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## The vomiting of pregnancy

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THE VOMITING OF PREGNANCY

BY

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A THESIS

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## INTRODUCTION

"It is a curious maladjustment of Nature that places pregnancy among conditions difficult to separate from the pathological. We are accustomed to refer the high mortality of gestation to the unhygienic influences of modern life, and love to refer to the Indian women who overtook the moving caravans of their tribes after a brief delay for partuition, but history says little about the women who never caught up with the caravan. Today obstetrics in India, China, and Africa deals with the same ponderous process and meets the same formidable hazards as in Europe and America. The comparative study of gestation reveals throughout the animal kingdom a certain lethal tendency reaching its acme in some orders of insects in which ovulation necessarily entails death. Indeed the human family is comparatively fortunate in many of its natural relations to the propagation of the species, while increasing medical intelligence should eventually shield maternity with effective safeguards not provided for the lower animals."

The preceding statement was made by James Ewing (28), professor of Pathology of Cornell University, in 1910. Probably foremost among these hazards is the condition of vomiting of pregnancy, or pernicious vomiting of pregnancy. It is granted that pernicious vomiting in its strictest interpretation - also called hyperemesis gravidarum, or the obstinate, the uncontrollable, the incoercible, vomiting of pregnancy - is a rather rare disease, occurring in from one-eighth to two-thirds of one percent of pregnant women.

However, when one realized the fact that so-called "morning sickness", or the mild type of hyperemesis gravidarum, occurs in from 40 to 60 percent of pregnant women, and that each and every one of these cases is a potential severe case, then only is the importance and significance of the vomiting of pregnancy appreciated. Add to this condition the fact that the disease is a disease of theories and that no basic or fundamental causative or etiologic factor is definitely known, necessitating the employment of empirical or symptomatic treatment, and then the rationale of the statement that hyperemesis gravidarum is probably the most formidable hazard of pregnancy becomes evident.

As stated above, there is a rather varied terminology applied to the condition of vomiting of pregnancy. As a cause or a result of these different terms, there is some controversy as to which cases belong in the group classed as hyperemesis gravidarum, or the pernicious, the uncontrollable, the incoercible, vomiting of pregnancy. In general, this condition is recognized as vomiting due to the pregnancy so frequent and severe as to put the life of the mother in danger. Williams (98) adds that it is not a physiological condition. It appears that he is conveying the idea, or at least the impression, that the mild type of hyperemesis gravidarum, or the so-called "morning sickness", is a more or less physiological condition. If this is true, should the half of the pregnant women who are not bothered by this condition be considered pathological?

Franz Arzt (7) of St. Louis, sums up the idea as follows:- "Today, toxic vomiting of pregnancy is recognized not

as a sudden, specific toxemia, but an entity which originates with "morning sickness" and gradually becomes worse due to starvation and dehydration. Much work has been done to overcome this end result, while serious treatment in the early stages of the condition has been neglected. If we had some uncomplicated way to prevent nausea and vomiting of pregnancy at the very first or, if already it had started, we could quickly stop it, is it not probable that in a majority of cases the more serious toxemias could be prevented?" It is the prevalent attitude of too many physicians, and of practically all the women who become pregnant, that the condition (morning sickness) is to be expected and endured by the patient. The condition is to be expected, but not necessarily endured.

Therefore, in the compilation of this paper, it will be my endeavor to include a discussion of the mild cases of vomiting as well as those of the severe type.

## HISTORY

In the treatise of Hippocrates and Galen (59), we find numerous, though rather confused, references to the diseases recognized today as the toxemias of pregnancy. Such irregularities in the normal course of gestation as manifested by constitutional disturbances were usually attributed to retention of various "humours", and while distinct references are made both to excessive vomiting and convulsive seizures, there are no specific explanations offered as to their cause, nor definite recommendation for their treatment. Likewise, Soranus of Ephesus (35) observed the disease in 20 A. D. Occasional reference is found in the Italian medical works of the Middle Ages, but it is not until the 18th Century, that we meet with well recognized descriptions of the toxemias of pregnancy. Mauriceau (59), in the latter part of the 17th Century, presented certain definite notions of these disorders; he attributes intractable vomiting to the cessation of menstruation, which caused "corrupt humours cleaving to the insides of the stomach". Burton of London, in 1751, repeated the earlier contention that some of these disorders arise solely from the stoppage of the menstrual flux; others from the motions and bulk of the fetus, secundines and waters. In Bard's "Compendium of Midwifery" (1815), there are extended references to hyperemesis. He refers to the necessity in severe cases of having the patient refrain from eating and giving her nourishing "clysters". If the vomiting becomes troublesome at the end of pregnancy, "it is proper to detract



blood and confine the patient to bed. Cloths dipped in laudanum should be applied to the pit of the stomach and a grain of solid opium given internally". But he does not say anything about induction of abortion in such cases nor mention the possible fatal result. Delorme (35) in the 19th Century, called attention to the danger of pernicious vomiting of pregnancy. In 1813, Simmond was the first to interrupt pregnancy as a therapeutic measure. Doctor J. Johnson (97) of the Westminster Medical Society, in 1838, reports a case of fatal vomiting in a pregnant woman. He treated this case by means of enemas of milk and nutrient broth with opium; also various salines, anti-emetics, counter-irritation over the epigastrium, leeches, and acetate of morphine sprinkled over a blistered surface. At the same time, Hastings, Hardwicke and Clarke report good results with creosote; Costello cured a case by repeated venesection.

That the condition of vomiting of pregnancy was attracting some attention in the latter part of the 19th Century, is evidenced by a rather unique case reported in the Proceedings of the Obstetrical Society of Philadelphia, April 5, 1888 (37):- "Dr. Hamill remarked that the occurrence of morning sickness in the husband, after the fact of pregnancy was known or suspected, he had frequently noted; but the case which he was about to speak of was unique from the fact that the sickness appeared in the husband at such an early period of pregnancy. Two weeks after the appearance of menstruation for the last time, the husband had daily morning

attacks, and not until it was time for the next menstruation had the woman any other evidence that conception had taken place. The husband's attack continued for two months. During his wife's previous pregnancies he had suffered from like attacks, but not until he and his wife had both become aware of the existence of pregnancy."

## ETIOLOGY

The causative factor of the condition of vomiting of pregnancy is unknown, and because of this lack of knowledge, numerous theories as to its etiology have been presented. Because of this disagreement, numerous corresponding types of treatment have been and are being pursued. According to Carter of New Orleans (16), this fact adds somewhat to the difficulty of the condition; especially in the handling of these cases: "It would be a useless task to detail at length the theories which have been advanced to explain the disease. Indeed, it may safely be held that the supposed necessity of providing a theory which would explain all the facts of the condition has done more to surround it with obscurity than even the difficulties of the subject itself. If any real advance is to be made, it can only be by adopting a humble attitude, by admitting that we are only on the threshold of the inquiry, and by a careful observation of the clinical facts, without drawing from them too positive deductions." Andrews of Norfolk, Virginia, (6) adds to this statement his opinion that there is little justification for any arbitrary classification as to type (cause), as the condition is the same in all, the only difference being that some features may be more prominent in one case than another.

Sage (75) lists four facts which must be accounted for by an acceptable theory, viz: 1. The toxemias of pregnancy are associated with the products of conception in the maternal organism. 2. Removal of the products of conception usually leads to rapid recovery. 3. The condition is more

frequent in primiparae, than multiparae, and in the majority of cases does not recur in subsequent pregnancies. 4. Pernicious vomiting occurs in the first half of pregnancy, while pre-eclampsia and eclampsia are complications of the last trimester. In his opinion the "glycogen deficiency theory" of Harding and Duncan, Titus, and others makes the fewest assumptions and is consistent with the greatest number of facts. He believes that all cases are undoubtedly toxemic in origin.

As a result of the various theories as to etiology of vomiting of pregnancy, there are a number of different classifications of this aspect of the condition. Possibly the oldest and most referred to classification is that of Williams (98). He makes a general hypothetical statement that there is an increased sensitiveness of the nerve centers of the woman to the 'toxins' of pregnancy; or that there may be an increase in amount or in potency of this "toxic substance" that causes morning sickness in 50 percent of pregnant women. Under predisposing factors, he lists functional neuroses, reflex nervous conditions, and associated disease aggravated by pregnancy. He believes that a functional neurosis is present in a majority of the cases of pernicious vomiting. In many of these cases there is undoubtedly an underlying toxemic condition, which in itself is negligent but in neurotic women it acts as an aggravating cause of the vomiting. In the reflex group there is supposedly a vomiting reflex originating from some structural or physiological abnormality in some part of the body, usually the genitalia, which is aggravated by the pregnancy. Among these conditions he lists malpositions of the pregnancy,

rapid distention of the uterus, inflammatory conditions of the uterus and adnexae, tumors and malpositions of the uterus, etc. The reflex phenomenon may arise from an aggravation of a pre-existing or an associated disease, such as peptic ulcer, cholecystitis, appendicitis, peritonitis, etc. The rest of the cases, Williams places on a toxemic basis; a condition which he believes is always present in the pernicious type. He states that these cases are very serious and are often fatal. As possible sources of these toxins he lists the following conditions:- a depletion of the glycogen stores of the liver; a solution of syncytium of the chorionic villi in the maternal blood, forming syncytiotoxin which is not neutralized by sufficient antitoxin; deficiency in one or more of the internal secretory organs, such as the corpus luteum, thyroid, hypophysis, adrenals, etc; focal infection; intestinal tract intoxication; anaphylactic conditions, maternal versus paternal and fetal; changes in metabolism of the fetus; etc. Most of these theories have been upheld by various authorities and will be discussed in more detail later.

In general, it appears that the theories may be grouped into two large classes, namely, neurological and physiological. Under neurological types I include the nervous reflex, the neurotic and the psychic. Under the physiological class is grouped the theories of endocrine disturbances, impaired functions of the liver and other organs concerned in body metabolism, anaphylactic phenomena, intestinal and focal infection intoxication, etc.

It is possible that no one factor is responsible for the disease, but that it may result from a combination of

several factors, anyone of which may or may not be of sufficient consequence to cause the nausea and vomiting. Goodall (32) and others are of the opinion that it is doubtful whether a true toxemia of pregnancy without an element of neurosis superadded ever exists in the human race; he doubts also if ever a true neurotic vomiting of pregnancy occurs without a basic element of toxemia.

Kane and Ellerson (52) of Washington, are of a similar opinion. They believe that it would perhaps be more nearly correct to designate two types, the reflex and the neurotoxic. They say that: "Every case has psychic and toxic aspects, while some have the reflex element as well. In the absence of pelvic pathology, hyperemesis is both neurotic and toxic in the end if not from the beginning. Any vomiting patient sooner or later becomes highly nervous, and cases in which nausea may be psychic at first, develop toxemia as a result of lack of nourishment".

Both Schwab and Lynch (32) are true believers that a neurosis is the basis on which to explain most cases of vomiting of pregnancy. Brindeau is also a firm adherent of the hysteria theory for etiology of vomiting.

Regardless of the specific cause of hyperemesis gravidarum, there are a number of commonly accepted facts associated with the disorder: Nausea and vomiting occur earlier more constantly, and more severely in primiparae than in multiparae.

DeLee (21) disagrees with this statement. He maintains that, although morning sickness occurs earlier, more constantly,

and more severely in primiparae, and is less severe in succeeding pregnancies, the condition of hyperemesis gravidarum is more frequent and more often fatal in multiparae and when it recurs in subsequent pregnancies the toxemia is more severe.

These conditions do not as a rule recur in succeeding pregnancies, but if they do they are usually less severe. They tend to occur more often in nervous, high-strung individuals; in those who, as Mussey (68) of the Mayo Staff states, "cultivate intellect at the expense of physical and nervous stamina".

The reflex or the reflex-neurosis theory of etiology of pernicious vomiting of pregnancy has had and still has a large number of adherents. Practically every discussion of the treatment of pernicious vomiting includes a statement that pathology and displacement of the uterus, adnexae, etc., should be cleared as a preliminary therapeutic measure where possible and expedient. This may be an admission that the reflex phenomenon plays at least a part in the etiology, or it has become a part of our more or less empirical treatment of the condition.

This theory was apparently quite popular in the 19th Century. Hewitt (44), of London, presented his views on this subject in 1872: "Sickness of pregnancy is due to the combined effects of the increasing distension of the uterus and an associated flexion of the organ. The explanation I have to give of this occurrence is, that the tissues of the uterus, including the nerve ramifications pervading it, are compressed at the seat of the flexion, and that this is the cause of the sickness. It is certainly a curious corroborative fact that, under ordinary circumstances, where the sickness is not particularly troublesome,

it is observed to occur generally when the patient arises from bed. The taking of the erect posture aggravates and increases the existing tendency of the uterus to fall forwards, the tissues of the uterus at the region of the upper part of the cervix are compressed thereby, and the reflex disturbance is thus produced, resulting in sickness. By treating the flexion the sickness becomes relieved. This is accomplished by means of pessaries".

As early as 1849, Bennet (9) of England, drew attention to what he considered a frequent cause of "obstinate sickness of pregnancy": viz, chronic inflammation of the body or of the neck of the pregnant uterus; he observed that when this was cleared, then vomiting ceased or was mild. This treatment consisted of local surgical treatment of the cervix, emollients, astringents, caustics, etc; the body of the uterus was supposedly treated by antiphlogistic means, hip-baths, emollient injections, external application, leaches externally and evenly internally to the cervix.

Similarly, Jones (49) of Chicago, believed pernicious vomiting to be due solely to reflex irritation from the gravid uterus, with the stomach as the sympathizing organ, and presents five cases which were completely cured after from one to three applications of solid silver nitrate to the os and the cervix, after other methods had failed. Allt (2) obtained similar relief, after seven hours, by use of silver nitrate solution (25%). Atkinson (8) adds to this early sympathetic reflex condition the idea that the vomiting later in pregnancy is due to direct pressure upon and interference with the function of



that viscus. As a note of somewhat historical interest, and as an example of the reasoning process in the development of one of the many theories of the etiology of this disease, the original article of James Oliver (70) of London, written in 1887, is presented: "Many theories have been adduced regarding the cause of morning sickness during pregnancy. All, however, appear to have been too speculative, and no one has met with anything like universal sufferance. Evolution may aid us in arriving at a just and feasible interpretation. From the earliest period of existence every organism has been endowed with two distinct qualifications. 1. That of maintaining self; 2. That of perpetuating its species. At first the double function was performed by a uniform mass, free from any semblance of structural differentiation. Habitual localization of function, however, produces eventually a specialization of structure, and with it the evolution of a nerve tract whereby the interdependence is maintained. It is therefore feasible to suppose that the nerve centre which regulates the process of assimilation is either in apposition or at best in direct communication with that which presides over the organs of generation. All the visceral functions are now performed automatically, and are regulated by nerve centres located in the medulla oblongata; the uterine, by inference, being no exception. Considering the close relationship that exists throughout life between the two processes of assimilation and reproduction, there can be no doubt that the representative nerve centres act and react upon each other. When the uterus becomes the nidus for a developing germinal mass, the molecular disturbances radiated therefrom to the reproductive

centre are liable to be transmitted to the pneumogastric as well, and induce either a feeling of nausea or actual emesis. Usually, however, in the course of a few months, through habit, the pneumogastric centre becomes tolerant, and the symptom evidencing disturbance at the same time disappears. It is difficult to understand why the sickness should be experienced more especially in the morning, unless it be that the change from the recumbent to the erect position after sleep renders the whole nervous system more liable to explosive disturbances. Frequently we find patients who only suffer from disturbances associated with epilepsy on assuming the erect position after sleep. The more highly unstable the nervous system is generally, the more likely is a woman who becomes pregnant to suffer markedly and for a lengthened time from sickness, whether matutinal or more or less constant. It is well, however, to remember that the molecular radiations from the uterus itself may, for some reason or other, be materially augmented; and such, acting on a nervous system otherwise apparently healthy, may induce an aggravated train of events".

In 1925, Rucker (74) of Virginia suggested that vomiting of pregnancy is associated with increased congestion of the cervix. He said that one often sees the same type of nausea in non-pregnant women when they have large congested cervixes. Treats condition by painting cervix with 2% mercurochrome every other day until relieved; has used vaginal suppositories with 2% mercurochrome, but with less satisfactory results.

A different source of the reflex stimulation was

presented by Keaton and Nelson (54) of the University of Illinois in 1930: "In the average early pregnancy there are sufficient changes in the pelves of the kidneys and the ureters to act as powerful reflex stimuli of the vomiting mechanism. If in this average pregnancy a chronic focus of infection exists or an acute upper respiratory tract infection develops, then the probabilities that the urinary tract will exert reflex effect on the vomiting mechanism are increased".

Kane and Ellerson (52) believe that the most common reflex cause is retroversion of the uterus, correction of which often produces nearly instantaneous improvement. Endocervicitis is the second most important associated condition.

DeLee (21) is of the opinion that the reflex-neurosis theory explains very few cases of hyperemesis. He states that many cases formerly thought to be reflex are toxic, e.g.: metritis, endometritis, polyhydramnion, twins, hydatid mole; cervicitis, cervical erosions, pelvic inflammation, and focal infection. He agrees that close connections do exist, between the stomach and the genitalia, via the sympathetics and the vagus, so that the reflex is easy, but that there must be a special predisposition on the part of the gravida, because all the diseases proposed as causes of hyperemesis often exist in marked degree without disturbing the stomach.

As stated before, Williams (98), is of the opinion that a functional neurosis is present in a majority of cases of hyperemesis gravidarum. Very often there is an underlying toxic element, which in itself is negligent, but which may indirectly be responsible for the vomiting in neurotic patients.

In 1922, Carlton Oldfield, of London, (69) concluded that all cases of pernicious vomiting of pregnancy are of a neurotic origin, basing his observations on a series of 29 cases. He said the so-called toxemic cases are usually, if not always, a later state of neurotic vomiting; the effect and not the cause.

Kennedy (57) of Detroit, also stresses the neurotic type of vomiting of pregnancy. He states that: "Most cases of vomiting are not toxic and will get well regardless of type of treatment".

FitzGibbon, of Rotunda Hospital (30) maintains: "The psychic or neurotic element in these cases must not be overlooked. The early onset of nausea and the development of vomiting very soon breaks down the patient's self-confidence and produces a longing that the pregnancy should be terminated, although there may be the keenest desire for a child. It is essential to obtain the confidence of the patient and to impress on her the fact that she can successfully go through her pregnancy when the vomiting, which is an accidental association, is eliminated, and that there is no inherent reason in the pregnancy why the vomiting should return.

DeLee (21) draws the following conclusions as to the neurotic or psychic element: A functional disturbance of the nervous system is at the bottom of many cases of hyperemesis, rarely is an organic nervous disease, such as brain softening, tubercles or other tumors, meningitis, or polyneuritis. It often occurs in hysterics, in pure neurosis, and sometimes it is a psychologic manifestation; if the pregnancy is abhorrant

or fearful the patient may go on a "hunger strike" and vomit. Hyperemesis is very amenable to suggestion and most cases are due to it: e.g., drugs, hypodermic injections, isolation, lavage, etc. "Treatment of a local condition relieves the patient of a local irritant and the vomiting ceases because the whole nervous system has regained its equilibrium." If the patient dies of neurotic vomiting, the course is very chronic and the clinical picture and pathological findings are those of starvation. In toxemic cases, the course is rapid, with little emaciation, and death results from profound change in the general metabolism.

Another aspect of the psychic factor in vomiting of pregnancy is presented by Holman of Portland, Oregon (45): "In speaking of the psychic factors, I have reference to those women who have long desired pregnancy and who feel that nausea and vomiting are a real part of it. When one of these women misses a period, she eagerly looks for the onset of morning vomiting to clinch the proof that she is pregnant, and when it appears, she gives it all the aid in her power. Also, there are women who are resentful because they have become pregnant and who desire to show their husbands what they go through in having a baby. Many vomit and gag whenever there is an audience, particularly if the husband is present". Frequently, if this type of vomiting persists, it merges into the type with definite alterations in physiology.

Discussing the various theories surrounding the etiology of vomiting in pregnancy, Allen(1) concludes that a neurotic element is usually found at the outset. The vomiting

and the consequent lack of food in the stomach result in an increased flow of hydrochloric acid, which irritates the nerve endings in the mucous lining of the stomach, causing a continuance of vomiting. Then as a result of the starvation and the associated chemohistological changes, the glycogen reserve is exhausted, the patient begins digesting her own fats, and the case becomes toxic.

Although Crossen (18) and Dieckmann and Crossen (24) of St. Louis, adhere quite strenuously to the carbohydrate deficiency theory, nevertheless they believe that there are undoubtedly a large number of cases in which neurosis plays an important role in converting ordinary vomiting of pregnancy into vomiting of severe grade. In addition they state:

"The exciting cause of the change from morning sickness to severe vomiting of pregnancy may be constipation, some nervous irritation, a period of starvation, a dietary indiscretion, a nasopharyngitis or sinusitis causing vomiting, etc. Once vomiting has started the vicious circle has begun, and starvation and dehydration with their sequelae soon produce the well-known blood and urinary findings, and probably the lesions of the liver associated with vomiting of pregnancy follow these".

As noted previously, there is a group of conditions which have been referred to by various authorities as possible and probable etiological factors in hyperemesis gravidarum which I have chosen to place under the general head of a "physiological class". These conditions have a bearing upon and are related to the general or specific physiological functions of the body; among them are such theories as those of endocrine disturbances, impaired physiological functions of the liver, kidneys and other organs concerned in body metabolism, anaphylactic phenomena, intestinal and focal infection intoxication, etc.

A physiologic explanation for the nausea and vomiting of pregnancy, somewhat related to the reflex theory, has been offered by Alvarez alone (3) and in conjunction with Hosoi (4). They have demonstrated in pregnant animals a disturbance in the normal intestinal gradients, namely, reversal and inhibition of peristaltic rushes and slowing rate of travel of these waves. Reversal may conceivably be brought about by an increase of metabolic activities of the muscles in the lower part of the bowel, an increase related in some way to an increase in metabolic activity of the pelvic organs.

A possible cause, which is not stressed a great deal and which, according to Calkins (14-15), can explain the symptoms, is that of protein intoxication through the intestinal tract, resulting from intestinal stasis or partial intestinal obstruction.

Somewhat along the line of an intestinal toxemia is the theory that Gardiner of Toledo, Ohio (31), advanced in 1928. He states it is well known that there is a relationship between

the genital and intestinal tracts, as evidenced by the fact that many women who need laxatives most of the time must refrain from taking them while menstruating. His theory is that some substance with a local sphere of influence causes a condition of inactivity when impregnation occurs. This extends by contiguity through the tube into the intestine, causing the involuntary muscle of the intestinal tract, in order to protect the ovum, to quiet down, even to such an extent as to simulate a partial or at times complete intestinal obstruction, which in turn gives rise to reverse peristalsis, thus producing nausea and vomiting. He believes that this protective substance arises from the zygote or the chorionic villi. By his theory he accounts for the fact that man is the only animal that suffers from the vomiting of pregnancy, because he is the only one who has assumed the upright position, thereby bringing the intestine to rest more closely upon the genital tract. Based upon this idea, his treatment is to separate the two tracts by placing the patient face down and elevating the foot of the bed so that the buttocks are on a level above the shoulders. This position, plus sedatives and fluids by bowel, has given him some very good results. He believes that the immediate cause of death is exhaustion.

Sage (75), Kosmak (59), Grogan (35), and others are of the opinion that there is always an underlying toxemic condition. Williams (98) says that all of the pernicious type are due to this condition.

Likewise, DeLee (21) believes that a majority of cases of hyperemesis are on this basis, as shown by the clinical



picture and the fact that the pathology is a definite entity, not simply due to dehydration and starvation. He cites two cases of pyelo-ureteritis in cases of vomiting of pregnancy, the vomiting probably being due to a toxemic element possibly associated with a reflex factor. He states that the nature of the toxins is unknown, but the kidney and liver damage accompanying the condition throws two groups of toxins into the blood, in addition to those of starvation and dehydration. The mechanism of these toxins in producing nausea and vomiting is also unknown: is it a direct stimulation of the vomiting center, or does the stomach excrete the toxins with a reflex from it, or is the reflex from the liver?

Bugbee (12) also suggests that the frequency of renal infections in association with toxemia is not generally realized. The process is hematogenous in a large percentage of cases and it originates in the colon. An important element is lowered resistance or interference with drainage, due to pressure on the ureter from the enlarging uterus, particularly on the right side, or due to torsion, stretching and kinking of the tube. He states that whether the development of bacteria has anything to do with the production of the toxemias of pregnancy is still an unsolved problem. However, the elimination of toxic material due to intestinal putrefaction through the kidneys must be borne in mind when considering the problem of etiology. Hence the necessity for improving drainage from the colon by appropriate measures. This would mean a diminution in the number of bacteria passing through the kidneys and of their influence

on these organs.

Another possible source of the toxic substance (if present) is suggested by Talbot (83) who found x-ray evidence of chronic sepsis in or around the dental structure in all of 97 cases of toxemia of pregnancy.

A possible etiological factor which has had and still has quite a number of ardent supporters is that of some endocrine unbalance or dysfunction. In his discussion of this subject, Dickson of Canada (23) sums up some of the observations on endocrinology and draws some conclusions as to its possible role in the etiology of the vomiting of pregnancy: During pregnancy the function of the endocrines must necessarily undergo some modification. The pituitary gland bears a large responsibility for the digestion of food through its gastro-enteric activity, normally it aids in controlling uterine contraction and tone, and in all cases of carbohydrate intolerance it is involved. The activity of the pituitary is enhanced by the interstitial secretion of the ovary, the activity of which is in turn increased by the pelvic congestion of pregnancy. If the power of the pituitary to contract the uterus was as great during pregnancy as at other times, or was this power not otherwise controlled, intrauterine gestation would be impossible, as the uterus would be automatically emptied. It is probable that there is a hormone which, by inhibition or otherwise, prevents what pituitrin there may be in the blood stream from exerting its full contracting effect on the uterine musculature. This hormone is probably that of the mammary body, corpus luteum or placenta, acting singly or in concert to offset the

enhanced activity of the pituitary body during gestation. During pregnancy there is also an hypertrophy of the suprarenal cortex. Both this hormone and that of the posterior pituitary body accelerate the glycogenolysis in the liver; this may be due to the relationship which is known to exist between the pituitary and the internal secretion of the islands of Langerhans of the pancreas, which is probably the stabilizer of the output of glycogen from the liver. If this internal secretion is deficient or inhibited the output of sugar is above normal. Possibly adrenalin inhibits the action of the pancreatic hormone. In any event, during the state of pregnancy the action of the pituitary and the suprarenals is probably greatly increased, this producing increased glycogenolysis, hyperglycemia and glycosuria. The two latter conditions may not be present in vomiting of pregnancy, because of the glycogenolysis in excess, the maternal tissues are starved of glycogen and glucose, and all of the excess glucose is picked up and retained by these tissues. It is probable that the absence of a sufficient amount of glycogen in the maternal liver, in the vomiting of pregnancy, is due to a great increase in the function of the pancreatic hormone, causing sugar consumption. It is possible that this is due to a deficient or altered hormone which in normal individuals inhibits the pancreatic hormone when the proper amount of blood-sugar is present. In other words, adrenalin may act as this safety valve for blood-sugar stability. This adrenalin deficiency may be produced by the markedly enlarged suprarenal cortex, with resulting ischemia of the medulla of that organ

and permitting the posterior pituitary hormone to run riot in glycogenolysis. The corpus luteum and mammary hormones are the antagonists of the ovarian and pituitary hormones, the latter perhaps indirectly.

On the basis of the above observations, Dickson offers the following explanation of the vomiting of pregnancy: "We do not need to go outside the endocrine system in order to explain the cause of the maternal glycogen deficiency. Adrenalin is probably manufactured as a by product of tyrosin, as is suggested by the presence of the oxyphenyl group in the chemical composition of the hormone. Tyrosin is a by-product of protein katabolism. If there be not sufficient ingestion of protein to allow of tyrosin and amino-acid derivatives being produced, the suprarenal bodies have not the materials from which to make adrenalin, except from their 'tissue protein'. Once allow the vomiting of pregnancy to get well under way and at once a vicious circle is established, which circle must be broken if life is to be conserved. On the assumption that during pregnancy the pituitrin constituent in the maternal blood is precluded from having its full effect in the pelvis, it finds a natural and necessary outlet for its activity in the gastro-enteric organs. It is essential that the increase in gastric juice brought about in this way, by pituitary effort, should be used up. The increase in juice is obviously natural - there are two to feed. If the gastric juice be not 'fixed' by protein foods there will follow automatically sickness and vomiting, from the effect upon the gastric mucosa of this stagnant juice. There is, therefore, brought about a gastric

acidosis which, with its symptoms, prevents the ingestion of food, and a train of symptoms not unlike those of acid dyspepsia follows, which, in fact, is really the case in the pernicious vomiting of pregnancy, excepting that the picture in the latter is extreme. The maternal tissues are in a state of deficiency of glycogen, similar to that produced by starvation. All this while the fetal tissues must have glycogen, and they take it whence they can get it."

With this process in mind, Dickson bases his treatment largely on the administration of corpus luteal extract and mammary substance, preferably the latter as it has fewer disadvantages and is less deleterious. It may be given by mouth or the extracts (10%) hypodermically. In addition he maintains that, if in spite of vomiting, a largely enhanced protein diet is insisted upon, to the complete exclusion of all stimulants to gastric secretion which do not "fix" gastric juice, the condition automatically rights itself, if it has not been allowed to advance too far. If the latter condition exists, adrenalin injections will control the vomiting, so allowing the protein diet to be commenced.

Bessesen of Minneapolis (10), is of the opinion that most cases of gestational vomiting start with no organic pathology demonstrable. He agrees with Hirst the pernicious vomiting is due to a lack of absorption of corpus luteum. Every woman, during the period of sexual activity, is constantly absorbing corpus luteum. With the onset of pregnancy, this absorption ceases. The corpus luteum of pregnancy constantly increases in size until it reaches its maximum 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. This may be the underlying disturbance of the endocrine unbalance noted by Dickson above.

Carter of New Orleans (16) also favors the theory of endocrine unbalance, but he believes that it is probably the result of a dysfunction of the ovaries, and hence he recommends giving ovarian extract as part of the treatment. This procedure is not in accordance with Dickson's observations.

Kemp of Vancouver (55-56) made the observation that the first signs of adrenal cortex insufficiency in adrenalectomized animals and in Addison's disease are anorexia and vomiting. He suggests that the temporary and relative adrenal cortical insufficiency accompanying the hypertrophy of that structure during pregnancy might be the etiological factor in nausea and vomiting so common in the first trimester of pregnancy. It is assumed that the natural hypertrophy of the adrenal cortex incidental to pregnancy does not reach sufficient proportions to fully care for the mother's increased metabolic load until the end of the third month when the vomiting usually ceases. He believes that the proper function of the liver depends upon one or more autocoids from the adrenal cortex, and with an insufficiency of these the liver begins to show signs of insufficiency, with resulting further damage due to starvation ketosis.

The dysfunction of still another of the endocrine glands, the thyroid, is suggested by Falls of Chicago (29) as

probably being significant in the etiology of vomiting of pregnancy. He has found that some patients suffering from hyperemesis gravidarum have definite evidence of toxic goitre, and that treatment of this condition, by the use of Lugol's solution, has resulted in cure of vomiting. He has had satisfactory and rather spectacular results in several years' work and has not had to resort to abortion and has had no deaths since beginning the above treatment. He uses Lugol's solution as a prophylaxis in suspected cases. Crotti (19) is of the opinion that the co-existence of exophthalmic goiter and pregnancy is much rarer than is generally believed.

The realm of the anaphylactic phenomenon has its ardent supporters as a possible etiological factor in the vomiting of pregnancy. As noted before, Williams (98) suggests the possibility of a toxic substance arising from the solution of fragments of syncytial fragments in the maternal blood forming syncytiotoxin which is not neutralized by sufficient anti-toxin. In 1925, Hemmings (43) agreed with this contention, believing it to be the basis of the vomiting, secondarily aided by auto-intoxication and acidosis produced by defective elimination and injudicious eating. In advanced cases carbohydrate deficiency plays a large role.

About seventeen years ago, Harrower of California (41) assumed that hyperemesis gravidarum resulted from a form of sensitiveness or anaphylaxis to certain new placental proteins possibly toxic; possibly not - to which those women who developed serious nausea and vomiting during pregnancy evidently were peculiarly susceptible. Irritation of the vagus, by these toxic

substances, is believed to be responsible for the nausea and vomiting. On the strength of this assumption, he recommended an attempt to produce an immunity in these victims by gradually increasing doses of an extract of the placenta. He states that the clinical results have justified the assumption and the use of the placental extract, giving approximately 70% of real cure, regardless of how serious or advanced the cases may be. With the same idea in view, Johnstone of Edinburgh (48) in 1911, performed a course of experiments with placental extract injection of rabbits. However, his results were not conclusive.

Levy - Solal and Ravina of France (61) also sustain the theory that anaphylactic phenomena may be a determining factor in the uncontrollable vomiting of pregnancy. In a case of therapeutic abortion, the ovum was used for preparation of a glycerin extract. Injections of this extract a few days after the abortion induced in the woman a positive skin reaction, and reappearance of the vomiting which had been promptly arrested by the operative intervention. Pilocarpine-hydrochloride, given on the basis of this experience, induced remarkable results in several desperate cases in which all other measures for desensitization had failed.

A very interesting piece of research work and investigation was reported by W. W. Horn of Fort Worth, Texas (47), in 1925. This work was based on the belief of the Spanish obstetrician, Udaeta (94), that the toxemias of pregnancy, particularly vomiting, are the result of intoxication caused by the products of gestation. These toxins, he explains, are



due to the variation in the characteristic complex of the albumen molecule in various individuals and cites the reactions that follow blood transfusions to support his view. He assumes that the fetus acquires the father's characteristic albumen within the mother, which is responsible for the intoxication of pregnancy. Applying this principle in the treatment of hyperemesis gravidarum, he injected the mother with the husband's blood serum in five cases with astonishing results and prompt relief from symptoms. Following up this work, Horn collected data on sixty-five cases of pregnancy over a period of about ten years. Of these sixty-five pregnancies tabulated, forty were accompanied by vomiting and twenty-five were not. In the vomiting series, the blood groups of mother and child differed in every case except two, one being a neurotic and the other having only "very mild" nausea. In the "no vomiting", or normal series, the blood groups of mother and child agree in all except two. One was a group III mother with a group IV child, and, assuming that group IV is often non-toxic on the universal donor basis, this is not in disagreement with his conception of the underlying cause. The other case was explained on the basis of a temporary immunity following the abortion of a fetus of the same blood group as that of the present conception. Horn further states that the symptoms produced by injecting blood of one blood group (Jansky and Moss) into a person of another group are quite similar to those occurring in vomiting of pregnancy, although more acute and more severe. In treatment, he injects, intramuscularly, blood of the husband or, with better and more sure results, pooled blood from the remaining three blood groups.

He uses citrated whole blood at daily intervals beginning with 2 c.c. and increasing 2 c.c. each day up to 10 c.c. at the fifth and last injection. He is not sure whether or not the method of treatment establishes immunity or whether it is a process of desensitization; but, nevertheless, he has obtained spectacular results in a series of cases, with practically one hundred per cent cure.

A similar theory was presented by LaVake (60), in 1919. He believed that all forms of nausea and vomiting of pregnancy are manifestations of a toxemia due to the pregnancy per se; that the toxin is derived from the protein constituting the male element in the fertilized ovum and this toxin acts directly upon the vomiting center and the vital organs.

We come now to a discussion of a phase of the etiology of vomiting of pregnancy which, during the last fifteen or twenty years, has been the subject of a great deal of discussion and which, at the present time enjoys a great deal of popularity, namely: dysfunction of the liver, especially as it concerns carbohydrate metabolism.

James Ewing, Professor of Pathology at Cornell University (28), offered the opinion, in 1910, that fundamentally pernicious vomiting is due to a dysfunction of the liver, with subsequent autointoxication due to abnormal products of metabolism; this dysfunction affected especially protein metabolism and to a lesser degree that of the carbohydrates. He made the statement that glucose does not correct the acidosis nor relieve the symptoms, but that thyroid

extract does because it improves nitrogenous metabolism and facilitates urea formation. (He and others had tried glucose for several years.) In 1904, he ventured the statement that pernicious vomiting, acute yellow atrophy, and eclampsia are on the same etiological basis.

Also in 1910, Underhill and Rand of Yale (99) made the observation that the changes noticed in the urine in pernicious vomiting of pregnancy are similar to those found in inanition. They were of the opinion that this results from a disturbance of the carbohydrate metabolism arising from a dysfunction of the liver. They observed that the urinary components returned to normal after the administration of glucose by mouth or by rectum.

It might be added here that Jones of Washington (50), in 1929, offered a possible explanation of this liver dysfunction. He assumed a neurotic element to be present, explaining that a normal pregnancy is marked by heightened nerve reflexes. An unduly sensitive sympathetic nervous system will result in diminution of glycogen in the liver, because excitation of that system produces an excess of sugar in the blood at the expense of glycogen in the liver, which is followed by vomiting.

Following up the line of work of Ewing, and Underhill and Rand, Duncan and Harding of Montreal (27) also assumed that in the early toxemias of pregnancy the dominant factor is a metabolic one resulting in a temporary lack of carbohydrate supply, causing the fatty degenerated liver found in postmortem examinations of fatal cases. They en-

deavored to correct the deficiency of carbohydrate supply by administering glucose or lactose, but especially the latter.

In 1921, Prof. Harding of the University of Toronto (38) proposed that the primary etiological factor in the nausea and vomiting of pregnancy is a lack of glycogen in the liver of the mother, with intestinal intoxication and neurosis as secondary factors, the metabolic and neurotic factors reinforcing one another; fatty infiltration of the liver ensues, and consequent upon the subsequent nausea there arises a positive distaste and intolerance for food, resulting in starvation. The outcome is the so-called pernicious vomiting.

Thalhimer (88), Titus (92), Dieckmann and Crossen (24), Crossen (18), Stander (78), Titus and Dodds (93), and others, all agree with the above authorities that the vomiting of pregnancy is the result of a perverted carbohydrate metabolism with depletion of the glycogen store, especially in the liver. The latter two men further state that blood sugar readings taken under certain standard circumstances from patients with hyperemesis gravidarum indicate that in this condition low values predominate as a characteristic of this diseased state. Even among those patients showing normal values (80 to 100 mgm. per cent) the tendency is toward the lower rather than the upper limits of the average range. Such tendencies indicate a glycogen depletion. The lowest values indicative of the most profound glycogen depletion of the tissues are to be seen in the sickest patients. Hypoglycemic levels may be attained in hyperemesis which, if

compared to similar values obtained more rapidly from insulin overdosage would be expected to cause convulsions, but which fail to do so because this process of glycogen depletion is a slow one. Fulminating cases of hyperemesis, or "acute yellow atrophy of the liver," frequently show convulsions early in pregnancy which are comparable to these of eclampsia, late in pregnancy. The probability of an etiologic relationship between toxicoses of early and of late pregnancy<sup>is</sup> strengthened by these observations and findings.

A very enlightening and interesting discussion of the process involved in the development of the hypoglycemia is presented by Dieckmann and Crossen:

"The period of 'morning sickness' and vomiting of pregnancy begins with the third to sixth week and terminates, usually spontaneously, at the twelfth to fourteenth week. It is during this period that the rate of growth is greatest. By the end of the first month it has been calculated that the ovum has increased in size 10,000 times; at the end of the second month, 74 times; and by the end of the third month, 11 times; and during the tenth month the rate of growth is only 0.3 times. The actual increase in size is relatively small but the changes caused by pregnancy must be tremendous, for marked alteration in the maternal metabolism can be detected in the first month. Furthermore, the uterus in pregnancy increases in size from an organ weighing 30 grams to one of 1000 grams, and this growth is chiefly during the first three months. During this period the nutrition of the ovum is derived entirely from the surrounding serum.

Inasmuch as the food must go through cell walls, only fat, carbohydrates and amino acids are available. Fat has never been demonstrated passing through to the embryo or fetus, nor is there any special storage of fat in the endometrium. On the other hand, there is a large storage of glycogen in the premenstrual endometrium which is augmented in the decidua and continued by the placenta. Furthermore, glucose is not only more easily available than amino acids, but can gain entrance to the ovum by osmosis, while the amino acids, at least later in pregnancy and presumably in early pregnancy as well, require some fixing on the fetal side. In addition, it is at the end of the first trimester that the nausea and vomiting usually cease, and it is about this time that the placenta has become differentiated as we find it at term, so that amino acids and glucose can be absorbed by the villi from the circulating blood.

"It is well known that the liver is the great storehouse of glycogen and that the greatest part of the glycogen can be removed relatively fast. O'Neil reports that during typical canine anaphylactic shock the hepatic glycogen practically disappears and that the central half of each lobule often becomes free from suitable granules within three minutes. Mottram has shown that often in pregnancy of nervous or ill-nourished animals the liver becomes overloaded with fat, and that a simple hunger of a few hours' duration, in some animals leads to the same condition. Whipple et al, Opie and Graham, have each shown that a fatty liver is more liable to the central necrosis caused by systemic poisons,

for example, chloroform or phosphorus; and, conversely, that a liver with necrosis recovers in a shorter period of time if the diet is mainly carbohydrates. Thus, the pathologic lesion found in vomiting of pregnancy may be accounted for.

"Hofbauer considers that even in normal pregnancy the liver presents characteristic changes, so that one is justified in speaking of the 'liver of pregnancy.' The changes consist in the appearance of fat in the cells occupying the central portion of the lobules, the disappearance of glycogen, and the dilatation of the biliary channels, the central veins and the afferent capillaries. Opitz has cast grave doubt upon these statements, nor have we been able to find any increase of fat in the liver of patients dying during pregnancy; but should such changes occur as regular concomitants of pregnancy, they would offer a satisfactory explanation for several of the alterations in metabolism which characterize the condition."

Stevens (80) and Holman (45) also adhere to the carbohydrate deficiency theory. The former states that in early pregnancy the carbohydrate deficiency results from a combination of a low carbohydrate intake on the part of the mother, plus the extra burden of fetal requirements. Almost invariably, mothers report a preference for protein foods and an indifference or even dislike for carbohydrates, especially sweets. Sometimes they diet to reduce their weight. Holman adds the observation made by Carlson that a drop in the blood sugar is followed by marked gastric contractions. He has demonstrated that, by causing hypogly-

cemia, he can produce gastric contractions to the point of emesis. Holman believes that the pregnant woman has nausea and vomiting because of hypoglycemia. As a result of deficient carbohydrate and alkali intake, there is an increase in the ketone bodies in the blood with resultant ketosis, as well as a true acidosis resulting from an uncompensated alkali deficit. Added to this is the condition of dehydration.

Marchbanks of Kansas (65), feels that starvation is the whole cause of this disease and that the toxemia, so called, is the result of starvation with a resulting acidosis or alkalosis and not necessarily from the products of conception at all. He does not state what he believes to be the underlying cause of the nausea and vomiting.

Kobrinsky of Canada (58) made an interesting observation in connection with a fatal case of vomiting. Out of eleven sisters of the patient, two had previously died from pernicious vomiting of pregnancy: the first, nineteen years of age, at two and a half months of her first pregnancy; another, at twenty-six, in the third month of her fourth pregnancy.



## SYMPTOMATOLOGY

The mild form of pernicious vomiting, the so-called morning sickness, usually begins in the second month of pregnancy, more rarely in the fourth and seldom after the sixth month. It usually lasts from a few weeks to three months, but it may be fatal in two weeks; it may be intermittent for several weeks before it ceases spontaneously or becomes pernicious in type.

Dubois (21), whose account of this disease written in 1852 is considered classic, distinguished three periods or stages which are not definitely demarcated. In the first period, there is an intolerance for all foods and liquids, anorexia, loathing of food, and nausea with retching by mention or sight or smell of food. Vomiting may be caused by a change of position of the patient, entry of a person into the room, sight of the husband, etc. This condition continues through the night leading to exhaustion. Hiccough and pyrosis may be troublesome; there is extreme thirst, with a constant boring pain in the stomach, soreness of the ribs and muscles, etc. Salivation is occasionally very distressing and there may be double parotitis. Constipation is the rule, although it may be replaced by diarrhea. The vomitus is at first comprised of undigested food, mucus, and a little bile; later it changes to bile and mucus; finally, it contains blood, either bright red or coffee-ground in type, coming from the mouth, pharynx, or stomach; it is almost fecal in composition and medicine and food given by enemas may be detected in the vomitus. The urine becomes scanty, high-

colored, and finally albumen, casts, sometimes blood, bile, acetone, diacetic, indican and even sugar may appear; urea may be as high as four per cent; the ammonia-coefficient is high.

In the second stage, the above symptoms become aggravated; everything is rejected by the stomach; there is intolerable thirst; the patient is extremely irritable and weak, with frequent fainting spells, and a rapid loss of weight, even up to as much as a pound a day. The skin is pale, waxy, non-resilient, shrunken, and may be icteric. Cardiac hemic murmurs may appear; the pulse is rapid (100 to 140) and weak; the blood pressure is variable. The abdomen is scaphoid; there is great tenderness over the cardia and sometimes the liver. The lips are eroded by the vomitus; the gums are reddened and with sordes; the tongue is dry, red, brown in the middle, cracked, sometimes bleeding; the pharynx is dry, red, and sometimes shows petechial hemorrhages; the breath is fetid. There is usually a low-grade but continuous fever; sometimes the temperature is subnormal until just before death, when there is an agonal rise. There is a thickening of the blood as a result of the marked dehydration.

In the third stage, mental aberration, headache, somnolence, stupor, and coma occur invariably. The vomiting usually ceases, giving false hope to the patient and to those in attendance; the pulse increases in rate; the myocardium gives out; there is general prostration; icterus and cyanosis appear or become worse. The patient dies under a picture of

uncontrollable vomiting and acute poisoning.

The length of the three stages varies, but as a rule, the first is long, the second longer, and the third usually short. The disease should not be permitted to progress to the third stage, as therapeutic abortion then only hastens the end.

The fetus is usually alive during the course of the disease, and if at term, it may be large and fat in spite of the fact that the mother is very markedly emaciated. If the case is toxemic in origin, the fetus may suffer and abortion is more apt to occur. The vomiting often ceases on the death of the fetus, or upon its expulsion.

According to Crossen (18), for purposes of treatment the patient must be classified into two groups, i.e., mild and severe. In the mild group are placed those cases which present the following features: The nausea and vomiting is of an intermittent type, some water or nourishment being retained. The weight is stationary or there is only a slight loss. There is acetone or diacetic acid in the urine. The blood and urine findings are normal except for the ketonuria just mentioned. The severe cases are characterized by the following findings: The vomiting is so frequent that the patient retains very little nourishment. In very severe cases the vomiting continues between the meals causing a loss of gastric juice which becomes serious because of the loss of hydrochloric acid. Concentration of the urine with its attendant effects; acetone may be marked in the early stage, reaching a maximum and then decreasing, so that the

acetone and diacetic may be absent even in a severe case. Changes in the constitution of the blood are noted. Dehydration. Normal or elevated temperature and pulse, probably due to dehydration. Increased bile pigments in the blood and sometimes clinical jaundice. These changes are probably due to an increased production and a decreased secretion of bile pigments. The icteric index is helpful in following the progress of these cases. The Rosenthal test shows marked retention of the dye at times but this rapidly becomes normal when fluids and carbohydrates are supplied.

Stander (79) reports two cases of hemorrhagic retinitis occurring during the course of vomiting of pregnancy. He states that its appearance is of grave prognostic significance, and an indication for immediate therapeutic abortion. He believes that routine and repeated eye-ground examinations should be conducted on all patients suffering from severe vomiting of pregnancy. The character of the hemorrhages seen makes it probable that the eye lesions are caused by a change in the permeability of the capillary walls.

Tashjian (84) reports a very interesting case of multiple neuritis, with complete paralysis of the arms and legs and of the voice, following pernicious vomiting of pregnancy. McGoogan (64), in reviewing the literature in regard to this condition, finds that sixty-five cases have been reported; he adds to these five more cases. All of the seventy cases were associated with pernicious vomiting. He suggests that toxic neuronitis may bear the same relationship to pernicious vomiting that eclampsia bears to pre-eclampsia.

He states that twenty-eight of the seventy cases (40 per cent) ended fatally, including four of his series. Strauss and McDonald (82), in April, 1933, and Luikart (63), in June of the same year, presented the suggestion that this condition is the result of a dietary deficiency disorder similar to beri-beri, probably some portion of the vitamin B complex.

A case of scurvey complicating vomiting of pregnancy is reported by Swanson (52). He believes that this rather marked case of the disease was probably due to the fact that the patient had vomited for two months before admittance to the hospital, with a high carbohydrate diet and no fresh fruits. The scurvey responded to fruit juices and blood transfusion; the vomiting also stopped.

Peckham (41) makes the observation that a considerable percentage of the patients abort spontaneously some time after cessation of symptoms; a phenomenon which he states requires explanation and study.

## DIAGNOSIS

The first step in the diagnosis of hyperemesis gravidarum is the diagnosis of the pregnancy, which is not always such an easy matter, especially in the first trimester. It is then necessary to determine the causes of the vomiting: the basal or fundamental cause and the contributing or adjuvant causes. Is the vomiting due to pregnancy, or is it occurring during pregnancy?

DeLee (21) states that the separation of the neurotic from the toxemic form is very important in the treatment. The toxemic form is usually characterized by a rapid onset, evidence of profound alteration of metabolism, such as jaundice, fever, rapid prostration, with cerebral symptoms, marked acidosis, early albuminuria, with casts, blood, indican, much acetone and diacetic acid, tenderness over the liver, bloody vomitus, etc. The urinary findings, such as a high ammonia coefficient, are unreliable; the blood chemistry is not important, except as it shows kidney damage.

## LABORATORY AND PATHOLOGICAL FINDINGS

The metabolic changes in pernicious vomiting of pregnancy as shown by the blood and urine findings, as observed by Grossen (18), are as follows:

Blood changes:- The dehydration results from the decreased or lack of water intake. This in turn causes a concentrated, viscous blood which naturally decreases the volume flow through all organs and tissues thus decreasing the amount of food, water and oxygen carried to the cells, and permitting waste products to accumulate. In two autopsy cases of Ewing the blood was found remarkably thick, viscous and cohesive to an extent that he had never seen in any other condition and which must have been of itself dangerous to life. The dehydration also accounts for the apparent increase in cell volume and hemoglobin which of course are only relative; actually these are decreased. There is also a decreased electrolyte in severe vomiting due to the loss of body fluid. There is an elevated NPN, and urea and relatively increased uric acid in the blood. There is a mild or compensated alkalosis as shown by the increased carbon dioxide combining power, slightly alkaline pH and increased carbon dioxide content of the blood. In severe vomiting the total proteins of the blood are reduced due to the destruction of body proteins.

Urine changes:- As a rule, acetone or diacetic are found in the urine, but qualitatively they give no index as to severity of the case. Chlorides are decreased due to the effort on the part of the body to maintain the electrolyte equilibrium and also the acid-base balance. The ammonia-

coefficient of the urine is usually increased but this is valueless as to a prognostic aid, for the low total nitrogen found in cases of vomiting of pregnancy would naturally increase the proportion of urinary ammonia nitrogen. Furthermore, the ammonia is not produced solely by the liver as its use as a prognostic guide presupposes.

Stander (78-79) makes the observation there is an increased lactic acid content of the blood; also that in moderate cases the acid-base balance is apparently undisturbed, the pH and carbon dioxide combining power being practically normal, but that in very severe cases there is a decreased carbon dioxide combining power, showing a tendency toward acidosis. He states that dehydration, starvation, and incomplete oxidation of fatty acids following a high ketogenic-antiketogenic ratio, undoubtedly play the important role in the production of these chemical changes.

Peckham (71) says that in severe cases, in addition to a definite increase in NPN and uric acid, there is also an increase in the blood-sugar value. Harding and Van Wyck (40) agree that the majority of cases show an increased percentage of serum protein indicating dehydration; and that, in general, the occurrence of a high serum protein value is a good prognostic sign, while low values are of grave import. Hemmings (43) states that there is a constant rise of blood creatinine in advanced cases.

Drennan and Hicks of New Zealand (25) agree with Williams that the distinction between the two types of vomiting of pregnancy, namely neurotic and toxic, rests on the



ammonia-coefficient of the urine; in the toxic form the ammonia excretion remains high, but may show marked fluctuations, even in spite of clinical improvement; the neurotic type shows no increase in ammonia excretion, or only a transient rise, which may be due to other factors than toxic damage to the liver. This theory is not accepted by most authorities today.

Harding and VanWyck (40) observed that urobilinuria is present in about 80 per cent of all cases of nausea and vomiting of pregnancy admitted to the Toronto General Hospital, undoubtedly resulting from the impaired liver function. On resumption of food after evidences of dehydration have been removed the urobilinuria generally disappears. In some cases it remains persistent, usually correlated with a slow recovery from the vomiting and in some cases necessitating the use of duodenal tube feeding.

Franz Arzt of St. Louis (7) found that the free HCl and total acid of the stomach contents are lower in pregnancy than in the non-pregnant and that this deficiency is more marked early, at the time nausea and vomiting are most common; he believes that this absence of free acid is due to the fact that it is neutralized most likely by a regurgitation of the alkaline duodenal contents into the stomach. Gastric analyses made on six cases of nausea and vomiting of pregnancy, by Mason (66), showed in four a total absence of free HCl and in the other two, much decreased values; he believes, also, that it is the result of the neutralization noted above. Anderson of Scotland (5) found that achlor-

hydria occurred in 32 per cent of cases of emesis and hyperemesis gravidarum; he does not think that achlorhydria or hypochlorhydria is due to regurgitation of the alkaline duodenal contents into the stomach, as bile would be found more constantly in the vomitus if this were the case, but rather that it is probably due to the power of secreting HCl being lost or reduced, in association with the pregnancy.

The greatest and the most constant pathological lesions are found in the liver and the kidneys. The liver usually shows fatty degeneration with marked necrosis of the central portion of the lobules; the picture may vary from a mild fatty degeneration of only the cells around the central vein to an extensive necrosis of the whole lobule. There is little tendency toward hemorrhage, but there may be a diffuse hemorrhagic hepatitis, with all the findings of acute yellow atrophy. The organ may be slightly enlarged in the acute stage, but is smaller after degeneration begins. There may be thromboses in the branches of the portal vein; bile stasis is the rule. Pinard (21) believes that a mild degree of the changes noted above is constant in pregnancy, the so-called "liver of pregnancy."

The kidneys may show all changes from the "kidney of pregnancy" to acute parenchymatous nephritis. The glomeruli are, if at all, but little affected; there is a degeneration of the epithelium of the convoluted tubules with fatty infiltration. Hemorrhages are quite often found.

The heart and other parenchymatous organs may show fatty degeneration in bad cases, as in sepsis. The nerves are quickly attacked, and death may be due to polyneuritis.

Brannan and Cohen (11) reported two autopsies in fatal cases of pernicious vomiting in which the corpus luteum showed necrotic changes. Stander (79) states that necrosis in the anterior lobe of the hypophysis is sometimes seen in fatal cases. These findings probably have the same significance as has necrosis of the liver and kidneys in this disease.

## TREATMENT

We come now to the aspect of the subject of vomiting of pregnancy which is the paramount issue as far as the patient, her friends and relatives, and her physician are concerned, namely: treatment. After noting the great number of theories as to the possible or probable etiology of this disease, it is readily understood why there is no definite specific treatment and why our procedures have always been more or less empirical and symptomatic. Nearly every drug in the Pharmacopeia which in any way could be used has been tried in this disease; the realm of psychotherapy has been entered in practically every case, with its suggestion, reassurance, etc., in treating the neurotic element; physiotherapy is used in many of the cases, in the form of ultraviolet irradiation, electro-therapy, etc. In reading the literature, one is impressed by the fact that regardless of the type or the extent of the treatment, one is able to find records of spectacular and often dramatic cures of the disease in every type of procedure employed; on the other hand, one is also able to find instances of failures, using the same methods of treatment which have given these spectacular results. Thus, one realizes the problem and the task which confronts the physician who has one or more of these cases under his observation. As Kosmak (59) states: "The cardinal fact to be borne in mind is that no routine method applicable to any or all classes of case can be recommended, but in each instance, particularly in the more severe types, consideration must be given to the individual

patient. While we can follow certain general and well-recognized routine procedures in certain groups of cases, they must be changed as circumstances may dictate." In other words, treat the patient and not the disease.

Moore (67) recommends "a siege of sea-sickness for every doctor who attempts to treat a case of vomiting of pregnancy. It would put him in a receptive frame of mind to appreciate his patient's abhorrence of food. The truth is that, with such a patient, the very thought of food is nauseating, just as it is to the sea-sick patient."

The fact that the mildest type of hyperemesis gravidarum, the so-called "morning sickness" or "normal" vomiting of pregnancy, is taken for granted and as a matter of course by the patient, her relatives and friends, and also too often by the physician, is a grave mistake and it should be the endeavor of the members of the medical profession who come in contact with this condition to correct the error. Too often the pregnant woman bears this supposedly "necessary evil" of pregnancy for too long a time and visits her physician for the first time in the severe stage of pernicious vomiting. If early treatment were instituted in all cases with nausea or vomiting in pregnancy, there is no doubt but that some of the mortality, much of the morbidity, and a great deal of the distress and discomfort of pregnancy might be avoided.

As a first step in the treatment of mild nausea and vomiting in pregnancy, a definite critical diagnosis as to the cause of the illness must be made. Is it due to the

pregnancy, and its accompanying physiological changes, or is it due to some associated disease possibly aggravated by the gestation? Infections, especially about the head, should be recognized and treated, e.g., abscessed teeth, sinusitis with posterior nasal discharge, pharyngitis, etc. Abdominal disturbances, such as gall-bladder disease, chronic appendicitis, peptic ulcers, etc., have been factors in producing nausea and vomiting.

If the nausea and vomiting are found to be due to the gestation, the following factors, pointed out by Taylor (85), must be considered in the treatment: a possible neurosis, restriction of activities, increased elimination, diet, medical and gynecological procedures.

As already suggested, a neurosis may be the underlying and, in mild cases, the only etiological factor. If this element is found to be present, its true nature should be ascertained and suggestive treatment employed to correct it. It is needless to say that to accomplish this the physician must have the absolute confidence of the patient and her relatives, he must be sympathetic and yet absolutely firm and definite in his handling of the case.

There should be a definite restriction of the activities of the patient. Probably the first essential for success is the prohibition of coitus. If the patient can sleep alone and even have a separate room, the conditions are at once improved. She should rest as much as possible, lying in bed longer in the morning when the nausea is generally aggravated. She should be relieved as much as possible

from the duties of cooking, and also of general house-keeping. As Speidel (77) suggests: "The old advice to send the young bride home on a visit to her mother has much to commend it. It undoubtedly eliminated the nostalgia which could readily be a factor with the young girl just torn from her home surroundings and suddenly initiated into the mysterious experiences of the marital state. It removed her from the embraces of the husband and the household duties incumbent upon her marriage." Social activities should also be restricted as long as the nausea and vomiting persist.

Elimination by way of the bowels and kidneys should be functioning properly. This may be accomplished by giving large quantities of fluids, such as fruit juices, water, milk, coffee, tea, ginger-ale, ordinary soda-pop, etc. Laxatives are usually indicated. Tablespoon doses of milk of magnesia at bed-time will generally be effective and will alleviate the existing pyrosis. As a rule, cathartics are best taken in pill form by these women. Among those used are small doses of bile salts, phenolphthalein, calomel, extract of cascara, aloes, etc. Occasionally, half ounce doses of castor oil can be taken by some patients. The cathartics are usually given in the evening followed by a soap-suds, or salt and soda enema in the morning. Mild, cleansing enemas may be tried twice daily, for instance at 8 a.m. and 8 p.m.

Diet: Often those who are suffering from mild nausea and vomiting of pregnancy are nauseated at regular hours everyday, usually in the morning before breakfast, about 11 a.m., commonly from 4 to 4:30 p.m., and frequently in the

evening before retiring. This nausea occurs because nausea increases as the stomach becomes empty. Hence, if instructions are given to eat small meals six or seven times daily, and to anticipate the onset of nausea by taking food, much distress can be alleviated. The food should be high in carbohydrates, consisting of cereals, toast, crackers, potatoes, lean meats, etc.; candy and sweets, such as jello and sweetened fruit juices should be taken between meals. Salted popcorn will stay when nothing else can be retained and the dry cereals, puffed rice, corn flakes, etc., are in the same class. Calhoun (13) has had good results by giving a cleansing enema of soap-suds in the morning. Following this a retention enema of eight ounces of 5 per cent glucose is given, to be retained throughout the day. During the day the patient only takes small quantities of fluid every two hours. A 10 per cent solution of lactose taken in small quantities is advantageous. At bed-time the retention enema is repeated as in the morning. Speidel (77) is of the opinion that the rectal route of administration of fluids and drugs should be retained for the absorption of sedative medication possibly needed later on, the rectum sometimes becoming irritable and rejecting solutions introduced over too long a time.

The instructions as to the diet should be detailed and pertinent. Cornell (17) finds the following printed instructions for the patient, to be helpful: "Have a small quantity of soda crackers, social tea wafers, or any biscuit beside the bed; also a thermos bottle containing hot coffee, hot or cold milk or hot tea, whichever is preferred. Prepare these in



the evening before retiring, Whenever you wake during the night eat two or three biscuits and drink a small cup of fluid. When you wake in the morning do the same and then rest quietly for at least an hour. Shortly after arising, eat your regular breakfast. Thereafter eat at least every two hours, oftener if the nausea returns. The taking of food, promptly, should relieve the nausea. Do not , under any circumstances, drink liquids of any kind without taking solid food. With the exception of highly seasoned, fat-fried or indigestible foods, no restriction is placed on the variety of foods which may be taken. Pop-corn will frequently alleviate the nausea. If these instructions do not prove successful in eliminating your unpleasantness in a few days, report at the office."

Medical treatment: It would be impossible to discuss, in a discussion of this type, all of the drugs which have been used and have apparently given good results in cases of nausea and vomiting of pregnancy. Only the more common and more widely used drugs will be discussed.

Some type of sedative is usually employed. The bromides, such as the sodium salt, the elixirs of pentabromides and triple-bromides, have been and are quite popular; phenobarbital, sodium luminal, and other barbiturates have many adherents; small doses of chloral and opium and codeine may be used occasionally. The sedatives are given in rather light dosages, and for the purpose of reducing the irritability and nervousness of the patient, and for providing her with pleasant, restful sleep at night.

As has been shown by Arzt (7), Mason (66) and others, the gastric acidity is very low or absent during the time in pregnancy when nausea and vomiting are common. On this basis, many authorities give their patients with the mild type of hyperemesis, ten to fifteen drops of dilute HCl thrice daily before or after meals. Arzt found that caffeine citrate in these cases has a marked ability to cause an increased secretion of hydrochloric acid, and so he used this drug in the treatment in place of dilute HCl which is very unpleasant to take, especially in a nauseated person. He states that "Muriatogen" (a proprietary coated HCl tablet) is more pleasant and easier to take than HCl.

Extracts of certain of the endocrine organs have been and are quite popular in the treatment. The most commonly used one of these is the extract of corpus luteum. This is administered in various ways and in various dosages, e.g.: corpus luteum tablets, gr. 2, four times a day; one ampule of the extract intravenously daily; gr. 3 daily by hypodermic injection, intramuscularly, etc. Extract of whole ovary has been used by some. Others use desiccated suprarenal cortex, orally, the daily dose being 9 to 18 grains, divided.

Gynecological abnormalities or pathology: A very careful pelvic examination must be made on all patients complaining of nausea and vomiting of pregnancy. Displacements of the uterus are quite often found, which may or may not be a factor in the illness. At any rate, they should be corrected by manual or instrumental replacement, the use of

proper fitting pessaries, exercises, etc. Endocervicitis, cervicitis, cervical erosions, and other inflammatory processes in that area, should be treated; this is accomplished by means of local applications of cauterants and antiseptics, such as silver nitrate, mercurochrome, tincture of iodine, etc.; the electric or actual cautery is good in case of endocervicitis and cervical erosions. Importance is placed on stenosis of the cervical canal as an etiological factor, by some authorities. Some recommend instrumental dilatation of the canal, by means of dilators, sounds, etc; there is danger of infection and of abortion by this method. Others recommend the use of vaginal tampons soaked in antiphlogistics and antispasmodics, such as glycerin and borax suggested by Richmond (73), who claims that it takes only from one to four tampons, each left in for two days, and that he has never had a failure. Certain tumors of the uterus, ovaries, etc., may have to be removed, as a possible factor in the vomiting.

Treatment of the severe type of hyperemesis gravidarum:- Although the ideal time to begin the treatment of hyperemesis gravidarum is in its mild form or even when it is merely threatening, it is not often that the average physician gets the opportunity of doing this. The majority of serious cases come to him as such and it becomes his duty to treat this stage of the disease. There is quite a variety of different forms of treatment of these cases, but fundamentally there are about seven conditions or factors which must be taken into consideration in the severe cases, namely: pregnancy, hypoglycemia, starvation, ketosis, dehydration, acidosis, and a possible neurosis or reflex factor. Although, as has been stated, each case must be treated individually and not merely as another case of hyperemesis, yet a definite course of treatment and certain routine, empiric procedures must be kept in mind. In order to present this very important phase of this disease in a concise, organized manner, the writer is taking the liberty of presenting a course of treatment outlined by Paul Titus of Pittsburgh (92). The opinion of other authorities on the subject who differ with Titus in the matter of treatment will be discussed later.

The outline of treatment recommended by Titus for use in moderately severe and in serious or "pernicious" cases is as follows:

General Directions:- 1. Patient should be isolated from visitors, and the best and most rapid results are obtained if she is sent to the hospital. The husband may be permitted (not oftener than once daily) to make short visits,

but no one else of family or friends is to be admitted except by special arrangement with the doctor.

2. Patient should be absolutely at rest in bed until four or five days after vomiting has entirely subsided.

3. At 8:30 a.m. and 8:30 p.m. daily, an enema is to be given, unless bowels have moved freely shortly before. This is to be followed by the injection into the rectum of a solution containing sodium bromide grs.xxx, chloral hydrate grs. x in one-half to one ounce of warm water (starch water if bowel is irritable). As patient begins to improve omit the evening dose of these sedatives first, and presently stop the morning dose.

4. As soon as nausea and vomiting have subsided sufficiently that it may be retained, a cathartic dose of milk of magnesia should be given every day or two at bed-time.

5. Gastric lavage should be employed from one to three times daily if vomiting persists in spite of the period of rest when no food or water is being taken by mouth. Magnesium sulphate ( $1\frac{1}{2}$  oz.) should be introduced through the tube once daily at the end of the lavage. Drinking one or two glassfuls of warm sodium bicarbonate solution is a poor but useful substitute for the stomach tube.

6. Glucose, or lactose, (10 per cent) and sodium bicarbonate (2 per cent) solution is to be given by enteroclysis as continuously as can be tolerated. The "tidal stand" method of Harris is preferred to the "Murphy drip," but the latter may be used.

7. Intravenous injections of glucose solution

should be begun promptly if vomiting is excessive, or does not cease immediately with the simple measures of diet restriction and rest. These injections should be given from one to four times daily depending on indications and response to treatment. The usual mistake is to give too few injections of too weak solution. The therapeutic dose of glucose is 50 grams in 200 c.c. of distilled water (25 per cent). Continue injections until patient is relieved of vomiting and taking food freely. Strong hypertonic solution (25 per cent) of glucose is best for intravenous injection. If more water is needed to combat dehydration, five to ten per cent sterile glucose solution may be injected under the breasts and into the axillae. This is preferable to salt solution as the latter may be toxic in these cases. From one to three thousand c.c. may be given over a period of several hours' time. There is danger of slough or abscess formation if any solution is given by this method either too rapidly, too frequently, or not carefully sterilized. Submammary infusion is not a substitute for intravenous injection of glucose solution.

8. Frequent feedings are essential after the initial period of rest, and carbohydrates should predominate. The amount and kinds of food should be increased slowly but steadily as outlined in the diet list. Nourishment should commence at 7 a.m., or even sooner if patient is awake.

9. In order to determine exactly when acetone and diacetic acid disappear from the urine, each specimen voided is to be sent separately to the laboratory. Each specimen,

therefore, is to be measured, the amount voided and time recorded on chart, the specimen bottle marked in the usual way with the addition of the time voided, and sent immediately to the laboratory. Night specimens are to be kept on ice until morning. Request general analysis with special attention to acetone and diacetic.

10. A specimen of blood is to be taken by the interne as soon as practicable after admission, for estimation of blood sugar and blood alkali reserve. To be repeated each morning before the first intravenous injection of the day, until patient shows - - - (Evidently one or more lines were omitted from the article.)

A Diet List and Regimen is also presented in detail. Space will not permit its repetition here. Essentially, it calls for hourly feedings from 7 a.m. to 9 p.m., begun after the initial rest period of six to twelve hours and followed by another twelve hour period during which half ounce doses of water are given every fifteen minutes. The diet is largely carbohydrate, consisting mainly of fruit juices, hot tea, and glucose and soda solution for two or three days; after that time, if improvement in the patient's condition is noted, gruels, cereals, dry foods (crackers, cookies, etc.), and broths are gradually added, the time interval between feedings being gradually lengthened. Changes in the diet are made as the patient expresses a desire for any particular articles of food, if not unreasonable. Relapses may occur in the first day or two, but after a short period of rest, the treatment and dietetic regimen should go

forward, after washing out the stomach, as though nothing had happened. Glucose and soda by mouth as well as large amounts of sweets occasionally nauseate after a few days. In such case they may be temporarily omitted, depending on starches for the necessary carbohydrate, and adding proteins (chops, chicken, or steak), to chew and eat for variety and appetite. Do not let the patient decide because she may have no appetite or is not hungry that she will not eat at a stipulated meal time. At least small amounts of nourishment must be taken at each designated time regardless of any lack of desire for food. Foods which are actively nauseating to a patient are to be avoided. Milk and milk preparations usually are not well tolerated by these patients.

Good results have been obtained by Titus by following the above course of treatment, as shown by his tables. In the moderately severe cases: 83.3 per cent were relieved within seven days; there were no failures. In the "pernicious" cases: 78.2 per cent were relieved within seven days; there was 8.8 per cent failure, with 7.2 per cent mortality. Three of the patients who died were clinically cases of acute yellow atrophy, and the other death was an early case in the series. "Relieved" indicates not only cessation of vomiting but return to soft or general diet, and patient ready for discharge. The corrected mortality of all cases treated was 1.8 per cent.

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Most authorities consider strict hospitalization of severe cases to be imperative, and many have given up



trying to treat them in the home. There are too many interruptions in the routine, too many household details to watch, too many telephone calls, too many door-bells ringing, and too many thoughtless friends who harp on the patient's illness. According to D'Arcy (20) and Peckham (71) in the majority of cases the kind of treatment seems to make little or no difference provided isolation and reassurance are stressed; they claim that admittance to a hospital will cure the majority of patients who have had serious vomiting at home. On the other hand, some physicians say that it is possible to treat these cases in the home; among these are Speidel (77) and Green (33). This can be accomplished if the physician has sufficient knowledge of the general course of pregnancy and labor, has confidence in himself, and can "sell" himself to the patient and the relatives; the patient should be isolated in the brightest and sunniest room in the house and as far away from the kitchen as possible.

Various authorities differ as to the drug which should be used for producing the necessary sedation. Calkins (14-15), Andrews (6), and others use sodium bromide alone without the addition of chloral hydrate. They give 60 grs. of sodium bromide in two to three ounces of water by rectum, repeated four times daily (every six hours) for the first two or three days; they say it is important that 60 grs. are given every six hours, as 50 grs. does not suffice (Calkins). After two or three days the dosage is cut to 40 grs.; then at the next step begin 20 gr. doses by mouth. Although most of their patients cease to vomit before the

third dose is given, the medication should be continued in small doses (10 to 20 grs. t.i.d.) over a period of two to three weeks after the heavy medication is stopped. Andrews, because of the danger of bromide psychosis if too much bromide is given or in susceptible persons, checks the quantity of bromide in the blood and attempts to keep it below the level of toxic reaction, approximately 150 mgm. per cent. The barbiturates, such as phenobarbital and sodium luminal, are quite popular sedatives for the treatment of these cases; they are given hypodermically, by rectal suppositories or retention enemas, by proctoclysis, and by duodenal tube, in three to six grain dosages, three or four times daily, the dosage being adjusted to the case. Holman (45) uses veronal grs. 10 and sodium bromide grs. 60 in a retention enema every six hours. Speidel (77) believes that a hypodermic injection of pantopon with an ampule of scopolamine is sometimes necessary in the initial treatment of hyperemesis to give the patient a temporary respite from the incessant retching.

There is a certain amount of disagreement as to the use of sodium bicarbonate in these cases. Cornell (17) agrees with Titus; he gives 4000 c.c. of 5 per cent glucose, 2 per cent sodium bicarbonate, with 160 grs. of sodium bromide by Murphy drip every 24 hours. Marchbanks (65) maintains that the determination of the carbon dioxide of the blood is very important in the treatment and prognosis. He states that alkalosis occurs if there is frequent vomiting and no retention of food, so that the carbon dioxide combining power is high; this is a grave condition. He gives

large amounts of salt solution (3 per cent) by hypodermic injection until the carbon dioxide level is down to near normal; carbohydrate foods and glucose by rectum are forced. The cases of acidosis (carbon dioxide between 12 and 25 volumes per cent) are treated with glucose-insulin method of Thalhimer, with also 23 grs. of sodium bicarbonate in 300 c.c. distilled water intravenously, 600 c.c. of 3 per cent glucose subcutaneously, and as much 5 per cent glucose and 2 per cent sodium bicarbonate by proctoclysis as they will retain. Dieckmann and Crossen (24) likewise maintain that alkalies in the treatment are not only not indicated, but are actually dangerous, for there is either a normal acid-base balance, a compensated alkali excess, or a compensated alkali deficit (rare).

Probably the greatest controversy met in the methods of treatment of pernicious vomiting is whether insulin should or should not be used in conjunction with intravenous glucose. Duncan and Harding (27) and Harding (38), in 1918, were among the first to stress the importance of glucose intravenously and to use it on a large scale. Likewise, Titus, and Titus and Dodds, beginning about 1920, used glucose alone, with very satisfactory results. These men do not approve of the use of insulin, for the reasons given by Titus (92): "In the non-diabetic acidosis sugar in the form of body glycogen is lacking and storage rather than combustion of the injected sugar is the desired effect. It is illogical to inject glucose only to burn it up by the addition of insulin, and with the lowered blood sugar reading in

the majority of these cases it may be even dangerous to inject insulin. I believe that the good results which have been reported following this combined treatment are due to the fact that the injections supply water to the patient, and that not enough insulin was added to burn up more than part of the glucose injected. The beneficial effects might readily be due to the persisting excess of sugar and in spite of the insulin." A similar opinion is held by Stevens (80), Haskins (42), VanWyck (100), and others. On the other side of the argument is Thalhimer (86-87-88), who, as early as 1923, began to recommend the use of insulin along with the intravenous glucose administration in order to overcome more rapidly the acidosis which is present in severe cases of vomiting of pregnancy. Dieckmann and Crossen (24) agree with him, stating that experimental work indicates that insulin with intravenous glucose restores glycogen stores much more quickly than intravenous glucose alone and, if true, insulin with large amounts of glucose may give better results than glucose alone. Seidl (76), Waters (96), D'Arcy (20), Stander (78), and Keeton and Nelson (54) all are enthusiastic over the results of this combined treatment. The latter men suggest that the benefit which a pregnant woman derives from the use of small doses of insulin given twice daily is the same that comes to a non-pregnant woman with a tendency to anorexia and nausea unassociated with an organic etiological factor. The insulin increases the gastric hunger contractions, reverses the peristalsis, and abolishes the nausea consequent upon the intestinal antiperistalsis and

duodenal dysfunction. The average dose of insulin in these patients is from five to twenty units twice daily, subcutaneously. Lewis (62) offers the suggestion that in milder selected cases 20 c.c. of 50 per cent glucose solution containing five units of insulin may be given intravenously, as an office procedure.

Haskins (42) states that the therapeutic dose of glucose for an adult of average size is from 50 to 75 grams, and that smaller doses do not give the desired effect; that hypertonic solutions, preferably 25 per cent, act more promptly and favorably than weak solutions; that single injections are safer than a continuous flow but must be repeated from one to three times daily. Speidel (77), on the other hand, uses 15 per cent glucose solution intravenously, stating that stronger solutions used in sufficient quantities cause glycosuria, resulting in a profuse diuresis, a condition which he maintains is not desirable at the onset in an already dehydrated individual. Some men prefer the use of continuous venoclysis in place of repeated intravenous injections. They believe that more fluid can be administered with less risk and discomfort to the patient.

About 1920, A. B. Kanavel first suggested feeding patients with vomiting of pregnancy by means of the duodenal tube. This method is recommended by Crossen (18), Speidel (77), VanWyck (100), and others, after intensive glucose therapy has not brought about marked improvement of the patient after two to four days. Larger amounts of carbohydrates, in the form of glucose or lactose solutions (10 per cent)

may be given by this method, as well as proteins in the form of skimmed lactic milk, buttermilk, proprietary high protein milks, etc.

When intensive glucose therapy, with or without insulin, fails, Polak (72) and Stevens (80) recommend transfusions of 300 c.c. of whole blood, to which is added 500 c.c. of physiological sodium chloride solution. They report good results; Polak did not have to empty a uterus for vomiting of pregnancy for nearly five years after beginning this treatment--(up until the time he made the report.)

Corpus luteum extract, one ampule given once or twice daily, intravenously, is quite a popular element of treatment. It is doubtful if it is of any therapeutic or psychic value in these severe cases.

The subject of therapeutic abortion has received much comment by various physicians and obstetricians as a part of the treatment of hyperemesis gravidarum. Holman (45) maintains that it is unnecessary to consider termination of the pregnancy; that these patients, without exception, will get well provided they are given adequate intensive treatment. Abortion, he states, has absolutely no place in the treatment. Oldfield of London (69) also believes that abortion is seldom or never necessary. Hall (36) says: "Abortion is not indicated in these cases as a therapeutic measure. You are dealing with two lives in place of one, and when you do an abortion you are admitting fifty per cent failure."

At the other extreme on this question, are DeWes-

selow and Wyatt (22) who resort only to early termination of the pregnancy after the diagnosis of hyperemesis gravidarum is made.

Undoubtedly, the best stand to take on this question is a conservative one. Abortion is advisable in cases which do not show rather marked relief from the vomiting after about a week of intensive treatment, if the acidosis is not improved, if jaundice persists or increases, if the blood-pressure falls daily, if the urine becomes more scanty and of higher specific gravity, etc. The case should be watched very carefully and if there is any turn toward the worse, abortion should be performed before it is too late. If the patient enters the final or terminal stage, abortion will only hasten the end.

Reference might be made here to two entirely different types of treatment which have been used in small series of cases, of both mild and severe type, with quite spectacular and satisfactory results. Jones of Arkansas (51) uses the galvanic current applied over the vagus nerves. Holman of Iowa (46) uses ultra-violet irradiation over the body, with practically 100 per cent cure. The mechanism of the cures is not known, and it seems hardly possible that the marked physiological disturbances noted in severe cases can be so readily corrected by such simple means.

The intramuscular injection of whole blood recommended by Horn has been discussed under Etiology.

## SUMMARY

Although the condition of vomiting of pregnancy has been noted and recognized for centuries, yet it was not until the nineteenth century that the disease received much serious consideration and more or less definite, empirical forms of treatment were resorted to. The greatest advancements have been made within the last two decades, or so, in regard to the possible etiology and the treatment.

The etiology of this condition is still unknown. Numerous theories have been suggested, some of which are logical and quite conclusive, and yet they do not explain all findings and assumptions. In this paper, the etiological theories have been presented in two large groups: the neurological and the physiological. Under the neurological types are included the nervous reflex, the neurotic and the psychic; under the physiological are grouped the endocrine disturbances, the impaired functions of liver and other organs, the anaphylactic phenomena, the intestinal and focal infection intoxications, etc. The most widely accepted theory, and probably the most logical, is that of a disturbance of the carbohydrate metabolism of the pregnant woman. Underlying this there may be a temporary endocrine imbalance. The work of Horn on the question of fetal intoxication as a cause of the vomiting is very impressive and quite conclusive; I believe that it warrants further investigation. Of course, the neurotic, psychic and reflex phenomena should be considered in all cases.

The symptoms vary with the severity of the condi-



tion. They have been summarized very well by Dubois, who wrote a classical paper on the subject in 1852.

The blood and urine changes are slight or absent in mild cases, but are fairly typical in severe cases. The most constant pathological lesion is a central necrosis of the liver, varying in degree and extent. A degeneration of the convoluted tubules of the kidneys is quite often found; similar necrotic changes may be found in other parenchymatous organs.

The treatment of this disease is varied and necessarily largely empirical, because of the unknown etiology. In the mild cases, the neurological group of factors must be seriously considered, as well as in the severe cases. Certain endocrines, such as ovarian and corpus luteum extracts might be tried, combined with a more or less prophylactic high carbohydrate diet, sufficient rest, etc. In the treatment of severe cases, there are five additional factors which must receive consideration, namely: hypoglycemia, starvation, ketosis, dehydration, and acidosis. The majority of these conditions are met and corrected by the intensive glucose therapy of Titus, Duncan and Harding, Thalhimer, and others. If this intensive treatment fails and the patient shows no marked improvement after about a week, or is getting worse, then therapeutic abortion is resorted to, and should not be postponed too long so that the patient enters the terminal stage of hyperemesis gravidarum.

Six more or less typical cases of pernicious vomiting are presented, taken from the literature.

## ILLUSTRATIVE CASES

## Case I:- Successful Treatment in 1787.(95)

The patient, a secundigravida, thirty-one years of age, "of very delicate frame, much subject to nervous affections," had been bothered with nausea and vomiting which had begun "at the earliest period," and at the time that she came under the care of Dr. Vaughan, in her seventh month of pregnancy, she was unable to retain practically anything by mouth. For ten days she had been bothered by drenching sweats, and tortured by horrid dreams, so that she was getting practically no rest: "In this emaciated state, worn down with sleepless nights, exhausted by profuse sweats, terrified with horrid dreams, and seized with perpetual vomiting." A number of attempts had been made to stop the vomiting, but to no avail. Dr. Vaughan's treatment was as follows:

"The lower bowels were first emptied, by a clyster of mutton broth; this being accomplished, a pint of new milk just taken from the cow, with twenty drops of laudanum, was ordered to be injected as a clyster, morning and evening, and every endeavor to retain it was employed. Four ounces of bark were directed to be boiled, in three gallons of skimmed milk, and the feet and legs being first well rubbed with a warm cloth, were to be immersed in this warm pediluvium for an hour, three or four times a day; an anodyne liniment was also applied to the region of the stomach."

This comprised the complete medical treatment and was continued for three days, by which time the vomiting had ceased and the patient felt much improved and on the fourth

day she ate "a plate of meat and drank a pint of beer with great pleasure."

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Case II:- "Neurotic type" of hyperemesis (68).

A woman, aged twenty-one (first pregnancy), was referred to the Mayo Clinic by her physician in the sixth week of pregnancy on account of a history of vomiting for two weeks, apparently associated with an adherent retroverted uterus. The patient drove to the clinic in a small car, and possibly the jolting was responsible for the ante-flexion and anteversion present on examination. The uterus was about the size of a six weeks' pregnancy.

The patient entered the hospital and was given glucose intravenously for three days. The urine output increased from 550 c.c. to 650 c.c., 1050 c.c., 1600 c.c. and 1800 c.c., in four days. She was also given ninety grains of bromide daily and water by mouth. She retained her food and seemed well enough to go home. However, at this time some relatives visited her, and she began to vomit again. Glucose was again given intravenously. Emesis continued, but the daily output of urine averaged 1000 c.c., although the patient apparently retained little or nothing by mouth. The daily intake by rectum was approximately 2000 c.c. The pulse rate did not go beyond 100, the skin was moist, and the patient did not appear toxic. After four weeks in hospital she was finally convinced that pregnancy would not end in miscarriage as she had previously been told. Normal diet was resumed almost immediately and progressive and rapid im-

provement followed.

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Case III:- "Toxic type" of hyperemesis (68).

A woman, aged seventeen (first pregnancy), was seen in consultation with her family physician in July, 1926. She had not menstruated for three and a half months. For more than two months she had vomited almost all food taken, although she had not been in serious condition until July 1. Since then nausea and vomiting had been continuous and two days prior to her admission to the hospital the vomiting became severe and there was severe pain in the abdomen. The vomitus had been blood tinged for two days. Several days previously she had refused to enter the hospital as advised by her physician. She was five feet two inches tall and normally weighed two hundred four pounds. She had lost forty-four pounds since the onset of her illness.

At the time of the first consultation the extremities were cold and the skin was cold and dry. The systolic blood pressure was 98 and the diastolic 62. The pulse rate was 140 and the rectal temperature 97.3. There was a marked icteric tinge of the sclerotics. The uterus was the size of a three months' pregnancy.

She was immediately brought into the hospital and 500 c.c. of 20 per cent solution of glucose was given intravenously and proctoclysis started. Six hours later 1000 c.c. of 10 per cent glucose was given intravenously, followed by 10 units of insulin and four hours later another 10 units. This dosage, with fluid by mouth and proctoclysis, was given

daily for four days. This patient's condition was such that had a therapeutic abortion been attempted she would probably have died. The improvement was remarkable in view of the fact that she was practically comatose for the first three days. She was on a full diet the ninth day after admission, and was able to return home after the tenth day.

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Case IV:- "Toxic type" with therapeutic abortion (68).

A woman, aged twenty-one (first pregnancy), came to the clinic for examination July 27, 1926, in the eighth week of pregnancy. She had vomited frequently for the last three weeks, and had been in hospital for a little more than two weeks, during which time she was given glucose intravenously, insulin hypodermically and sedatives. She improved under this regimen and on the fifteenth day was dismissed to go home; by that time she was on a practically full diet. She did not follow instructions and returned nine days later in a weakened condition. The pulse rate was 120 and dehydration and icterus were present. On the third day after admission, in spite of intravenous medication, the pulse rose to 140 and temperature to 100. The output of urine was 250 c.c. in twenty-four hours. Because of this and of the onset of vaginal bleeding, it was thought necessary to terminate pregnancy. The patient recovered rapidly and was dismissed in good condition about ten days later.

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Case V:- Severe case with toxic neuronitis (64).

The patient, a primigravida, negress, age 25, was

admitted to the hospital May 15, 1932. Her last regular period occurred August 17, 1931. She was well until September 17, when she began to experience nausea and vomiting, which continued until December 19, at which time she was put on a starvation diet and confined to her bed. After being under treatment for one week the vomiting improved somewhat, but there appeared a sensation of coldness in all four extremities, with weakness and a temporary loss of memory, especially for recent events. A few days later she was unable to stand because of weakness in the legs. The vomiting slowly lessened and ceased about the end of February, 1932.

During these months the patient had continued weakness of the hands and legs, with greater involvement of the extensor groups than the flexors. About one week prior to her admission to the hospital the patient thought that she could notice a slight increase in motion in the flexor muscles of the hand.

Physical examination: Patient well nourished and lying quietly in bed. Pulse rate 90; blood pressure 120/70. There was paralysis of the extensors of the fingers and wasting and atrophy of the muscles. There was a bilateral foot drop with atrophy of the muscles of the lower extremities, and paralysis of the extensors of the lower leg and thigh. There was a loss of sensation to light touch in all the fingers of the right hand and in the little and ring fingers of the left hand. There was a similar loss of sensation below the knees in both legs, especially on the medial surfaces. Proprioceptive sensation was normal. The deep reflexes of the knees and ankles were absent; negative Babinski.

Laboratory: Urine negative except for a few leukocytes and hyaline casts. Blood count and chemistry essentially normal, except for rather low sugar (78 mgm.) and carbon dioxide combining power (36 volumes per cent).

Progress: Because of the partial resemblance of this case to some due to vitamine deficiency, particularly beri-beri, it was thought advisable to place the patient on a diet containing a high vitamine content. This was done, has been continued to date without effect. On May 22 the patient vomited several times and felt much worse than she had for some time. A medical induction of labor was without result. This was repeated on May 30, combined with rupture of the membranes. The labor was short and the patient delivered herself spontaneously. Following the delivery the patient has shown some improvement in the power of the muscles of the hands and of the left leg. She also claims to have some improvement in sensation over the areas involved. She is still a patient in the hospital.

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Case VI:- "Fetal intoxication type" of hyperemesis (47).

On April 4, 1924, a quintipara reported to us at the end of the seventh month of pregnancy. She was extremely toxic, having retained nothing by mouth for a period of ten days. The vomiting had begun at the fourth week of pregnancy and had continued uninterruptedly, regardless of efficient treatment. She had been referred for therapeutic abortion as the only means of saving her life. This patient's blood was matched against her husband's and a double crossed

agglutination occurred. Accordingly, a subcutaneous injection of 1 c.c. of the husband's blood was given; 24 hours later, 5 c.c., and two additional injections of 5 c.c. each at 24-hour intervals. At the end of 48 hours the patient was feeling fine, had no nausea, and was eating and drinking as freely as she desired. I had used glucose intravenously to combat the extreme acidosis, but no further treatment was given and the symptoms did not recur. She gained five pounds during the first four days of treatment. This case showed the most phenomenal relief of symptoms of any case of vomiting of pregnancy I had ever seen, regardless of therapy. A perfectly healthy child was born two months later. The mother's blood was found to be in group III, the father's in group II, and the child's in group II.



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