la myelite it
            des polynevrites, Ann. de Gynec. et d'obst.
            8:129, 1911. Cited from Berkwitz, N. J.,
            and Lufkin, N. H.: Toxic Neuronitis of Preg-
            nancy, Surgery, Gynec. and Obstet. 54:743-
            757, 1932.

29.   Jolliffe, Norman; Goodhart, Robert; Gennis, Joseph;
            and Cline, J. K.: The Experimental production
            of Vitamin B$_1$ Deficiency in Normal Subjects:
            The Dependence of the Urinary Excretion of
            Thiamin in the Dietary Intake of Vitamin B$_1$,
            Am. J. M. Sc. 198:198 (Aug.) 1939.

30.   Jolly.: Uber paraplegie in der Schwangerschaft,
            Neurol. Zentralbl. 4:305, 1885.

31.   Kast.: Myelitis in Gravidit., Jahrb. d. Hamb.
            Staatskrankenanst 2:140. 1891. Cited from
            Berkwitz, N. J. and Lufkin, N. H.: Toxic
            Neuronitis of Pregnancy, Surg. Gynecol.
            and Obstet. 54:743-757, 1932.

32. Korsakow and Serbski.: Ein Fall von Polyneuritis-
       chen Psychose mit Autopsie, Arch. f. Psych.
       23:112, 1892.

33. Kramm, H.: Beitrag Zur Polyneuritis in der Schwang-
       erschaft, Centralbl. f. Gynec. 62:234-258,
       1938.

34. Lindemann.: Zur Pathologische Anatomie des un-
       stillbaren Ebrechens der Schwangeren, Cent-
       ralbl. f. allg. Path. u. path. Anat. 3:625,
       1892.

35. Luikart, R.: Avitaminosis as a likely Etiologic
       Factor in Polyneuritis Complicating Preg-
       nancy, With the Report of a Case, Am. J. of
       Obst. and Gynec. 25:810-815, 1933.

36. McGoogan, L. S.: Toxic Neuronitis in Pregnancy,
       Journal-Lancet 52:735-740, 1932.
       Unpublished Paper- to be Published in 1941.

37. Meiklejohn, A. P.: Is Thiamin the Antineuritic
       Vitamin? New Eng. J. Med. 223:265-273
       (Aug. 22) 1940.

38. Mellanby, E.: The Presence in Foodstuffs of Sub-
       stances Having Specific Harmful Effects under
       Certain Conditions, Journal of Physiology
       24:61, 1926.

39. Moebius, P. J.: Beitrag zur Lehre von der Neuritis
       puerperalis, Muenchen. med. Wchnschr. 37:247,
       1890. Ueber Neuritis Puerperalis 34:153, 1887.

40. Patten, C. A.: A Case of Multiple Neuritis Assoc-
       iated with the Toxemia of Pregnancy and the
       Possible Influence of Retained Fetal Products,
       Arch. Neurol. and Psychiat. 21:721, 1929.

41. Plasz, E. D., and Mengert, W. F.: Gestational
       Polyneuritis, J. A. M. A. 101:2020-2023
       (Dec. 23) 1933.

42. Polk, W. M.: Mania and Multiple Neuritis in Preg-
       nancy, Med. Rec. 37:526, 1890.

43. Reynolds, E. S.: Peripheral Neuritis Connected with Pregnancy and Puerperal State, Brit. M. J. 2:1080, 1897.

44. Robinson, W. D., and Melnick, D., and Field, H. Jr.: Urinary Excretion of Thiamin in Clinical Cases and the Value of Such Analyses in the Diagnosis of Thiamin Deficiency, 19:399-408 (March) 1940.

45. Schlesinger, H.: Polyneuritis bei Hundernden, Wien. Klin. Rundschau. 33:236, 1919. Cited from Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy, Surg. Gynec. and Obstet. 54:743-757, 1932.

46. Schultze, W.: Schwangerschaftsneuritis und B_1 Vitamin, Zentralblatt fur Gynakologie 62:2533-2538, 1938.

47. Siddall, A. C.: Vitamin B_1 Deficiency as an Etiologic Factor in Pregnancy Toxemias, Am. J. Obst. and Gynec. 35:662, 1938.

48. Solowieff, G.: Ueber einen Fall von Hyperemesis Gravidarum begleitet von der Neuritis Multiplex, Zentralbl. f. Gynec. 16:492, 1892.

49. Staehler, F.: Untersuchungen Ueber den Vitamin B_1-Stoffwechsel gesunder und polyneuritiskranker Schwangerer und Wochnerinnen, Deut. Med. Wchnsehr. 64:1137, 1938.

50. Stander, H. J.: The Toxemias of Pregnancy, Medicine 8:1, 1929.

51. Stembl, L.: Ein Fall von Schwangerschafts-polyneuritis nach unstillbaren Erbrechen, Deut. med. Wchnschr. 21:461, 1895.

52. Strausz, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy A Dietary Deficiency Disorder, J. A. M. A. 100:1320-1323 (Apr. 29) 1933.

53. Theobald, G. W.: Neuritis in Pregnancy Success-
       fully treated with Vitamin B₁, Lancet :834,
       1936.

54. Titus, Paul.: Hyperemesis Gravidarum, J. A. M. A.
       85:488, 1925.

55. Tuillant, A.: Dela nevrite puerperale, These de
       Doct, Paris, 1891. Cited from Berkwitz, N.
       J., and Lufkin, N. H.: Toxic Neuronitis of
       Pregnancy, Surgery, Gynec. and Obst. 54:743,
       1932.

56. Vandel, D. T.: Polyneuritis, Vitamin Deficiency
       Disorder, J. Missouri Med. A. 30:407-409,
       1933.

57. Viet, J.: Ueber Albuminurie in der Schwangerschaft,
       Berl. Klin. Wohnschr. 39:512, 1902. Cited
       from Berkwitz, N. J., and Lufkin, N. H.:
       Toxic Neuronitis of Pregnancy, Surg. Gynec.
       and Obst. 54:743, 1932.

58. Vorhaus, M. G., Williams, R. R., and Waterman, R.
       E.: Studies on Crystaline Vitamin B₁, J. A.
       M. A. 105:1580-1584, 1935.

59. Wechsler, I. S.: Unrecognized Cases of Deficiency
       Polyneuritis (Avitaminosis?), Med. Jour.
       and Record :441-444, 1930.

60. Whitfield, D. W.: Peripheral Neuritis Due to
       Vomiting of Pregnancy, Lancet 1:627, 1889.

61. Williams, P. F., Griffith, G. C., and Fralin, F. G.:
       The Relationship of Vitamin B₁ to the Reprod-
       uctive Cycle, Am. J. Obst. and Gynec.
       40:181-192 (Aug.) 1940.

62. Williams, R. D., Mason, H. L., Wilder, R. M., and
       Smith, B. F.: Observations on Induced
       Thiamine Deficiency in Man, Arch. Int. Med.
       66:787 (Oct.) 1940.

63. Williams, R. R., and Cline, J. K.: Synthesis of
    Vitamin B_1, J. Am. Chem. Soc. 58:1304, 1936.

64. Wilson, K. M., and Garvey, P.: Polyneuritis a
    Presumable Toxemia of Pregnancy, Am. Jour.
    Obst. and Gynec. 23:775-787, 1932.