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Pernicious vomiting of pregnancy with particular reference to etiology and neurological complications

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PERNICIOUS VOMITING OF PREGNANCY WITH PARTICULAR REFERENCE
TO ETIOLOGY AND NEUROLOGICAL COMPLICATIONS.

By

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INTRODUCTION

Many pregnant women suffer from the so-called "morning sickness" of early pregnancy. It is so common that it is hardly considered as abnormal. In fact, it might be regarded as one of the most reliable of the presumptive signs of pregnancy. Sometimes, however, the condition becomes exaggerated and the nausea and vomiting are no longer "morning sickness" since these symptoms are not confined to the morning hours after arising.

They may even continue throughout the day and night. Not only is food ejected, but the vomiting may continue even when the stomach has emptied itself. This condition may continue and become so grave that it endangers the well-being of the unfortunate victim or even threatens her life. Thus the morning sickness has become pernicious vomiting.

This subject is as old as the medical profession itself. It is a comparatively common condition and is frequently met with, yet efforts to solve the mystery of its cause have not been successful though they have been numerous.

The situation is most adequately expressed by Crowley(6) who says, "From the dark ages of ancient medicine down to

modern medicine of today pregnant women have suffered from this condition and many have paid the price with their life, because of lack of knowledge of its cause and means to combat the effects of the emesis incident to the gravid uterus; and many an unborn child has been sacrificed because of the inability of the profession to cope with this distressing condition known as Hyperemesis Gravidarum. In the early years of what might be termed modern medicine patients suffering from this condition were left to fight their own battle. If they survived the ordeal, well and good, if not it was, to say the least, most unfortunate. Medical writers have given us very little that would guide the doctor in the care and management of this grave malady, and it is only in recent years that real investigation into the cause and effect of the condition, that we have been able to reduce the mortality to a very small percent when compared with the high mortality of former years."

Thus, a conception of the gravity and severity of the disease can be gained. It is unnecessary to point out the need for thorough and intensive investigation into the cause and prevention.

Involvement of the nervous system, since it is always preceded by severe vomiting (19), must therefore be considered a complication. While these neurological

complications are not so very common, they are by no means to be taken lightly since the involvement frequently results in high mortality. Or even if the life of the patient is spared she may spend many weeks and months recovering from residual weakness and paralysis or mental symptoms.

Even though these complications which involve the nervous system are an occasional result of pernicious vomiting there are additional factors in their etiology which go beyond the conditions which are commonly regarded as being concerned in the etiology of pernicious vomiting. Likewise, the pathology is more extensive and the symptoms are more numerous. For these reasons, the neurological complications will be considered separately in the chapter of that name.

The treatment of hyperemesis gravidarum is extremely extensive and varied. In the literature are to be found innumerable single case reports - each with its own successful treatment. On the other hand, there are also to be found many methods of treatment which, although successful in the hands of some practitioners were futile in the hands of others in spite of the fact that the conditions were quite similar and the procedure duplicated most carefully. Thus, the treatment is something which must be carefully worked out and adapted to fulfill the

needs of each individual case. For that reason it will not be included in this paper.

The pathology of hyperemesis gravidarum is not extensive, the picture being mainly that of starvation. The pathology of the nervous system will be considered under the neurological complications.

TERMINOLOGY AND CLASSIFICATION

In general, it might be said that hyperemesis gravidarum as defined by the majority of authors is a condition of vomiting which has passed from the physiological to one of a pathological condition leading to changes which, if unrelieved, cause abortion or death.

Hemmings (17) says, "It appears to me that there is much confusion in the term "hyperemesis gravidarum" itself. What really are its limitations? Just at what point simple vomiting passes into hyperemesis gravidarum is still a greatly disputed question. Would it not be more plausible and logical to classify this condition under the caption of "persistent vomiting" or better, toxic vomiting of pregnancy."

It is universally agreed that the so-called "morning sickness" is the mild feeling of nausea and vomiting which is experienced on or shortly before arising in the morning during the early months of pregnancy. This simple condition is generally relieved by the taking of a small amount of food when the patient awakens in the morning.

It is Garnett's (15) opinion that nausea occurs in from one-third to one-half of normal pregnancies, usually a mild "morning sickness" appearing about the

end of the first month and lasting for six to eight weeks. During this time there is no known pathological change and the condition is accepted as being normal since the cause is unknown. He also states that it is difficult to recognize the time when vomiting of pregnancy passes from a normal condition to an abnormal one. He believes that vomiting of pregnancy should be considered of the pernicious type when there are certain chemical changes in the blood and urine. However, he does not state specifically just what these changes are.

Morning sickness is considered to be a self limited condition by Ainley(53), - "The vomiting of pregnancy which so frequently begins with nausea or morning sickness about the fifth or sixth week of pregnancy and is accepted lightly as a temporary discomfort to be expected, becomes of greater importance when considered in relation to the development of so-called pernicious vomiting and its sequel polyneuritis or neuronitis of pregnancy. Ordinarily the morning sickness is a self limited condition which, when with the advance of pregnancy, clears up spontaneously by the fourth month, but occasionally the vomiting persists, increasing to such violence that the consequent dehydration, starvation and ketosis, will lead to death unless proper treatment is instituted; and those cases which recover from the vomiting show a definite predisposition to the development of neuronitis."

Turner (45) says that here again, as in the case of eclampsia, the term "vomiting of pregnancy" is purely empirical. He repeats the old phrase that vomiting is a symptom, not a disease; and in this case it is the chief symptom of a condition, the essential of which, is not yet fully understood.

Morning sickness and pernicious vomiting are termed "physiological nausea" and "pathological" respectively by Wright (52). It is believed that the so-called "physiological nausea" takes place in about fifty percent of pregnant women. He continues that this condition must not be confused with the "pathological" type of vomiting, in which there is constancy of nausea and frequency of vomiting, exhaustion, loss of weight and of sleep, salivation, hematemesis, fever, and rapid pulse, and apparently all ingested food is returned, the patient becoming dehydrated, jaundiced, etc. These things, if not corrected, in due time lead to acidosis, coma and death.

He believes that this above classification is more practical than those generally advocated by other authors. Under the physiological division he includes such terms as reflex and neurotic, which conditions usually respond to a correction of a misplaced uterus, or treatment of an eroded cervix, with rest in bed in connection with a general line of treatment for the psychological effect;

while the pathological classification embraces only those cases in which there is a toxemia, with a definite pathology.

In addition Wright further says that the toxic type of vomiting may be distinguished from the milder form in the greater gravity of its symptoms, and, second, through blood chemistry, Although DeLee (8) has worked along this line without forming a definite conclusion as to the merits of blood analysis as a basis on which to determine the necessity for emptying the uterus in toxic cases. "In the true toxemic cases there are evidences of disturbed metabolism in the blood and urine, upon which a differential diagnosis may be based."

INCIDENCE.

Most writers agree that about fifty per cent of all pregnancies are nauseated or vomit sometime during their gestation, but very few offer any information beyond that, except to say that the true pernicious type is comparatively rare or does not often occur. This is probably accounted for on the basis of the fact that the line of division between morning sickness and true hyperemesis gravidarum is vague and indefinite.

John Bell (2) of Detroit found in a series of one thousand one hundred and fifty-four pregnancies in the Rotunda Hospital only one case of the true pernicious type. In Harper Hospital during the year 1921, there were eleven cases diagnosed as vomiting of pregnancy admitted. Of these five were aborted instrumentally shortly after admission. Four recovered under conservative treatment, and one left the hospital partially recovered. In the Obstetric Department of Providence Hospital for the years 1919 to 1921, the figures were as follows: In 1919 of one thousand one hundred fifty-seven cases admitted, there were four cases of pernicious vomiting, with one death. In 1920 there were one thousand five hundred twen-

ty-five cases admitted with two cases of pernicious vomiting. In 1921, there were one thousand one hundred seventy-two cases admitted with five cases of pernicious vomiting. Thus, there was a total of three thousand eight hundred fifty-four pregnancies, and of these eleven were of the pernicious vomiting type.

Hemmings (17), judging from available statistics in the medical literature, says that one-eighth of one percent would be the proper figure for the true pernicious type.

Both Calkins (4) and Hall (16) claim that fifty per cent of pregnant women suffer from a greater or lesser degree of nausea and vomiting. Andrews (1) places the figure at sixty per cent, only fifty percent needing treatment, however. In addition he says that since the mortality records are not reported under obstetric casualties, it is difficult to ascertain the exact figures as to loss of life from this cause, but at least one observer expresses the belief that the total loss from this cause is as great as from eclampsia.

About the most complete and careful observation of incidence up to 1928 was done by Peckham (36) of Baltimore who very carefully studied a series

of sixty cases of hyperemesis gravidarum admitted to the Johns Hopkins Hospital. A portion of his discussion is as follows: "Despite the large number of women suffering from nausea and vomiting during the first trimester of pregnancy, very few develop the pernicious type and require hospitalization. The upper classes contribute a much larger percentage than the lower types of white women; and in general it may be said that colored women are more apt to be afflicted than white women of the same social status. The incidence seems to be greater in a warm than in a cold climate. Germany and the British Isles are said to have a very low incidence. Several of our white ward patients were of French or Italian extraction. A rather large percentage of patients returned to the hospital following a relapse, but none of these were private patients. Crowded ward conditions necessitate the early discharge of the public patient, in this series often within a week of the cessation of vomiting. Two weeks would probably give more lasting results, and if the financial condition of the patient permitted, an intermediary sojourn at some resort between hospital and home would seem to be beneficial."

A portion of Peckham's work may be summed up thus:

1. Vomiting of pregnancy sufficiently severe to warrant admission to a hospital occurs about once in one hundred and fifty pregnancies, and severe cases occur once in four hundred.

2. Women in the upper walks of life are more prone to the disease, but negro women are not immune to it.

3. The age and parity are not predisposing factors.

4. Severe vomiting usually starts before the eighth and occasionally before the fourth week of pregnancy.

ETIOLOGY.

The theories advanced as to the cause of pernicious vomiting of pregnancy are most numerous. All have some scientific foundation. "Any one of them may explain fully and satisfactorily any one case, but none of them has ever satisfactorily explained all cases. The various theories have this in common, however, that most all concede the presence of an underlying toxemia, although they differ as to the nature and origin of the toxin. In recent years, however, the tendency has been to regard the toxin as metabolic in nature and hepatic in origin." (39)

Williams (50) of Johns Hopkins, in his 1906 monograph describes three types of vomiting: the reflex, neurotic, and toxemic. He also recognized, in the fatal cases, the analogy of the liver lesions to those observed in acute yellow atrophy. Also in his monograph of 1906 (50) he states that the finding of an anatomical lesion makes the diagnosis of reflex vomiting possible, and that this generally presents no great difficulty. In the absence of such a lesion, however, a much greater difficulty presents itself in the differ-

ential diagnosis between a neurotic and a toxemic vomiting. He lays a great deal of stress on the ammonia coefficient, and states that in the neurotic type this coefficient is normal, while the toxemic type may be diagnosed when the coefficient reaches ten to fifteen percent and that this percentage affords sufficient reason for the termination of pregnancy.

Schultze (41) on the other hand, is of the opinion that the significance of the ammonia coefficient has been exaggerated, if not entirely misinterpreted. The presence of a high ammonia coefficient simply diagnoses an acidosis while the acetone bodies are indicative of a disturbed metabolism and neither of them in any way diagnoses the type of vomiting that is being dealt with nor the presence or absence of any other underlying toxin.

In the fifth edition of his text-book, Williams (51) expresses an opinion quite different from that given in his 1906 monograph. He admits that a high ammonia coefficient⁺ may result from the inanition occasioned by a prolonged neurotic vomiting as well as from a toxic vomiting; that a coefficient of five percent or less indicates a neurotic vomiting, that a high ammonia coefficient does not nec-

+ (The term **ammonia** coefficient is used to express the relation of the ammonia nitrogen to the total nitrogen in the urine)

essarily predicate the existence of toxemic vomiting, but that when it exceeds fifteen or twenty percent it clearly indicates that the patient is seriously ill.

DeLee (8) recognizes four distinct classes:

1. Those in which the vomiting is a reflex from the genitalia;
2. when it is due to some disease of the stomach, some abdominal disorder, or some abnormal condition of the blood;
3. where the nervous system is at fault; and,
- 4., where the general metabolism is disturbed, the clinical picture being that of toxemia.

In hyperemesis he has two classes, the primary toxemia and the secondary toxemia. In the primary group he places the fulminating cases that present the clinical picture of acute toxemia, in the secondary he places the milder forms of toxemia usually produced by starvation including dehydration.

Veaux (48) considers that there is "an hysterical or neurotic substratum often in evidence through the numerous spontaneous and induced stigmata and symptoms of these conditions. Reflex excitability is also a powerful factor in determining the paroxysms of vomiting, and we therefore sometimes find evidence of a casual connection

between various lesions and malpositions of the uterus and emesis." He holds that in essential vomiting of pregnancy, there are two types; namely, auto-toxic and non-toxic. In the auto-toxic type there is a decided manifestation of the toxemia of pregnancy, as shown by the clinical symptoms, and unless relief can be obtained promptly, death occurs within a few days. In the non-toxic or inanition type the vomiting lasts for several weeks, and unless the physician is able to control the emesis, the patient dies purely from starvation.

In discussing the causes of hyperemesis DeLee (8) states that, "One must not lose sight of the generally increased nervous excitability of pregnancy which would tend to exaggerate the action of any irritant located at any part of the body. Uncontrollable vomiting is more common in neurotic, neurasthenic, and hysterical women, but it is particularly likely to develop if there is some irritant which may act on the stomach via the nervous system or blood."

Ewing (13) in 1910 takes the position that the disturbance is always of toxic origin, that the anatomical basis is found in the degenerative

changes in the liver and kidneys; and says that early vomiting is but the early sign of a train of metabolic disturbances which, if allowed to progress, end in fatal vomiting, malignant jaundice, and acute yellow atrophy. The weight of the evidence seems to point to a functional disturbance of metabolic origin in the liver, as the essential factor.

The presence of acetone bodies in the urine has frequently been noted in cases of pernicious vomiting, but that these were the causes of the toxemia was vigorously denied by Ewing, who, discussing the question from the general standpoint of acid intoxication, pointed out:

"1. That acid intoxication, as evidenced by the appearance of ammonia and acetone bodies in the urine, occurs in many well investigated conditions without the appearance of toxemic symptoms.

"2. That the administration of alkalies (diabetes) and carbohydrates (pernicious vomiting) removes the evidence of acid intoxication from the urine, but leaves the symptoms (clinical) unaltered.

"3. That acids have never been obtained from the blood in anything like the quantity required to produce the symptoms while the administration

of acids in large quantities is required to produce the toxic symptoms in healthy animals, and even then, these symptoms do not closely resemble those of the true toxemias."

Duncan and Harding (11) of the University of Toronto, Titus, Hoffman, and Givens (56) are a few of several authors who favor the theory that nausea and vomiting of pregnancy are due to a deficiency of glycogen in the maternal liver, or in the idea that the glycogen content of the maternal liver is far too low for the requirements of the pregnant organism. "Of the various metabolic factors, the one most susceptible to disturbance is well known to be that of the carbohydrate. In endeavoring to trace out how such a disturbance could take place, the author's attention was directed to the work of Imre (21) and of Mottram (32). The former has shown that the growing fetus is greedy of unsaturated fat. The latter, that often in the pregnancy of nervous and ill-nourished animals, the liver becomes overloaded with fat, that is, there is an increase of fat present, which has come in from the fat depots. Mottram has also shown that a simple hunger of a few hours duration, in some animals, led to the same condition. The

phenomena are more or less phenomenal in character, as the effect on the liver is a transitory one. It seemed possible then, that these two factors, pregnancy and a short period of hunger, might account for the periodicity of morning sickness, and that the metabolic factor here concerned was a temporary relative lack of glycogen in the liver. Such a condition, it is well known, leads to a fatty infiltration of that organ.

"Two things should follow from this view. Such a condition of the liver is usually associated with an acetonuria, accompanied generally by acetoacetic and oxybutyric acids, evidence of which should be found in the urine of these patients. Such a condition is obviated by keeping present in the patient an adequate supply of carbohydrate.

"We may say at once in all cases of nausea and vomiting in pregnancy which we have studied, except in two of the very mildest ones, we have found the acetone bodies present in the urine. Those cases where we found it absent were mild ones of morning nausea, but in these particular cases we were not able to obtain and examine the freshly voided over-night specimen which we wished. It must, at this point, be clearly emphasized that

we do not regard the presence of acetone bodies as the cause of the nausea or vomiting. We regard them as a secondary result. Ewing's arguments on this point are conclusive.

"As stated previously, the basis of our work has been an attempt to trace out the influence of the metabolic factor in this nausea and vomiting. Lack of glycogen in the liver, with it's precursor, insufficient carbohydrate diet, was held to be a possible disturbing element in the early forms and our success with carbohydrate feeding bears out this supposition (11).

Several of the conclusions from a paper by Titus, Hoffman, and Givens are as follows:

"2. The development of a course of treatment, the success of which seemed to depend on the use of carbohydrates in large amounts, led to the assumption that a deficiency in carbohydrates has an important bearing on the origin of toxemia of pregnancy.

"3. Carbohydrate deficiency during pregnancy is of twofold origin; (a) a relative deficiency due to an unexpected demand for glycogen on the part of the fetus and the uterus, and (b) an actual deficiency, augmented in the presence of nausea and vomiting, from lessened carbohydrate intake.

"4. Carbohydrate deficiency in the maternal organism causes a glycogen depletion of the liver, because this is the organ in which carbohydrates are stored for as needed.

"5. There is experimental evidence to show that liver function is impaired and the body flooded with toxins after carbohydrate starvation.

"6. Pathologic changes in the liver lobules which are similar to those of fatal toxemias of pregnancy can be produced experimentally by the use of certain chemical poisons. These changes can be made to disappear rapidly by the ingestion of carbohydrates."

"This above theory makes the fewest assumptions and is consistent with the greatest number of facts."(39)

Mack (27) suggested that a toxin or poison produced by the fetus or placenta may be the cause of vomiting of pregnancy, and that normal pregnant women become immune to the toxin. "No such toxin has, however, been isolated, and it is conceivable that it may prove to be an intermediate or end product of metabolism rather than a foreign poison. It certainly seems that the neurotic element, as a factor in the etiology of the disease, has been greatly overemphasized in the past. All cases of vomiting in pregnancy are undoubtedly toxic in origin, although they may vary greatly with

respect to the role which a neurosis may play in the course and prognosis of the disease". (39)

Peckham (36) of Johns Hopkins feels that the vomiting of pregnancy is a toxemic process resulting from detached masses of chorionic villi and chorionic epithelium which invade the maternal vessels. He says that, "It is believed in this clinic that the underlying basis for every case of vomiting of pregnancy lies in a toxemic process. This is based upon the fact that in every pregnancy, whether normal or not, histologic evidence can be adduced to show that fragments of chorionic villi and detached masses of chorionic epithelium can be demonstrated in the maternal vessels. In other words, there is an invasion of the maternal blood by fetal elements. Normally, this foreign protein is broken down by the tissues of the mother and is rendered innocuous. On the other hand, if the process be interfered with, it seems justifiable to suppose that toxic symptoms may develop.

"In the majority of cases this leads to few or no clinical manifestations so long as the nervous equation of the mother is in fair equilibrium, but when it is unstable symptoms follow. Consequently, in most such cases nature is able to care for the underlying toxemia if the mental condition can be alleviated.

This affords a rational explanation for the rational results attending treatment by isolation and suggestion and justifies the employment of the term neurotic vomiting in clinical parlance. At the same time it must always be remembered that this is a clinical conception and that the underlying cause is always to be found in a toxemic process.

"On the other hand, in rare instances the underlying toxemia is so intense that such treatment is useless, as organic changes soon develop which will inevitably lead to death if the pregnancy is not interrupted. In exceptional cases in this category the fatal issue may occur within one week, and these represent toxemic vomiting par excellence. Furthermore, when death occurs after an illness lasting for weeks, it is usually attributable to changes consequent upon dehydration and inanition, rather than to lesions directly dependent upon the toxemic process."

Peckham, while advancing the toxemic theory, is inclined to discount the neurotic element. He says that a great majority of his cases gave as the time of onset before the eighth week of pregnancy. Seven cases began to vomit before a menstrual period had been missed. For these reasons it is rather difficult to conceive of a neurotic element causing the onset of trouble in these

cases.

By far the greater number of the cases of vomiting of pregnancy, and all the pernicious cases, according to Partridge (35), are toxic in origin. He says that they are as truly toxic in origin as eclampsia in nature.

In direct contrast to this opinion is that of Oldfield (33) of England. He stated in 1922 that for more than twenty years he had been of the opinion that all cases of pernicious vomiting of pregnancy were neurotic in origin and he treated them accordingly. He reported twenty nine cases during that twenty years and all of them recovered under his treatment based on a neurotic cause, and in only case was abortion induced. He says that all his cases were toxemic but that he regarded the toxemia as a result of the vomiting not a cause of it.

Tweedy (46) thinks that the cause of hyperemesis lies in food poisoning. He expresses his theory thus, "I shall now consider the manner in which I conceive that food under certain conditions may produce untoward results. Sterile milk or other foodstuffs, if injected directly and repeatedly into the blood, is apt to exercise a poisonous effect. It is said that this poisonous effect is due to an absence of specific antibodies,

for those present in the blood are incapable of rendering harmless the food particles until they have been modified by first passing through the mucous surfaces of stomach or intestines. We now know that in early pregnancy a foreign albumin appears in the blood, and I suggest that the normal food antibodies are interfered with thereby. Thus, the early sickness of pregnancy becomes understandable, it may be considered Nature's effort to reject food incapable of proper neutralization. It is also probably eliminatory in its effects, for its occurrence in the early morning will remove from the system the digestive excesses of the previous day. When it fails to do this thoroughly toxic symptoms arise. In most instances tolerance to food is eventually established, but the extent of the failure of the food particle to unite with its antibody is the measure of the severity of the toxemia. The fact that the kidney inflammation is rarely seen in the early months of pregnancy may be due to the efficient eliminatory action of morning vomiting. In the worst cases of hyperemesis the alarmed stomach fails to discriminate between harmful and harmless stimuli and endeavors to eject everything, even the presence of spring water can no longer be borne, and, indeed, retching can be induced by mere suggestion."

Hirst (18) is one of several exponents of the theory that abnormal secretions of corpus luteum are responsible for the excessive vomiting. He states that every woman, during the period of sexual activity, is constantly absorbing corpus luteum. No sooner is the corpus luteum of one menstruation disposed of, than another appears to take its place. With the onset of pregnancy, this absorption ceases. The corpus luteum of pregnancy constantly increases in size, until it reaches its acme about the third month. From this time on, it is gradually absorbed. The nausea of pregnancy, beginning during the period of non-absorption, disappears about the time that the corpus luteum begins to decrease in size. He then asks the question whether it is reasonable to assume that this is not coincidence, but cause and effect, and that the corpus luteum plays an important part in relation to the nausea. At the end of his paper he says, "I feel that a series of one hundred and eleven consecutive cases, gives a fair basis for drawing conclusions. The fact that ninety-nine (eighty nine and two tenths percent) were favorably influenced proves, I think, that the lack of the normal corpus luteum absorption is a factor in the nausea of pregnancy, and that in the great majority of cases the nausea can be relieved by the hypodermic

intramuscular injection of corpus luteum extract."

All the above mentioned theories are but a fraction of the total number which have been expressed in the literature. Thus, one can readily gain an impression of the size of that total number. Many theories which were thought to be logical and which apparently had been proved have in the passing years been disproved or discredited. Other theories were conceived to take their places and the value and truth of those of the modern day remains to be seen. At any rate, the true etiology of hyperemesis gravidarum remains unknown up to the present time.

SYMPTOMS & SIGNS

Vomiting is the most constant sign in hyperemesis gravidarum. It usually begins early in pregnancy and its onset is often quite mild and is seldom viewed with alarm. Symptoms of the pernicious type usually begin in the second or third month and steadily increase until the patient shows a marked condition of toxemia, by the loss of weight, constant vomiting, and changes in the blood and urine.

The nausea and vomiting seem to be constant and not influenced by the food taken. Garnett (15) says that at first the vomitus is composed of undigested food and mucous, later mucous and bile, finally, bloody and of a coffee ground appearance. The patient refuses to take any food by mouth on account of fear of increasing the condition. The urine at this time is diminished in amount, highly colored and usually contains albumen, bile, acetone, and diacetic acid.

In addition he says that the changes in the urine are apparently due to toxemia, the nature of which has not been found and the vomiting cannot be attributed to the acidosis which seems to be a result and not the cause of the poisoning. The symptoms grow progressively worse until the patient reaches the stage

of constant and uncontrollable vomiting and acute starvation.

Paddock (34) of Chicago divides the vomiting of pregnancy into three stages: "First, there is the disagreeable nausea with slight vomiting of mucous which comes on soon after the first missed menstrual period. The patient may crave food which usually is indigestible and unpalatable, rejecting other foods and able to keep down the former.

"The second stage is ushered in with constant nausea, all foods and liquids being rejected and soon the vomitus contains bile and blood. The urine becomes scanty and albumin and casts appear. The skin becomes dry and hot, although there is little if any rise of temperature. Diacetic acid and acetone are present. This condition goes on for a week to two weeks, the patient gradually becoming dehydrated, the symptoms increasingly severe.

"The third stage is ushered in with marked acidosis, perhaps less vomiting and more or less delirium. Scanty urine with an increase in casts, blood and albumin, a thready, weak pulse and a slight rise of temperature. Frequently, at this time all vomiting ceases and the patient seems on a fair way to recovery, food is taken and apparently the organs are functioning nor-

mally, but the damage already done to the liver and kidneys is too great and the patient dies."

Munro Kerr (24) points out that when vomiting ceases in severe cases the possibility of paralysis of the cerebral center has to be considered, a fatal ending being not far distant.

Headache, if persistent, should never be overlooked according to Dame Louise McIlroy (30) of London. She states that it may be due to anxiety, hypertension, eyestrain, or intracranial pressure, and should never be overlooked. It is sometimes the first danger signal of the onset of eclamptic convulsions.

NEUROLOGICAL COMPLICATIONS.

"We recognize a number of serious conditions which may complicate pregnancy, designated as the toxemias, including eclampsia and preeclamptic toxemis, nephritic toxemia, pernicious vomiting, and the like. While we still have to admit a profound ignorance in regard to the exact etiology of these conditions, they are universally regarded as being of a toxia origin and all may present marked disturbances of general metabolism.

"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 we may include certain psychoses, excessive salivation, the non-contagious skin lesion impetigo gestationis, a rare but highly fatal malady, and certain examples of multiple neuritis. This latter is a condition which is quite distinct from the more frequently seen traumatic and infections types.

"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 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. These patients may be regarded as suffering from a mild form of peripheral neuritis of possibly toxic origin. The 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 so 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 paralyzes 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 high and is generally about twenty-five per cent." (43)

INCIDENCE AND OCCURRENCE

The term "toxic neuronitis" is the one most frequently seen in the literature, although there are other terms such as peripheral neuritis, polyneuritis, and toxic myelitis of pregnancy. The name, toxic neuronitis of pregnancy, has been used by Berkwitz and Lufkin (3) since the nerve cells are involved as well as the peripheral nerves. Taylor and McGoogan (54) speaks of "a series of neurological phenomena known as toxic neuronitis". In the latest literature this is the most popular terminology.

Up to the present time there are few figures available as to the frequency of this severe complication of pregnancy. This is true chiefly because the literature on toxic neuronitis is rather limited. "No estimate of the frequency of polyneuritis can be offered, although it is undoubtedly less rare than is commonly thought. Many cases of so-called late toxic vomiting of pregnancy should be placed in this category, as can be demonstrated by a careful survey of the reports in the literature. In other instances 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. In any doubtful case, careful neurological examination is demanded, since it is only in this way that polyneuritis can be diagnosed" (37)

Berkwitz and Lufkin (3) in a survey of the literature presented an excellent summary. They have selected forty-eight cases in which the diagnosis is unquestionable and present four cases of their own. Plass and Mengert (37) in a paper read before the meeting of the Missouri Valley Medical Association reported eight cases of their own. Caffier (7) and Hornung and Creutzfeld (20) have reported two more cases. Wilson and Garvey (57) have reported three additional cases." (28) McGoogan added five in 1932 and Taylor and McGoogan five more cases in 1937. (54)

"The disease occurs more commonly in those pregnant for the first and second time, although women with a greater number of previous gestations are not exempt. There is no age relationship; the majority of cases occur between the ages of twenty and thirty-five, when child-bearing is more common. Patients who have previously exhibited evidences of mental instability may be more susceptible. (37)

It is also Hoffman's (19) belief that toxic neuronitis most frequently occurs in the first or second

pregnancy. In addition he states, "It is always preceded by vomiting of the pernicious type. Its symptoms usually begin after the vomiting has ceased during the fourth or fifth month. It is characterized by tachycardia, muscular weakness (especially extensor muscles), absence of reflexes: knee, biceps and tendon of Achilles, stupor, loss of appetite, loss of memory, and blurring of vision, and not infrequently optic neuritis".

Taylor and McGoogan (54) say that the onset occurs as a rule during the early months of pregnancy, from the twelfth to the twentieth week.

The symptoms can be well brought out and perhaps better fixed in mind by giving a short, typical case history.

"Mrs. S., age thirty-two, Para. II, entered the hospital April 16, 1932. One child eight years, one abortion seven years ago. Patient of neurotic type, faints easily and has always been nervous. Family history negative. R.C. she menstruated last November 28, 1931. In January she began to vomit, was treated for two weeks at home by a doctor and became no better. She was then hospitalized for twelve days and returned home feeling much improved. Although she had slight

nausea and vomiting, her appetite was good and she gained weight. On April 6, she noticed some neurotic pain principally in her legs and she developed on the following day weakness of the extensor muscles of her legs and her nausea ceased. April 13 she was unable to urinate and was somewhat irrational.

"April 16 there was difficulty in swallowing and legs were almost completely paralyzed.

"Physical examination revealed a patient markedly obese with complete paralysis of the legs and partial paralysis of the arms. Knee tendon and arm reflexes were absent. Partial paralysis of throat muscles. There was marked tenderness of the nerve trunks of legs and arms. Her vision was blurred and there was a slight lateral nystagmus. Retinal examination showed flame hemorrhage in the right eye with bulging of the nerve head. Abdomen showed tumor mass of pregnancy of about five months. Pulse 134, blood pressure 116/74.

"Her mental state was confused. She tried at times to cooperate but seemed worried. She could not remember recent events. She did not remember what month it was. The laboratory data was essentially negative, HB. 72, RBC 3,820,000, WBC 10,100, Normal differential. Urine was ^{HIGH} in specific gravity with

only a slight trace of albumin. Spinal puncture gave pressure 6mm. and normal cell count. She died on April 18, at 8 P.M."(19)

Etiology

"Many divergent suggestions have been offered to explain the etiology of neuronitis of pregnancy. In 1859 Churchill (5) offered anemia, uremia, rheumatism, and hysteria as possible causes. Jaccoud (22) in 1886 made a highly theoretical suggestion that the paralysis was due to exhaustion of the nervous system by prolonged and continual excitement of the cord, and that the impulses were transmitted by the uterine nerves, exhausting the excitability of that particular segment of the cord and closing the avenues by which motor impulses pass. A little later Jolly (23) ascribed the paralysis to hysteria. Moebius (31) in 1887 was one of the first to suggest a theory of autointoxication, a concept which is generally accepted at the present time. He believed that "some morbid condition of the blood" of the pregnant woman was the causative factor. Tuillant (44) noticing that severe vomiting preceded the neuritis, suggested that the lack of nourishment was the probable cause. To refute this theory, Lindemann (26) 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 (40) and others, but histo-pathological studies have been largely neglected." (3)

It has been commonly assumed that toxic neuritis is the direct result of the action of a toxin which is produced by the products of conception and which has an especial affinity for certain parts of the nervous system. Plass and Mengert (37) claim however, that no evidence is available to support this hypothesis, which moreover, is rendered improbable by the fact that termination of the pregnancy frequently fails to arrest the progress of the disease. " More recently Berkwitz and Lufkin (3), McGoogan (28), Hoffman (19), and Strauss and McDonald (43) have called attention to the similarity of the nervous manifestations to those of beri-beri and pellagra and have suggested that a deficiency of vitamin B (complex) may be responsible" (37) Wechsler (49) also is of the opinion that the condition is due to dietary insufficiency.

Luikhart (58) in discussing a case history says that when the patient's 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 symptoms unless

vitamin containing nutrition was administered with the water and glucose. In an abstract of a discussion by Plass and Mengert he states, "Cowgill (59) of Yale demonstrated the lack of foundation for hypothesis that polyneuritis is caused by a toxin. He has shown that, if the disturbance is not too advanced, relief can be procured by stabilizing the vitamine balance, particularly the vitamin B complex. This includes the antineuritic part of this vitamin, which formerly was called vitamin G. A patient with severe vomiting in pregnancy developed symptoms almost identical to beriberi, Horsokoffs syndrome and pellogra. Forced feeding of the vitamin B complex was instituted, and because of the results, the case was reported at the obstetric meeting at Memphis last October. The paper by Strauss and McDonald, referred to by the authors, emphasized the important fact that there is a decrease and often a lack of free hydrochloric acid in the gastric juice. of a pregnant woman. In all these conditions there is a history of vomiting, diarrhea, loss of appetite, emaciation, or some hepatic disturbance. It is well known that avitaminosis causes a lack of appetite, which in turn prevents ingestion of vitamins, thus establishing a vicious circle. In these various disturbances evidenced by polyneuritis, the etiology

simmers itself down to a failure on the part of the individual to digest, assimilate, or metabolize the needed vitamins to maintain a proper vitamin balance."

Fouts, Gustafson and Zerfas (14) are also in accord with the avitaminosis theory. They firmly believe that patients who vomit continuously or those who can't absorb the vitamin B complex from the gastrointestinal tract should receive extensive vitamin B therapy.

Vayrynen (60) believes that the process is due to an autointoxication as a result of pregnancy and cites the other evidences of a toxemis - vomiting, albuminuria, icterus and convulsions - as proof of his theory. Most of the cases which he reports point toward a disturbance in the liver function, and apparently this author feels that toxemia is associated with liver damage. In other words, he believes it to be one of the true toxemias of pregnancy.

Pathology

Autopsy report of the case reported above, with the exception of evidence of passive congestion of kidneys and spleen was negative. The histological study of nerves and cord had not been completed.

The very few authors who give pathological data all report mild degenerative changes in the various organs - kidney, heart, liver, suprarenals, and the like. Grossly, the brain, spinal cord, and peripheral nerves usually appear normal, with the possible exception of occasional petechial hemorrhages. Plass and Mengert (37) state that these petechial hemorrhages may be detected, especially 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, according to Plass and Mengert (37), and the involved muscles show marked degenerative changes.

Luikhart (58) in an autopsy report states that all gross findings were negative. Sections of the liver, kidney, and spleen showed cloudy swelling.

Gross examination of nerves was negative. Microscopically the sections revealed definite degeneration of the anterior horn cells with occasional polymorphonuclear leucocytes and plasma cells. The lumbosacral nerves showed definite Marchi degeneration.

Probably the most complete pathological report to be found in the literature up to the present time is that of Berkwitz and Lufkin (3). The report of one of their cases is as follows:

"Autopsy was done one hour after death. In the pelvis was found 250 cc. of blood, the obvious source of which was a recently sutured operative incision in the anterior wall of the cervix and anterior peritoneal cul-de-sac. The liver and kidneys showed a moderate degree of cloudy swelling, but their weights were well within normal limits. None of the other organs were abnormal in even the slightest degree. Gross pathological changes were entirely lacking in the brain, spinal cord, and peripheral nerves.

"About the centers of the lobules of the liver was a minimal amount of fatty metamorphosis. The cells of the convoluted tubules of the kidneys showed moderate swelling and granular degeneration of their cytoplasm. All other organs of the abdominal and thoracic cavities were normal. The thyroid gland was normal.

"In the lumbar portion of the spinal cord there was advanced chromatolysis of the anterior horn cells. In the larger number of these cells distinct Nissl bodies were entirely lacking, and the cytoplasm was stained a dirty blue. Many of the cells were greatly swollen and almost spherical in shape. Nuclei were frequently eccentric, and occasionally even protruded, in part, beyond the margins of the cell body. The characteristic staining reactions of some cells were lost. The irregularity in outline and structure of these cells made it obvious that they were in the early stages of necrosis. In both the gray and white matter of this portion of the cord were a number of tiny, fresh petechial hemorrhages. No inflammatory lesions were found, however, either in the cord or in its meninges at this level. The glial tissue and blood vessels seemed entirely normal and there was no evidence of tract degeneration. In one section, taken from the thoracic portion, a small inflammatory lesion was found in the pia arachnoid. This consisted of mild proliferative changes in the fixed connective tissues, and infiltration by a few lymphocytes and nonnuclear wandering cells. There were no changes in the nerve cells at this level, and no hemorrhages were found. The cervical portion was without histological changes. Careful search

of the brain failed to reveal pathological changes by any method of study. Marchi preparations of the left femoral nerve and the phrenic nerves revealed outspoken degeneration of large numbers of fibers. Fat droplets were numerous and large, and in many portions of the neurilemmae of the affected fibers were collapsed and empty. There were no proliferative or exudative changes in any of the nerves examined.

Korsakoff's Psychosis

The coincidence of Korsakoff's psychosis in the complications of hyperemesis gravidarum. This syndrome, the main features of which are mild mental clouding, confusion and fabrication, and impairment of immediate memory was first described in 1887 by Korsakoff (25) who found it to be a very frequent complication or symptom of alcoholic multiple neuritis. Of interest is the statement of Van Hosslin (47) who finds that the Karsakoff syndrome is reported as having been observed in the multiple neuritides following toximias of pregnancy long before Korsakoff placed his syndrome before the scientific world, and in addition, observes that, pro rata, the incidence of this psychosis following gestational toxemia is greated than in alcoholic neuritis.

Ely (12), in a more recent contribution, described four cases of multiple neuritis following hyperemesis gravidarum, and in each patient a memory defect of Korsakoff type was observed.

Van Hosslin (47) is further responsible for the following conclusions pertaining to this subject; "That there is a form of multiple neuritis which takes its origin in the toxemia of pregnancy, which is wholly independent of any infection; that this malady may have its onset either

before or after delivery; that when recognized therapeutic abortion should be resorted to; that the termination of pregnancy hastens recovery; that convalescence is protracted,"it having been four years before the patellar reflexes returned in one case which came under his observation, and that isolated neuritides may occur in place of the disseminated type, their location being determined frequently by intercurrent circumstances, such as slight trauma and stretching of the nerve trunks during the violent physical activities incident to delivery, or as the result of pressure of the fetal head in the mother's pelvis.(12)

A clinical history reported by Prior(38) clearly illustrates the occurrence of this psychosis. "The examination of her mental condition showed that she was fully conscious. Her attention could be obtained, but she cooperated poorly in the examination. She had some illusions but she denied any hallucinations. She exhibited poverty of ideas and was at times irrational. She had changing delusions of persecutory nature, such as the imminence of her being left naked on a beach by a party of foreigners and subsequently being put into a gaol. Her remote memory could not be tested, but her recent memory was definitely bad. She had no idea of the day and thought it was the early part of 1933 (in

reality, it was late in the year 1933); neither was she oriented as to place. She was very miserable and dull, as well as markedly labile, weeping copiously, and childishly emotional.

"Her psychomotor activities were decreased. She lay in bed in a helpless state and made no attempt to help herself. She was rather irritated by questions and carried on a disconnected conversation with herself, repeating phrases numberless times.

"With regard to her habits, she was noisy at times and tended to be faulty. She was difficult with food."

Prior also states that recovery would appear to begin after the supply of the main noxious influence is stopped. The length of time necessary before full function is restored must depend on the amount of damage done to the actual nerves involved. He states also that the course in these cases is apt to be prolonged even after treatment.

Prognosis.

Hoffman (19) in his paper presented before the Nebraska State Medical Association in 1932 said that the higher in the body that the process extends, the poorer the prognosis. He states further that, "The prognosis is dependent largely upon the stage of the disease in which the case is recognizes."

Following is a table of fatal cases extracted from recent literature:

Author	No. of cases	Deaths	% Mortality
Berkwitz & Lufkin(10)	4	3	75
Hoffman(19)	1	1	100
McGoogan(28)	5	4	80
Taylor & McGoogan(54)	5	3	60
Strauss & McDonald(43)	3	0	0
Wilson & Garvey(57)	3	3	100
Plass & Mengert(37)	<u>12</u>	<u>8</u>	<u>67</u>
Total	33	22	68.8

"When recovery does occur, it is usually slow but reasonably complete. Occasionally, however, the nerve changes are too extensive and the patient never regains the use of the involved extremities. Patients who survive more than two weeks after the diagnosis

can be made on physical examination have a relatively good chance of complete recovery. In fulminating cases death may ensue within three or four days of the first symptom." (37)

SUMMARY AND CONCLUSIONS

1. Pernicious vomiting of pregnancy may be defined as a condition of vomiting which has passed from the physiological to one of a pathological condition leading to changes, which, if unrelieved, causes abortion or death.

2. Approximately fifty percent of all pregnant women vomit to a greater or less degree at sometime during their period of gestation.

3. Vomiting of the true pernicious type occurs in approximately one-eighth of one percent of pregnancies.

4. In spite of the tremendous amount of investigation and study which has been done, the true etiology of pernicious vomiting of pregnancy remains, up to the present time, unknown.

5. The most popular term given to the complications which involve the nervous system is "toxic neuronitis of pregnancy"

6. A survey of the literature reveals that approximately seventy five cases of toxic neuronitis of pregnancy have been reported in which the diagnosis was unquestionable.

7. The etiology of toxic neuronitis of pregnancy is unknown, although the theory of avitaminosis is the most

widely accepted.

8. Gross findings at autopsy are consistently negative with the exception of occasional petechial hemorrhages in the brain and spinal cord.

9. Sections of the liver, kidney, spleen, and heart show cloudy swelling.

10. Sections of the peripheral nerves frequently 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.

11. No pathological findings except petechial hemorrhages have been discovered in the brain.

12. Mental clouding, confusion and fabrication, and impairment of immediate memory, as originally described by Korsakoff, are occasionally with pernicious vomiting of pregnancy, and are considered among the phenomena indicative of central nervous system involvement.

13. The mortality of cases of toxic neuronitis of pregnancy reported in the literature is approximately sixty-eight and eight-tenths percent.

14. The prognosis of toxic neuronitis of pregnancy depends upon the stage at which the condition is recognized and checked.

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