Vomiting of pregnancy, emphasis upon hyperemesis gravidarum

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VOMITING OF PREGNANCY

EMPHASIS UPON HYPEREMESIS GRAVIDARUM

Mary L. Swayze.
OUTLINE of CONTENTS

A. Introduction
   a. Definition of toxemias of pregnancy
   b. Classification of the toxemias of pregnancy
   c. Purpose in constructing this thesis

B. History
   a. Chronological order of selected historians
      1. Hippocrates
      2. Galem
      3. Socrates
      4. Mauriceau
      5. Burton
      6. Bard
      7. Simmond
      8. Duncan
      9. Williams
     10. Stone
     11. Ewing

C. Terminology and Incidence

D. Etiology
   a. A convenient classification of theories
      1. Toxemic
         (a). Blood stream invasion of fetal elements
         (b). Sensitization of mother to placental extract
      2. Disturbed metabolism
         (a). Faulty absorption of food particles
         (b). Carbohydrate deficiency
            1. Relative
            11. Actual
            (c). Dehydration
            (d). Alkalosis
            (e). Acidosis
      3. Neurotic
      4. Reflex
         (a). Infections about the head
         (b). Abdominal disorders
         (c). Local disturbances of the genital tract
         (d). Mechanical displacements of the genital tract
         (e). Renal infections
5. Endocrine Dysfunction  
   (a). Ovarian deficiency  
   (b). Adrenal deficiency  
   (c). Thyroid hyperactivity  
6. Reversed Peristalsis  
   (a). Intestinal Phase  
   (b). Metabolic gradient  

b. Etiological Conclusions

E. Symptomatology  
F. Diagnosis  
G. Prognosis  
H. Laboratory Findings  
   a. Chemical Analyses  
      1. Blood  
      2. Urine  
      3. Gastric  
   b. Necropsy Reports  
I. Treatment and Conclusion  
J. Case Histories  
K. Bibliography
INTRODUCTION

Fortunately, in the great majority of cases, gestation pursues a physiological course. However, there is no condition in which the borderline between health and disease is less sharply marked, since a very slight irregularity often suffices to convert a physiological and normal case into a pathological and abnormal state.

Quoting McGaughy (48) the toxemias of pregnancy may be defined as a group of disorders associated with pregnancy which have a number of varied manifestations with an etiology as yet hidden from our present knowledge.

Stander (59) suggests the following practical and useful classification of the toxemias of pregnancy.

1. Vomiting of pregnancy
2. Low reserve kidney
3. Nephritis complicating pregnancy
4. Pre-eclampsia
5. Eclampsia
6. Acute yellow atrophy of the liver

I have chosen then in brief, to review the gradual development in a particular condition found in the field of toxemias of pregnancy, namely that of excessive vomiting of pregnancy. Numerous etiological factors have been advanced to account for this well known condition, but the problem has not been solved and treatment remains largely empirical. The symptomatology in the individual case appears to be the chief determining factor in the treatment of the more severe forms, but a large proportion of the investigators rely upon a more or less uniform
routine in the handling of the minor manifestations. Obviously, because of the doubt as well as the danger which surrounds the condition the aim in every case of pregnancy should be in the direction of prevention.

HISTORY

The task of writing a historical introduction to this subject is lightened by the usual procedure adopted by the most medical writers of going back to the fathers of all things medical, Hippocrates and Galen for the necessary beginnings. In their treatises as they have come down to us, 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 reference was made both to excessive vomiting and convulsive seizures there are no specific explanations offered as to their cause, nor definite recommendation for their treatment.

It is generally stated that Soranus of Ephesus observed the disease in the year 20 A.D. Occasional references are found in the Italian medical works of the Middle Ages, but it is not until the latter part of the 17th century that Mauricenau presents 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, which being impossible to be evacuated by so many preceding vomitings because they adhere so fast, must be purged away by stool; to effect which they need a dissolveht which may be a gentle purge... In perturbations and dejections of the belly, and in spontaneous vomitings, if the matter be purged away the patient finds
ease and comfort, if not, the contrary... Burton in his essay 'Towards
a New System of Midwifery' London 1751, in the part devoted to the dis-
eases of the pregnant woman states, "These vomitings seem to be occa-
sioned by various causes which require different methods of relieving them.
First, they may be caused by too great distention of the blood vessels
whereby the nerves may be so pressed as to occasion that convulsive
motion of the diaphragm, stomach, bowels and abdominal muscles which
we call vomiting. Secondly, the vomiting may be occasioned by the remains
of undigested food, or the appetite very often is deprived from the be-
ginning of pregnancy for the blood vessels being so much distended by
pressing on the nerves may hinder their action, so as to prevent their
use in causing the sensation of hunger.

In Bard's 'Compendium of Midwifery' published in New York in 1815
relief of intractable vomiting is obtained only from a removal of 5 - 63
of blood for three or four days. Simmond(28) in 1813 was first to inter-
rupt pregnancy as a therapeutic measure in pernicious vomiting with good
results. Previous to a final stage, therapeutic abortion has given defin-
ite and prompt recovery and we have thus for over a hundred years been
performing and still doing it for the lack of any other satisfactory tr-
treatment that is uniformly successful. Paul Debois presented a thesis on
hyperemesis gravidarum in 1852 before the French Academy of Medicine,
which is still a classic.

Charlotte Bronte, (28) the author of Jane Eyre is said to have had
died from the disease in 1855. She was married for the first time one
year previous in her late thirties. In 1879 Duncan brought to our att-
tention that pernicious vomiting was associated with definite liver les-
ions. These lesions are apparently the same as those found in acute yel-
low atrophy with necrosis in the central portion of the liver lobule.
Williams, Stone and Ewing were the first to describe this characteristic lesion. It has been reported that at times a marked fatty degeneration of the liver lobules may appear instead of hepatic necrosis.

**TERMINOLOGY and INCIDENCE**

The establishment of pregnancy is frequently manifested by disturbances of the digestive system more particularly that of nausea and vomiting. This "morning sickness" as the name implies usually comes on in the earlier part of the day and passes off in a few hours, although it occasionally persists longer or may recur. Usually it appears about the end of the first month and disappears spontaneously six or eight weeks later, but some cases may last for a longer period of time. The great difficulty then in the discussion of hyperemesis gravidarum lies in the definition of what is meant by the term. If we assume that in all cases of pernicious vomiting death ensues unless the pregnancy is terminated, the disease is rare in this country; if on the other hand all cases in which excessive vomiting occurs during pregnancy are regarded as definitely toxemic, this disease is comparatively common. Under the term "hyperemesis gravidarum" it is possible to include any condition of vomiting in excess of the morning sickness of normal pregnancy, which may be due to indiscretions of diet, constipation and neuroses. Peckham has found that vomiting of pregnancy severe enough to demand hospital admission occurs in about once in every 150 cases and severe cases occur once in 400 pregnancies.

John B Haskins states that vomiting of pregnancy occurs in 45 - 70% of all conceptions and that about 10% approach the pernicious type. (37)
Wilkins[65] reports a series of fifty-one cases of pernicious vomiting from the University Maternity Hospital of Michigan as follows:

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Total number of cases</td>
<td>51</td>
</tr>
<tr>
<td>Average age</td>
<td>25.5</td>
</tr>
<tr>
<td>Youngest</td>
<td>18</td>
</tr>
<tr>
<td>Oldest</td>
<td>39</td>
</tr>
<tr>
<td>Primiparas</td>
<td>27</td>
</tr>
<tr>
<td>Multiparas</td>
<td>24</td>
</tr>
<tr>
<td>Illegitimates</td>
<td>4</td>
</tr>
</tbody>
</table>

However, Peckham[56] reviewed sixty cases of hyperemesis gravidarum occurring at John Hopkins Hospital and found that women in the upper walks of life are more prone to the disease, but negro women were not immune to it. There was an equal number of cases in the white and black races. The age and parity are not predisposing factors.

Nausea and vomiting of pregnancy especially in its more severe forms is more common in this country than in England or Germany and is rare in uncivilized countries. (65)

ETIOLOGY

The etiology of hyperemesis gravidarum still remains a mystery. Notwithstanding the voluminous literature written on the subject and the numerous methods of treatment that have been described and devised we find considerable difficulty and even death occurring in connection with this diseased condition complicating pregnancy. I shall discuss the more accepted theories and will conclude by a summary of the most probable etiological factors.

TOXEMIC THEORY

Williams[66] assumes that the cause of vomiting in general must be sought
in some factor commonly present in normal pregnancy since pernicious vomiting is always preceded by the so-called morning sickness, which occurs in approximately every other pregnant woman, and consequently that pernicious vomiting is due an increase in the amount or potency of that factor, or to a decreased resistance to its actions on the part of the woman. The constant entrance into the blood stream of fragments of chorionic villi, the presence in the maternal blood of whatever substances give rise to the Abderhalden reaction as well as the increased amounts of "folliculin", which can be demonstrated in the urine all indicate the existence of a condition which by slight aberration might give rise to clinical symptoms.

Continuing, Williams(66) states, "Alterations in any of these factors as well as a decrease in the resistance of the mother to their action afford a theoretical basis for a 'toxemic' origin which I believe is concerned in all cases of vomiting of pregnancy. However, our knowledge along this line is so defective that any theory must be regarded as tentative."

Peckham(56) and his associates at John Hopkins find that during every pregnancy histological evidence can be adduced to show that fragments of chorionic villi and detached masses of chorionic epithelium can be demonstrated in the maternal blood vessels. There is an invasion of the maternal blood by fetal elements. Normally, the foreign is broken down by the tissue of the mother and is rendered innocuous. If the process is interfered with, it seems justifiable to suppose that the toxic symptoms may develop.

McConnell(47) thinks that the immediate cause of hyperemesis gravidarum is the presence of substances in the blood stream which act as toxic agents exerting a deleterious influence upon metabolism with resultant digestive disorders. In some few cases the disturbing element is of such a severe nature that the maternal organism is not able to successfully combat these evil forces, so the nausea and vomiting become more and more severe until
nothing is retained in the stomach. The patient becomes dehydrated, emaciated, extremely neurotic, toxic and devitalized.

Levy-Solal (58) found in the placenta of vomiting patients an antigen which is reactivated by human serum and which produces shock in guinea pigs. The antigen is not present in young normal placentae and at the end of pregnancy the placentae are without such an antigen. He concluded that women with vomiting are sensitive to placental extract and that after abortion they remain sensitive for two or three days, and after the fourth month these patients are no longer sensitive to such an extract.

Mack (58) suggests the use of serum from normal cases of advanced pregnancy in treatment of these patients believing the normal cases must become immune to these toxins. Earl C. Sage (56) states that no such toxin has been isolated and that it is conceivable that it may be proven to be an intermediate or end product of metabolism rather than a foreign poison.

THEORY of DISTURBED METABOLISM

Tweedy (58) is of the opinion that faulty absorption of food is the underlying factor resulting in hyperemesis gravidarum. He believes that a foreign element appears in the blood stream which interferes with the normal food antibodies. Vomiting of early pregnancy is nature's effort to reject food incapable of proper neutralization.

In 1910, Underhill and Rand (11) as well as Ewing showed that in hyperemesis gravidarum there was an underlying disturbance of carbohydrate metabolism. Van Wyk (67) states that carbohydrate deficiency as a primary cause of nausea and vomiting was first stated by Dunaan and Harding of Toronto, Canada in 1918 and published independently by Titus, Hoffman and Givens in 1920. The publication of this work resulted in a rapid spread of treatment by carbohydrate administration and the introduction in these cases of the intravenous method by Titus marked a great improvement. Although, not definitely established, this hypothe-
esis has met ready acceptance and in consequence treatment has come to include the use of glucose and insulin by many workers.

Hoffman, Givens and Titus(11) under the J.C. Oliver Memorial Research Foundation to St. Margaret's Hospital in Pittsburg describes carbohydrate deficiency with a two-fold origin. First, a relative carbohydrate deficiency due to the unexpected demand for glycogen on the part of the fetus and enlarging uterus. Second, an actual deficiency augmented in the presence of nausea and vomiting from lessened carbohydrate intake.

More recently dehydration has been thought a factor in causation, and therefore treatment has included the administration of large amounts of fluid.

McConnell(47) says, "If metabolic forces are not able to supply the liver with sufficient sugar to insure an adequate glycogen reserve, hepatic degeneration results and glycogen production falls even below its ordinary level and a vicious cycle is thereby established. The more the liver is damaged the less glycogen is produced and the more the glycogen reserve is depleted, the more liver damage ensues. It is probable this sudden need first throws the endocrines out of balance and once disorganized they in turn fall below ordinary efficiency."

Stevens(60) states that during vomiting, the fetus draws its nutrition from a failing mother at a mother's expense. Bessenen(8) is convinced that the woman does not ingest sufficient food because of the vomiting, and if she does ingest sufficient food she may not digest it or if digested it may not be absorbed, and if absorbed an insufficient amount may be assimilated.

Crossen(17) firmly believes in the alkalosis theory. He states that the hydrochloric acid of the stomach is formed from the carbonic acid and sodium chloride. The acid carbonate radical combines with the sodium to give sodium bicarbonate with a resulting increase in the carbon dioxide. Normally, the chloride ions are reabsorbed to be used again, but if lost by vomiting an excess of sodium bicarbonate collects and tends toward alkalosis.
Thalheimer, (17) believes acidosis prevails and may be over-balanced by the previously suggested alkalosis brought on by the vomiting and we have starvation.

Levy in 1926 (44) expressed a tendency toward acidosis in pernicious vomiting which is regarded as a toxemia of pregnancy. The toxin of pernicious vomiting produces a definite destruction of the liver lobule. This destruction of liver substance causes a derangement of carbohydrate metabolism and glycogen storage. He also states that blood sugar and the carbon dioxide combining powers are lowered and a state of acidosis is thus either eminent or present.

NEUROTIC THEORY

Katenbach (65) was one of the first to attempt to explain nausea and vomiting of pregnancy on the basis of a neurosis. Williams (66) states that fortunately the majority of cases, the toxic influence appears to act merely as a predisposing cause in neurotic women and becomes negligible after the nervous equation has been solved. These are the cases of neurotic vomiting which make up the bulk of those we are called upon to treat. Williams has abandoned the conception of reflex vomiting and regards it as a subdivision of the neurotic type. In general it may be stated that true toxemic vomiting is a very serious affection, which frequently leads to death, while neurotic vomiting is readily amenable to treatment and can usually be cured by suggestive means. Stander (59) believes toxemia may be obscured by a predominate neurosis.

Krebs and Diekmann (43) states that in the neurotic and toxic groups there is a definite relation between the degree of functional impairment of the liver as evidenced by the Rosenthal liver function tests. The vomiting whether neurotic or toxemic produces starvation which leads to acidosis such that the vicious cycle goes from bad to worse and ends in acute yellow atrophy of the liver and death ensues if the cycle is not broken by the administration of carbohydrates.
Schwab and Lynch\textsuperscript{(58)}, Goodall\textsuperscript{(27)} and Allen\textsuperscript{(1)} are of the opinion the hyperemesis gravidarum is based on an underlying neurosis. Shears and Peterson\textsuperscript{(65)} explain a neurotic and toxemic basis as the etiology.

**REFLEX THEORY**

The fact that nausea and vomiting follow manipulation of the non-pregnant uterus, it is quite probable that certain nervous adjustments as suggested by Kosmak\textsuperscript{(42)} are necessary before irritation from this source can no longer elicit reflex gastric disturbance. Mere neuroses can not be the entire explanation, because many women of markedly neurasthenic type fail to show any evidence of morning sickness while others who manifest no tendency in this direction and are apparently robust and calm may suffer much from these symptoms.

E.L. Cornell\textsuperscript{(15)} insists that a complete physical examination of the patient is most essential to rule out infections about the head as the cause of vomiting. Nasal accumulations discharging backward are not infrequent sources of vomiting. Abdominal distresses, such as gall-bladder disease, chronic appendicitis and ulcers of the stomach and duodenum, have been factors in producing the nausea and vomiting in several patients. One should not overlook local disturbances such as retroversion of the uterus, cervicitis and vaginitis. If any of these are present, they should be treated as indicated. "I have found it necessary to remove three appendices during the past ten years. Two patients have had their nasal infection treated by rhinologists; two have had abscessed teeth removed, and one patient had pyorrhea so badly that it was a factor in producing the nausea and vomiting."

Kane\textsuperscript{(37)} emphasizes the fact that relief from pelvic disorders such as the restoration of a retrodisplaced uterus to normal position often results in instantaneous improvement or cure. Endocervicitis secondary to retroversion is frequently found associated with hyperemesis gravidarum and usually responds to application of ten percent silver nitrate with corresponding relief from
nausea. 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. Further the classification of the etiology would be more nearly correct as reflex and neuro-toxemia.

The suggestion is made that the frequency of renal infections in association with hyperemesis gravidarum is not generally recognized. The process is hematogenous in a large percentage of the 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 or kinking of the tube.

Keeton states that there are sufficient changes in the pelves of the kidney and ureters to act as powerful stimuli to the vomiting mechanism. If in this average pregnant patient a chronic focus of infection exists or if an acute upper respiratory infection develops then the probability that the urinary tract will exert reflex effects in the vomiting mechanism are increased. He emphasizes importance of gall bladder disease and thyrotoxicosis as reflex stimuli.

It is very interesting to note that Meigs in 1849 regarded the disease as a sympathetic disturbance of the stomach, with grave derangement of the liver. G.S. Bedford in 1870 expresses the condition as a sympathetic irritation and advised premature labor to save the mother.

ENDOCRINE DYSFUNCTION THEORY

(1) Edward P. Allen in discussing the various theories surrounding the etiology of hyperemesis gravidarum states, "Although no completely satisfactory explanation other than the neurotic element has been brought out to account for the more mild degrees of nausea and vomiting, the work of recent years by Frank, Cook, and Harding on pernicious type of vomiting is to be commended. It is
Probably that the glands of internal secretion may act directly or indi-
uation through the sympathetic nervous system and play an important part in
causing this condition.

B. C. Hirst (8) insists that there is a constant absorption of corpus luteum
during sexual activity. No sooner is the corpus luteum of one menstruation
gone when another appears to take its place. With onset of pregnancy this
absorption ceases, and the corpus luteum of pregnancy constantly increases
in size until it reaches its maximum size in about three months. From this
time on it is gradually absorbed. The nausea and vomiting begin during this
period of non-absorption and disappears about the time that the corpus luteum
begins to decrease in size. Is it not logical to assume that corpus luteum
plays an important role in reaction to nausea and vomiting?

Sergent, Silvestri, Rebaudi and Rathey insist upon an insufficiency of
the adrenal secretion associated with polyglandular activity. Falls (25) is in
favor of hyperthyroidism as an important etiological factor, however, all
patients with hyperthyroidism do not have hyperemesis gravidarum. Lugols sol-
utum in treatment of certain cases gives good response.

THEORY of REVERSED PERISTALTSIS

Gardiner concludes after various investigations, that the intestinal tract
is affected while the zygote is still small. The zygote is able to produce the
protective influence in its journey down the remainder of the tube and in the
uterus. This protective substance appears to be associated with the dissolving
or penetrating substance of the trophoblast. The majority of the women in the
47% group begin to complain of nausea and vomiting at about the sixth week.
It is at this time that the chorionic villi are most active. This activity is
greatest for a period of from three to eight weeks at which time it begins to
subside. By the end of the fourth month or possibly the fifth month of gestation
the syncytiotrophoblast and cytotrophoblast of the layers of Langhans disappear and are replaced by a single layer of somewhat flattened cells. During this time there is the greatest disturbance in uterine tissue from the placental development which necessitates a period of the greatest inactivity on the part of the involuntary muscle of the uterus for the protection of the ovum and corresponding to the usual time of nausea and vomiting. The protective substance from the zygote influences the genital organs and in turn the intestines which is most logically the explanation of the cause of vomiting of pregnancy.

It would seem that if this idea were correct that all mammals would be affected by nausea and vomiting during pregnancy, but this does not seem to be the case. The reason for this difference may be in the fact that man is the only mammal who assumes an upright position and consequently the only one in which the intestine lies close to the genital tract.

R.W. Keeton (39) emphasizes the intestinal phase to the vomiting act. This phase finds its expression (motor) in a reversal of peristalsis and the pathologic regurgitation of the duodenal contents into the stomach. Simultaneous with this motor activity the patient experiences the sensation of nausea. This sensation was regarded as sensory expression of the duodenal dysfunction.

Clinical experience and experimental evidence are a unit in the opinion that the stomach may retain surprisingly large amounts of material during these periods of nausea. In some cases the patient may be annoyed by esophageal regurgitation, in other cases the quantity of material remaining in the stomach may be large but the anal-ward peristaltic waves may be absent.

J.H. Stander (58) states that high acids increase peristalsis. In pregnancy there is a lack of acids so we have a decreased peristalsis and a decreased emptying time. The stomach becomes slow to empty and the food by mouth empties by reverse peristalsis.
Walter C. Alvarez (2) indicates that lesions of the rectum, lower bowel and pelvis may be powerful in initiating this phenomena of reverse peristalsis. He has conceived of a metabolic gradient existing along the gastro-intestinal tract which is a determining factor in the direction and vigor of peristaltic waves. It is highly probable that such a condition of gastric stasis existed in the patient of the pre-insulin period and was responsible for her symptoms. Butatou and Carlson (2) have shown that this hypoglycemic reaction induced by insulin not only strengthens the individual gastric contractions of the empty stomach but also augments the tonus so that frequent periods of hunger tetany exist.

Haden and Guffy (2) found a low sodium chloride content in the blood and regarded the condition as analogous to the vomiting of intestinal obstruction and claimed successful treatment with large doses of sodium chloride.

**ETIOLOGICAL CONCLUSIONS**

Any single theory which will explain this illness, must also explain why this disease is present in some cases of pregnancy and not in all cases; why it is less common among the English and Germans; why some patients suffer from simple vomiting and others with the pernicious type, and why some patients have a high ammonia coefficient and others do not. As yet a satisfactory answer has not been reached. Probably the reason why the disease is less common among the English and Germans is because these peoples eat more frequently and plentifully; are more phlegmatic and their digestive tracts are more adaptable to absorption and assimilation through more effective action of the ovaries at the time of early pregnancy. (65)

Krebs (43) refers to the view promulgated by Young of Edinburgh that toxemia of hyperemesis gravidarum may be due primarily to placental infarcts by thrombosis of the uterine vessels. LaVake contends that the thrombosis is due an infection of some primary focus.

Constance E. D'Arcy (18) is convinced that the classification of toxemic
and neurotic etiology for hyperemesis gravidarum gives the students and young graduates the wrong impression and that many patients are allowed to slip too far by inexperienced medical advisers because the neurotic element has been over-stressed and given too much weight in judgement by medical attendants. It is a fact that nervous instability is more manifested in some patients than in others, but this should be regarded as a symptom rather than a cause.

Andrews(4) sees little justification for any such arbitrary classification as neurotic, toxemic and reflex, as the condition is the same in all, the only difference being that some features may be more pronounced in one case than in another.

H. Atles(65) says, "There is little or no doubt that the nervous element plays an important part in exaggerating symptoms, but that it can be the sole factor is impossible".

E. P. Allen(1) believes the nervous element started the vomiting which with lack of food intake carries an increased flow of hydrochloric acid. This causes an irritation to nerve endings in the mucous lining the stomach and so vomiting continues. Due to starvation and associated chemo-histological changes that take place digesting her own fats the case becomes toxic.

There is such a profound change in the metabolism of the pregnant woman during the early months of gestation that an abnormal response in certain patients is to be expected. It is true that the fetus must get its food supply particularly the carbohydrate and protein from its mother. From the work of Stander(58) and others on the respiratory quotient of the fetus it is fairly well established that the fetus utilizes mainly the carbohydrates for its energy requirement. This means a drain on the carbohydrates of the mother. The marked accumulation of acetone bodies in the hyperemesis patient means a profound disturbance of the carbohydrate and fat metabolism. There can be little doubt that the changed metabolism accompanying pregnancy which may so easily become
perverted as shown by the tendency toward acetonuria, in the pregnant woman is the underlying cause of all cases of vomiting of pregnancy. Apparently we do not know the starting point of this changed metabolism, but it seems rational that in the treatment we should attempt to restore the normal metabolism. Whatever starts the disease is not known, but the subsequent changes are essentially those of nutritional change. Of the four physiologic factors; ingestion, digestion, absorption and assimilation, one or all may be involved.

**SYMPTOMATOLOGY**

Hyperemesis gravidarum begins as a simple vomiting, during the early third of pregnancy, which gradually becomes so much worse that nothing can be retained by the stomach. The mere severity of the case gives no clue as to whether it is neurotic or a toxemic type. In the neurotic type the vomiting continues for weeks and the patient gradually becomes more and more emaciated and will die of starvation eventually if suitable treatment is not instituted. (66)

J.W. Williams is of the opinion that true toxemic vomiting is of two types, acute and chronic. In the former, the disease pursues a rapid course and the patient, after a few days of ordinary vomiting, may eject coffee-ground vomitus, soon passes into a somnolent or comatose condition, and dies within a week or ten days without emaciation. In the latter, and more frequent variety the patient may vomit for weeks, becoming markedly emaciated before the seriousness of the case is appreciated. Later she begins to vomit coffee-ground-like material, which she rejects in large quantity and without apparent effort. At this time, symptoms indicative of toxemia appear, and the patient becomes rapidly torpid or violently excited and finally passes into a condition of coma. In some instances, slight jaundice may appear, and toward the terminal stage of the disease, the urine becomes greatly diminished in amount and contains albumin,
casts, and even blood. Even in patients who ultimately recover, great emaciation may occur, so that losses of twenty to thirty pounds are not unusual, while a loss of forty-six pounds has been recorded.

Continuing, Williams states that formerly it was taught that in the later stages of the disease, fever was frequently present, and was associated with a rapid thready pulse and pronounced albuminuria. However, this has not been the experience of Dr. Williams, whose temperatures did not exceed 101 degrees Fahrenheit in any of his fatal cases. In some cases it soon became rapid and thready while in others it was scarcely accelerated. Several of the patients recovered with a pulse rate above one hundred forty, while in a fatal case it did not exceed ninety-six.

J. P. Gardiner, (26) states that the symptoms vary from a feeling of fullness in the abdomen and heartburn to persistent vomiting. Observation shows that the conditions associated with the vomiting are different from those of other vomiting. In this instance an individual apparently well, with little or no prodromal symptoms, vomit. This vomiting is not associated with any of the usual clinical precursors of vomiting. There is no colic, gas pain, intestinal obstruction, previous operative work or anesthesia. As far as can be seen there should not be any vomiting. The apparent ease with which this vomiting is produced in the normal person gives one the impression that here is an opportunity to study the mechanism of vomiting with the fewest complications possible. This study was made by means of the roentgen ray and barium with the conclusion that vomiting in many patients can be controlled during the barium diagnostic meal examination, but that in others vomiting occurred in spite of all efforts to control them, though roentgenologically nothing pathologic was found.
DIAGNOSIS

The diagnosis of hyperemesis gravidarum should be made whenever the vomiting is constant enough to seriously interfere with the nutrition of the pregnant woman. The toxemic and neurotic types are differentiated with difficulty at times, but as the latter is the more common, it is best to treat accordingly until isolation and suggestive therapy fail to bring about any definite improvement.

Quoting Williams, (66) "Acute toxemic vomiting is readily recognized, but from my experience it is impossible by a single clinical examination to diagnosticate the chronic variety. Thus, it may happen that two women may appear to be equally ill when first seen and to present the same degree of inanition, yet one will be suffering from neurotic and the other from toxemic vomiting, and the former will recover within a few days after suggestive treatment, while the latter may die within a few days after suggestive treatment, and even after abortion has been induced."

A complete physical examination should be done, and if any serious abnormality of the generative tract is noted, it should be corrected to eliminate the possibility of reflex stimulation of the vomiting center. If no abnormality is found then the diagnosis rests between neurotic and toxemic. The blood chemistry and urinary findings should be carefully studied and if they are within normal range we are dealing with the neurotic type, whereas if the ammonia coefficient is high, and the blood chemistry findings are abnormal then the diagnosis is not so clear cut in favor of neurois. However, if jaundice develops, and if the vomitus becomes coffee-ground in appearance the diagnosis of toxemic vomiting should be made and induction of labor instituted without delay. If these signs are lacking it will be necessary to note response to suggestive treatment before absolute diagnosis can be made.
Generally speaking, if no improvement follows five or six days of hospital treatment, the condition is probably not neurotic, and the propriety of emptying the uterus should be considered. (66).

PROGNOSIS

The prognosis in neurotic vomiting is very satisfactory since a cure can usually be effected within a week by suggestive treatment, provided the attending physician is sufficiently sure of himself to be able to impress his belief upon the patient. However, the prognosis is always grave in the toxemic type, as we have no means of determining to what extent the internal lesions have progressed, or whether it is possible for them to undergo repair even if the underlying cause of the toxemia be removed by terminating the pregnancy. J. W. Williams states that there is a certain proportion of such cases who will die no matter what may be done.

Continuing, that same author is of the opinion that with the exception of jaundice, coma, coffee-ground like vomitus, the clinical symptoms alone are of little aid in formulating a prognosis. Moreover, experience teaches that neither excessive loss of weight, rapidity of pulse, nor existence of fever, of albuminuria, or of acetone in the urine or breath is incompatible with recovery and the continuance of pregnancy.

Pernicious vomiting sometimes recurs, and many women suffer repeatedly from the neurotic variety in succeeding pregnancies. Unfortunately this may also occur in the toxemic variety, consequently the mere recurrence of vomit-
ing in a subsequent pregnancy does not necessarily indicate that one has to deal with the same type. Stander (58) states that a high specific gravity and small output the prognosis is bad.

LABORATORY FINDINGS

The clinical diagnosis of pernicious vomiting is easy and laboratory tests are of value, not for diagnosis, but as guides to therapy and in determining the severity of the patient's condition. The urine should be tested daily or oftener for acetone and diacetic acid, and the 24-hour volume should be recorded. A ketosis is usually present in untreated cases due to deficient carbohydrate absorption, and is a specific indication for giving glucose by rectum or vein. A decrease in the urine output is an indication for increasing the fluid intake. There should be a frequent determination of the alkali reserve estimation because if the ketosis or dehydration is allowed to become severe, there is a tendency for an acidosis to develop while a loss of hydrochloric acid from the stomach tends to produce an alkalosis. Hence, the alkali reserve may vary from high, low or normal irrespective of the severity, but any deviation from the normal is an indication for controlled therapy. The blood chloride estimation should be done, as a low estimation due to loss of hydrochloric acid is common indication for the administration of sodium chloride. A high urea nitrogen and non-protein nitrogen in the blood will be found in the more severe types, but should not occur in properly treated cases. The uric acid is increased in the blood as in all cases of starvation, but no information of value is secured by its determination. The only laboratory finding to which etiologic significance may logically be attributed is hypoglycemia, but its existence is disputed.
A blood glucose determination of the patient should be made when first seen, because after glucose therapy is started the results of blood sugar estimation will be of little diagnostic value. Albuminuria is not infrequent but does not alter the prognosis.

Edward P. Allen (1) states that the consequent lack of food in the stomach result in an increased flow of hydrochloric acid, which causes a continuance of vomiting. Franz Arzt, (5) after an extensive study of the gastric content in pregnyancy, concludes that free hydrochloric acid 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. This absence of free acid is due to the fact that it is probably neutralized by the regurgitation of the alkaline duodenal contents into the stomach.

R. J. Crossen, (17) characterizes pernicious vomiting by a persistent vomiting causing the 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 acetone and diacetic acid may be absent even in the most severe case. Increase in 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 štæric 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 fluid and carbohydrates are supplied.

Sellard's indirect method of estimating the depletion of alkali reserve has been referred to by different investigators, and in this method sodium bicarbonate is administered in successive doses, and the reaction of the urine examined one hour after the dose until an alkaline urine is obtained. In cases, where the plasma bicarbonate is at a low level, large amounts of the salt are
needed to produce an alkaline urine, whereas in normal individuals five to ten grams suffice.

The presence of an acidosis is detected by one or other of the following three methods: 1 - Ammonia coefficient; 2 - Plasma bicarbonate content; 3 - Alveolar CO₂. Even in normal pregnancy a slight acidosis is present. Losee and Van Slyke have shown that the plasma CO₂ falls from an average figure of 65 o. c. of plasma to 55.6, and Hasselbach and Gammeltooft found that the alveolar CO₂ tension fell from 38 mm. to 30 mm., returning after delivery to 38 mm. From the above it is evident that during gestation there is a slight diminution in the alkali reserve in the blood. (42)

W.J. Dieckmann (23) and O.S. Krebs classify hyperemesis gravidarum as the severe cases determined by (1) constant nausea and vomiting; these patients retain nothing by mouth and eject in addition body fluids. Vomitus at times of coffee-ground type; (2) marked ketonuria; (3) scanty, high colored and concentrated urine, which usually contains albumin with few casts, probably due to concentration, for albumin and casts disappear as soon as output is increased; (4) marked dehydration and emaciation characterized by dry, inelastic skin and diminished or absent panniculus; (5) temperature is usually elevated slightly, pulse increased and quality varies from good to thready; (6) patient is worried and restless, or at times apathetic or maybe comatose; (7) jaundice at times; (8) carbon dioxide combining power and alkali reserve usually high. N. F. N. may be slightly high due to concentration of blood.

Paul Titus and Paul Dodds (63) conclude by their findings that hypoglycemic levels may be attained in hyperemesis gravidarum, which if compared to similar values obtained more rapidly from insulin overdose, would be expected to cause convulsions. That they fail to do so may be attributed to the slow process of glycogen depletion. Fulminating cases of hyperemesis frequently
show convulsions early in pregnancy, which are comparable to those of eclampsia late in pregnancy. The probability of an etiologic relationship between toxicoses of early and late pregnancy is strengthened by these observations.

Titus and Dodds (63) give the following data as regards blood sugar values in several groups of cases of pernicious vomiting totaling forty.

<table>
<thead>
<tr>
<th>Below 80 mgm blood glucose</th>
<th>80 - 100 mgm</th>
<th>100 plus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>18</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Group II</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

The following chart expresses variance of cases ranging in normal value of 80 - 100 mgm per 100 cc blood.

<table>
<thead>
<tr>
<th>Cases</th>
<th>80 - 84 mgm</th>
<th>85 - 89 mgm</th>
<th>90 - 94 mgm</th>
<th>95 - 100 mgm</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Then in values below 80 mgm per 100 cc blood.

<table>
<thead>
<tr>
<th>Cases</th>
<th>20 - 29</th>
<th>30 - 39</th>
<th>40 - 49</th>
<th>50 - 59</th>
<th>60 - 69</th>
<th>70-79</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Group II</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Lowest values of blood sugar were seen in the sickest patients.

J.W. Williams (66) was the first investigator to observe a high ammonia coefficient in hyperemesis gravidarum and considers a coefficient of 10 or more to be very ill. He endorses the idea that it may be due to simple starvation. It is very interesting to note that in the toxic variety of hyperemesis there is a high ammonia coefficient. In 60 cases from our service analyzed by Peckham in 1929, the ammonia coefficient averaged 15.35 per cent, and in general
was low in the mild and high in the severe cases of vomiting; yet such striking exceptions to the general rule occasionally occur as to deprive it of any diagnostic significance. (66)

Numerous investigators have studied the blood chemistry in serious vomiting in the hope of learning more about the changes in metabolism and possibly of obtaining a clue as to the treatment to be pursued. These are well summarized in the papers of Peckham (1929) and Dieckmann and Grossen. In general, it may be said that there is little change in the mild, but that considerable changes occur in the severe cases. In the latter there is a definite increase in the non-protein nitrogen, uric acid and sugar content, a moderate decrease in the chlorides and little change in the carbon dioxide combining power, as shown in the accompanying table from Peckham's paper, giving the average findings in 60 cases studied in this clinic:

<table>
<thead>
<tr>
<th></th>
<th>Normal Early Pregnancy</th>
<th>Mild Vomiting</th>
<th>Severe Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Cases</td>
<td>7</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Non-protein nitrogen</td>
<td>34.3</td>
<td>33.3</td>
<td>57.5</td>
</tr>
<tr>
<td>Uric acid</td>
<td>2.4</td>
<td>3.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Sugar content</td>
<td>98.3</td>
<td>97.3</td>
<td>134.1</td>
</tr>
<tr>
<td>Chlorides</td>
<td>539.3</td>
<td>497.2</td>
<td>462.5</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>49.8</td>
<td>49.3</td>
<td>48.3</td>
</tr>
</tbody>
</table>

In general it may be said that the changes in the severe cases may be attributed to the dehydration which inevitably accompanies the process, while the striking rise in blood sugar speaks strongly against the views of Harding and Titus that the process is associated with hypoglycemia. Furthermore, the absence of change in the carbon dioxide combining power indicates that in most cases we do not have to deal with a pronounced acidosis. Naturally, it may be objected that such average figures may mask important variations, and that this
is the case is shown by the analysis of our findings. Thus, in four patients the CO₂ readings fell below 40, and in four others exceeded 60 volumes per cent. In other words, some of the patients presented a mild acidosis and others a considerable alkalosis, yet in each group three of the patients suffered from severe and one from mild vomiting. Such figures, however, are sufficient to indicate that general rules can not be laid down, and that variations in the blood chemistry do not afford unassailable indications for treatment, but rather indicate that the changes are the result rather than the cause of vomiting. (66)

Stander (68) concludes that the analysis of urine in hyperemesis gravidarum has revealed no outstanding differences from the normal, except a high ammonia coefficient, which is probably the result of starvation. Examination of the blood components has given us more specific information. According to Stander the N.P.N. and uric acid are usually increased in severe cases. Harding and Guffy, found in addition to an increase in the N.P.N. and uric acid, an increase in urea. These authors also report low values for sodium chloride. Harding regards the decreased chlorides as indicative of dehydration.

Diekmann and Crossen report normal or occasional increase in N.P.N. and urea nitrogen and an increase in uric acid in the blood. Killian and Sherwin found increased N.P.N. but decreased nitrogen inpernicious vomiting. The increased uric acid noted in their cases of vomiting of pregnancy, they ascribe to an impairment of renal function. Plass and his co-workers have studied the partition of nitrogen products in the blood stream in different forms of pregnancy both normal and abnormal, but could find no significant changes in the protein fractions in vomiting of pregnancy.

Runge and Juhl report increased amino acids in vomiting of pregnancy. In normal non-pregnant women they found 27.3 mgm %; in normal pregnant women 32 mgm % and in cases of vomiting of pregnancy from 45 - 76 mgm %. An increase in lactic
acid in the blood has been advanced by Loeser. The blood sugar in vomiting of pregnancy has received a great deal of attention. However, Stender(58) is of the opinion that the ketogenic/antiketogenic ratio has not been carefully studied, and it is probable that such an investigation may reveal a ratio exceeding the normal limits. If a carbohydrate deficiency is actually present we can explain the presence of acetone bodies in that there is not enough carbohydrate or antiketogenic substances present to complete oxidation of the fatty acids and thus we have a high ketogenic/antiketogenic ratio.

**Necropsy Reports**

**PATHOLOGICAL FINDINGS**

In 1879 Matthews Duncan pointed out that pernicious vomiting is sometimes associated with definite liver lesions; and Williams, Ewing and Stone have directed attention to what they consider a characteristic type of liver lesion in severe cases of pernicious vomiting. Necrosis takes place in the central part of the liver lobule quite contrary to the usual findings in eclampsia. Instead of hepatic necrosis being marked, fatty degeneration of liver lobules may make its appearance. It is questionable if we are justified in speaking of a typical liver lesion of vomiting because in the cases that have been studied in the post mortem room, there have been superimposed the effect of marked starvation and dehydration which in themselves produce typical histological changes. Because of the nature of the disease, we shall undoubtedly have to resort to animal experimentation to formulate a true concept of the pathological findings associated with vomiting of pregnancy.(58)

Continuing, Stander states:"From the work of Opie and others, that the central and mid-zonal necroses in the liver are usually the result of systemic poisoning, from which it would appear that vomiting of pregnancy may rest on a toxic basis."
Gardiner (26) states that the pathologic manifestations of vomiting of pregnancy, except in rare cases, seem to be little different from those of starvation and inanition. In the two cases in my series which came to autopsy the only changes were in the liver and kidney. In one case the periphery of the lobules and in the other the central portion showed cloudy swelling. In the kidneys of both the convoluted tubules showed cloudy swelling. The glomeruli were shrunken, but showed little change. The liver cells reacted to Sudan III more prominently than those of the convoluted tubules of the kidneys.

Winter, Hofbauer, Heinrichsdorff, Schickel and others have described similar fatal changes. In other fatal cases, the characteristic necrosis is absent, but the liver has undergone such marked fatty degeneration that upon staining frozen sections with Sudan the entire specimen seems to be filled with fat. This type of lesion is usually noted in women dying after a long illness, and is probably a manifestation of starvation, rather than of acute toxemia. The renal tubules, whose epithelium in many cases is necrotic and whose lumina are filled with debris. As a rule, the renal changes occur only in the terminal stages of the disease. Williams states further that as the hepatic necrosis is altogether different from that observed in eclampsia, in which the process begins in the periportal spaces and is primarily due to thrombosis, and that toxemic vomiting is an entirely distinct process, and that it has only three points in common with eclampsia, namely, that both occur in pregnant women, are manifestations of disturbed metabolism and are accompanied by hepatic lesions. It should not, however, be believed that the essential process in either disease consists in the liver lesions, but rather in the underlying toxemia to which they are due. (66)

Bell states that the necrotic liver lesions seen in pregnancy toxemias do not show the different various clinical types of toxemias which Williams believes to be characteristic of them. That is to say that the necrotic areas are by no means limited to the center of the lobules in hyperemesis gravidarum
nor to the periphery in eclampsia. Titus and his associates agree with this.

The genesis of the necrotic lesions has been explained as being the result of an excessive glycogen depletion of the hepatic cells, now known to be followed by a fat replacement. This may be duplicated experimentally by starvation and it is seen to a lesser degree in certain of the wasting or "hunger diseases". Sage continues (56), "We feel that there is an open question as to whether the liver lesions seen in pregnancy toxemias have distinctive characteristics. In Bell's cases there is little agreement in the liver lesions, which include passive congestion, localized fatty infiltration, acute yellow atrophy, infarction, hemorrhagic necrosis and cellular infiltration.

TREATMENT

With respect to the various aspects of treatment recommended by the authorities in hyeremesis gravidarum, G. W. Kosmak (42) states: "The cardinal fact to be borne in mind is that no routine method applicable to any or all classes of cases can be recommended, but in each instance, particularly in the more severe types, consideration must be given to the individual patient." In other words treat the patient and not the disease.

Continuing, the same author says: "While we can follow certain general and well-recognized routine procedures in certain groups of cases, they must be changed as circumstances may dictate. For example, in the vomiting of early pregnancy, the possible reflex or anatomical causes must be carefully sought before instituting treatment, because if they are present, the cases cannot be regarded from the toxic standpoint alone, but must be treated with measures which have been recommended for this type of vomiting."
H.F.Kane (37) states "That there is no satisfactory method of treatment is proved by the multiplicity of procedures. Until more is learned of the cause, treatment will continue to be based on empiricism, experimentation, or pure speculation as to its etiology. Disregarding the type of vomiting believed to be caused by reflex irritation from pelvic pathology, since no tenable theory has been advanced, it seems probable the endocrine dysfunction is the underlying factor, but Hirst's theory of corpus luteum deficiency, logical though it may be, it is not supported by therapeutic results. Thyroid and ovarian extract have likewise failed, and at the present time the most successful methods of treatment are frankly symptomatic. In fact, the present tendency in classification is into two groups... reflex and neuro-toxemic. It is in the matter of quieting the nervous system that the wide variety of procedures have been used. Practically every sedative drug in the pharmacopoeia has been used in an attempt to allay irritation of the nerves and the irritability of the stomach."

At this time I wish to review some of the older methods of therapeutisus. Tarnier used a concentrated solution of belladonna applied locally to the uterine neck and vaginal walls. Eulenberg of Berlin applied tincture of iodine to the os, and gave the patient thirty grains of chloral hydrate night and morning, rectally. (68)

S.C. Busey in 1878 used potassium bromide with decided and immediate relief. He gave thirty grains of potassium bromide dissolved in an ounce of beef tea to which brandy and laudanum may be added according to the condition of the patient. This was administered every four hours per enemata. (68)

Leeches to the os have been used by Clay and others, but their propriety is doubted by Playfair. (68)

Tilt says opium and morphine are first remedies to be used. Dr. Dubelski of Warsaw in the nineteenth century sprayed the spine with ether and obtained good results. (68)
Campbell of Augusta, Georgia called attention to rectal alimentation not only as a last resort, but to supply nutrition. He did not use carbohydrates, but used eight ounces of beef tea twice daily. (68)

W.N. Kemp (40) states that the rationale of adrenal cortex medication is well established by clinical and experimental facts, as follows:

1. Maternal adrenal cortex always undergoes hypertrophy during pregnancy.

2. The first signs of adrenal insufficiency in adrenalized animals are anorexia and vomiting.

3. The first signs of Addison's disease (adrenal cortex insufficiency in human beings) are aversion to fatty foods and morning vomiting, (regardless of sex); in the subsequent crises of this disease gastro-intestinal symptoms play the major role.

The conclusion states that until such a time as there is a compensatory hypertrophy of the maternal adrenal cortex (about the 3rd month presumably), the oral ingestion of a potent desiccated extract of beef adrenal cortex is effective in prevention and curing early cases.

Dr. Bec of Avignon (68) assumes that the blood of the mother contains defense proteins that neutralize the effects of the toxic proteins coming from the fetal blood and the placenta. These are diastases, whereby the Abderhalden reaction is exemplified. The blood of pregnant women contains, moreover a large number of abnormal substances, there is an excess of cholesterol, a substance considered antitoxic and antihemolytic. Mr. Bec therefore, conceived the idea of employing in women affected with grave vomiting, the blood serum of mares during gestation. This blood serum, collected in ampules for injection and sterilization was administered in these cases in doses of from 10 - 30 cc a day. The effects were remarkable. The vomiting, the aversion to food, and
the ptyalism are checked -- sometimes within a few hours, but within 2 or 3 days if the injections are repeated. Generally, after an adequate period of treatment, the effects become permanent and the pregnancy continues without further mishap. Some maternities are now keeping a supply in stock.

Crossen states that the ovum has increased in size 10,000 times by the end of the 1st month. End of 2nd month the ovum has increased 74 times in size, and by the end of the 3rd month 11 times its former size and during the last month only 3/10 the previous size. Therefore the actual increase is small, but the changes caused by pregnancy are tremendous. The uterus increased from 50 grams to 1,000 gms and most of the increase was during the first three months. (17).

Hirst has reported a large number of cases successfully treated with corpus luteum extract. Quigley reported 17 cases so treated, of these 12 permanently cured, 4 improved and 1 not benefited. Coffey reports unsatisfactory results following the use of hypodermic injections of corpus luteum extract. (58)

Cary has employed the desiccated placenta in treating hyperemesis gravidarum. He reports 13 cases with satisfactory results in 11 cases. This author agrees that if vomiting of pregnancy is due to lowered immunity to the syncytium as seems probable by the work of Acconi, the desiccated placenta may stimulate by acting as an antigen; and if the proteolytic ferment is lower, the desiccated placenta may increase the ferment content of the blood. He also believes that the placenta may be a gland of internal secretion and so may activate the thyroid and adrenals and thereby hasten the oxidation of the partially split products of protein which may be thrown into the blood stream.

According to Garnett, pernicious vomiting is probably a development of the physiological vomiting of pregnancy due to failure of the patient to produce a hormone antagonistic to the toxemia. He believes that the vomiting is caused
by a poison and that the only satisfactory treatment so far developed consists in transfusions from post-partum patients. This treatment has been used by others with unsatisfactory results.

Pougart reports 4 cases suffering from pernicious vomiting and after corpus luteum and adrenalin were of no avail they received 20 cc of their own blood mixed with 2 cc of sodium citrate and improvement followed. (58)

Lynch is of the opinion that the formation of the nervous habit of vomiting accounts for the majority of cases of vomiting of pregnancy. He, therefore, tries to break this habit and treats the underlying cause of hyperacidity by medication and diet. The patient is put to bed, all food and drink by mouth is stopped until there has been no vomiting for 24 hours. The bowels are kept open, the patient is given large doses of bromides as well as glucose and soda per rectum. Fruits and sweets are entirely contraindicated for many days, and until the diet has been extended to include vegetables. Brindeau of Paris, writes "In uncontrollable vomiting I believe there is always a psychiatric basis. I always treat them by isolation and I no longer practice abortion." (58)

Xray treatment is without convincing results. Fraenkel reports 4 cases successfully treated by Xray applied to the stomach. Luikart proposed the use of luminal stating that this drug always allays nausea and vomiting and advised that it be administered "H". (58)

Sieger starves his patients for 3 days and then gives them calcium and Ringers or normal saline solution together with bromides for the nervous system.

Duodenal feeding has been one of the recent methods of treatment. Haddock believes the principle indications for the use of the duodenal tube is loss of weight due to starvation and dehydration of tissues. Schaick thinks administration of water is most important medication and that by supplying large amounts of water, which rapidly absorbed in the intestines, the patient usually gets well. (58)
Since the work of Duncan and Harding in 1919, on the effect of high C feeding in vomiting of pregnancy, there has developed a wide-spread interest in the use of C in treatment of this disease. (58)

Thalheimer (69) stresses the importance of relieving the condition of acidosis. This is not the only objective of treatment, but is of very great importance. The best method of controlling acidosis in these cases, seems to hinge around the value of glucose and insulin, the administration of fluids, and the proper type of carbohydrates. Sedatives, colonic irrigations and gastric lavage all have their place in treatment. Excretion via the kidneys should be increased where desired.

Since Thalheimer is given credit for introducing a method of administering insulin with glucose, we append details of his technique herewith:

Method of Treatment: A caution should be given that only pure, tested glucose should be used in preparing the glucose solution. A 10% solution is convenient to use, as with it the patient receives a fair amount of much needed water along with the glucose. The solution should be run in slowly, about 200 to 300 cc an hour, and it is important that it should be kept warm; 1,000 cc is the amount usually given at a time. About 15 minutes after the injection is started, 10 units if insulin is given hypodermically (i.e. 10 of the new U-iletin units)

At intervals thereafter, 10 units is given until for 100 gm. of glucose (1,000 cc of 10% solution) 30 units of insulin given. One unit of insulin(U-iletin) causes the utilization of from 2 to 3 grams of glucose, but for safety a slight excess of glucose should be given to prevent a hypoglycemic reaction or insulin shock. It is wise to have epinephrin available for hypodermic use for treatment of a hypoglycemic reaction. Up to the present, however, this has never been needed.

Paul Titus (68) has done considerable clinical research on the value of glucose and carbohydrate feedings in the treatment of hyperemesis gravidarum.
For mild cases, Titus suggests that at least seven small meals should be taken during the day at definite intervals, carbohydrates being given in large quantities. Two ounces of a solution of 10% lactose and 3% sodium bicarbonate are given every two hours.

In moderately severe cases he adopts the usual plan of a short fast during which period water is given in small amounts. Enemas are given twice daily followed by chloride and bromides, while proctoclysis of glucose and sodium bicarbonate is given persistently. Semi-solid nourishment is allowed by the third day. Of course it is to be remembered that no routine treatment will fit all cases. In the pernicious type more vigorous treatment is instituted. Estimating the value of glucose and insulin injections in the treatment of hyper emesis gravidarum, Titus and Dodds, working in collaboration, emphasize the need for careful laboratory control of the blood chemistry of such patients with particular respect to their blood sugar values. Bokelman agrees with Titus that insulin is a dangerous drug. (58)

Robert D. Mussey (52) advises his patients to eat at least five small meals a day, the meals to consist largely of fruit, crackers, toast and cereals, with large amounts of water taken between meals, but none with the meals. He thinks sedatives should be used freely.

In certain cases the gastric secretions are strongly acid and in this group alkalis may be used with good effect. In others there is evidence of decreased acidity and dilute hydrochloric acid may be employed.

Those with more severe symptoms are required to rest in bed and a 5% glucose solution (50 to 100 gm. daily) is administered by the Murphy drip method. In these cases food is not given by mouth at the outset of treatment, but liquids may usually be taken and should be used freely. (52)

Falkins (58) is of the opinion that all women suffering from vomiting of
pregnancy are undernourished and that it is possible to prevent vomiting in most cases by dietary measures. He advocates an increase in carbohydrates.

Stander(58) states that when called upon to see a patient suffering from vomiting of pregnancy, it is essential first to determine the severity of the disease and whether starvation and dehydration have entered into the picture. If we are dealing with the results of starvation or dehydration our therapy should be to introduce nutrition and water. If the disease has not developed to this final stage it is advisable to determine how much if any neurotic element is involved and to treat the patient accordingly. After a careful clinical and physical examination, often the correction of physical defects improving the condition, he advocates:

1. Starve patient for 24 hours, before instituting therapy.
2. Strict isolation.
3. Glucose or glucose with insulin.
4. Small percentage of cases will not respond to any therapy.

J.H. Moore of Grand Forks, N.D. (70) tells the patient at the outset that food is her salvation. He continues, "I can vividly recall a 21 day crossing the Atlantic ocean, because for 17 days I was sea-sick. I would recommend 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 abhorance for food. The truth is that such a patient is nauseated with the very thought of food, just as it is to the sea-sick patient. The essential thing however, is to get the patient to take food. Carbohydrate must be crowded upon her in various forms, even to a point of producing an alimentary glycosuria, it takes time and patience and sometimes threats to accomplish the task, but it can be done. Tell the patient that you do not expect her to relish her food, tell her to regard it as the worse medicine she ever took, if necessary, but tell her above all else that if she will persist to take even
a small quantity of the diet prescribed at the hour indicated, she will recover quickly. Diet directions should be specific as to what foods you expect her to eat and what is just as important when to eat them.

E.C. Sage (56) institutes the following treatment. Hospitalization with isolation to be desired. An initial period of rest when no food or fluid is given by mouth for 24 to 48 hours, and the patient should be absolutely at rest in bed until 4 or 5 days after vomiting has entirely subsided. At 8:30 A.M. and 8:30 P.M. an enema unless the bowels have moved freely shortly before. Follow by rectal injections of 1/2 to 1 3 of warm water (starch water if the bowel is irritable) containing sodium bromide gr XXX and chloral hydrate gr X. As the patient begins to improve omit the evening dose of sedative first. Essentially the treatment consists of intravenous 25% glucose (75 gm in 300 cc distilled water) continuous enteroclysis of 10% glucose and 2% soda bicarbonate solution may be given subcutaneously.

Frequent hourly feedings are essential after the initial period of rest and carbohydrate should predominate. Nourishment should begin at 7 A.M. or earlier if the patient is awake and continued hourly until 10 P.M. The urine is checked carefully to determine exactly when the acetone and diacetic acid disappear and blood samples checked to determine estimation of blood sugar and blood alkali reserve.

Dietetic regime is outlined for 6 days at which time most patients are O.K. Relapses may occur in the first day or so, but after washing out the stomach the treatment is continued as if nothing had happened.

Constant reassurance and a refusal on the part of all individuals coming in contact with the patient to consider her condition in any way serious is also routine. (56)

R.W. Wilkins (65) states that abortion is indicated in a definite proportion of patients and once decided upon, should not be delayed. The
method involving the least shock and hemorrhage should be the one of choice. A therapeutic abortion should only under the rarest of circumstances be performed without consultation and not without the complete knowledge of the patient and family. An increase in the pulse rate shows weakening of heart muscle and is a danger signal. The mother should be given the benefit of the doubt. If her condition is steadily becoming worse she should be aborted, before her condition is so serious that emptying the uterus will be of no avail. The physician's regret is apt to be that he delayed too long, not that fetal life was destroyed. Wilkins gives the treatment as used in the University Hospital in Ann Harbor, Mich.

1. Put patient to bed immediately.
2. Complete general physical examination including optical fundi.
3. Complete laboratory including blood, Kahn test, urinalysis, serum bilirubin, blood sugar, CO₂ combining power.
5. Nothing by mouth, which should be kept clean and lips soft.
6. Colon thoroughly cleansed and rectal fluid started.
   A solution of 5% glucose in normal saline or Ringer's solution
   Usually an infusion of normal saline with 5% glucose is given
   subpectorally. Glucose intravenous 50% and followed by a
   solution of normal saline doubly distilled and fresh.
7. "H" corpus luteum also gastric lavage.
8. Sedatives as needed. Transfusions may at times be indicated
9. Feedings are resumed by mouth after a period of 24 - 36 hours.
   At first only fluids are given and teaspoonful doses. Gradually,
   the amount and frequency of the feedings are increased as the
   patient is able to tolerate the food.
Wilkins is of the opinion that the indications for abortion are as follows: Rapid and gradual weakening of the patient under suitable treatment. Change for the worse may come on suddenly. Laboratory findings will be of great help in determining prognosis, but one cannot rely entirely upon them. Jaundice is of grave importance. "No patient should be aborted without consultation". After an abortion has been decided upon, then one has to select the proper method. Of course, the methods depend to some degree upon the period of gestation. General anesthesias are contraindicated. The cervix is not very sensitive, and will usually stand the insertion of a bougie or moderate dilatation and removal of uterine contents without anesthesia. Prolonged uterine manipulation especially under general anesthesia takes the patient's last chance away.

F. H. Falls (25) has found that there are a considerable number of pregnant women who exhibit mild degrees of hyperthyroidism as evidenced by an increased B.M.R.; increased pulse rate; unstable nervous equilibrium; and heat intolerance. Not all patients exhibiting evidence of hyperthyroidism have a concomitant hyperemesis gravidarum. We have seen several exhibiting extreme degrees of these symptoms, that have had severe vomiting as a concomitant feature of this disease and some have been admitted to our wards, from our out-patient department with the diagnosis of hyperemesis gravidarum. In addition patients treated by well qualified obstetricians in other hospitals unsuccessfully for hyperemesis gravidarum and referred to our service. These patients have responded to the use of Lugol's solution, giving the ordinary dosage used by surgeons and medical men in treatment of toxic goitre.

In addition to these severe toxic cases, we have tried the effect of Lugol's solution in ordinary mild nausea and vomiting of pregnancy, with
on the whole, not very satisfactory results. In most cases the patient complains that the taste nauseates them. However, several who had severe and prolonged vomiting in previous pregnancies gave Lugol's solution a real trial even at the expense of a little discomfort, and were much improved. KI(saturated solution) 10 gtts doses as a substitute may be given and is much easier for the patient to take.

CONCLUSION

The carbohydrate deficiency theory of the origin of hyperemesis gravidarum is the most plausible etiology at the present time. The temporary lack of carbohydrate intake with the sudden and extraordinary demand of fetal and placental growth and uterine hypertrophy causes a glycogen deficiency of the body tissues especially the liver. The best results in therapy treating hyperemesis gravidarum can be obtained by the free use of intravenous glucose and frequent small feedings containing a large proportion of carbohydrates.

E.C. Sage (56) says, "We have treated a rather large series of cases at the University of Nebraska, College of Medicine, and in our private practice by this method, and it has proven efficacious. We have confidence in the success of such therapeutic measures. ............. However, we must remember that in a small per cent of the cases all therapy may be of no avail, and a therapeutic abortion inevitable. It must be pointed out that we can not lay too much stress on the value of complete isolation of the patient, especially from all relatives and of suggestion."
C.H. Peckham, (54) who reviewed sixty cases of hyperemesis gravidarum occurring at Johns Hopkins Hospital, calls attention to the following conclusions:

1. Women in the upper walks of life are more prone to the disease, but negro women are not immune to it. There was an equal number of cases in the white and colored races.

2. The age and parity are not predisposing factors.

3. Neither the time of onset, duration of vomiting, nor loss of weight indicates the severity of the disease nor affords a safe guide for prognosis.

4. A high pulse rate usually indicates severe vomiting, but not necessarily implies a serious prognosis. On the other hand, a low pulse may persist in a severely ill patient.

5. Fever due to dehydration is frequent.

6. The presence of urinary albumin is frequent, but is of slight prognostic importance. (Albumin was present in the urine of 40% of the patients)

7. Acetone bodies are frequently absent from the urine in severe cases.

8. A high ammonia coefficient is usually seen, but a low one does not necessarily indicate a mild case.

9. In mild vomiting of pregnancy, the blood chemistry is not essentially changed, although the uric acid tends to rise and the chlorides to fall.

10. In most patients isolation in a hospital and suggestive treatment will effect cure, but exceptionally all therapy fails and the induction of labor is indicated.

11. A considerable percent of patients abort spontaneously, sometimes after cessation of symptoms, a phenomena which requires explanation and study. 25.6% of this series aborted spontaneously at varying intervals after leaving the hospital, one was a case of hydadiform mole.
CASE HISTORIES

Case I.

W. N. Kemp of Vancouver B. C. bases his opinion that nausea and vomiting of pregnancy during the first trimester is due to the presence of "toxic metabolites" in the maternal blood stream resulting from a temporary relative insufficiency of the secretion from the vital adrenal cortex. The first two of my cases histories will be taken from Kemp's series. (40)

Mrs. M., aged 26; para 1; the patient of Dr. F. N. Robertson. This patient consulted her physician on October 28, 1931, for the relief of nausea and vomiting. Examination and history showed that she was seven weeks pregnant. She was advised to take suprarenal cortex (Armour) grains 3 t.i.d. Within 24 hours the vomiting ceased. The medication was continued for one week only. Within two weeks the nausea and vomiting returned. It was again effectively controlled by adrenal cortex therapy.

Case II.

Mrs. S., aged 34; para 3; the patient of Dr. Anson Frost.

Past History: Both previous pregnancies had to be terminated at the seventh month on account of pernicious vomiting.

Present Illness: When the patient was seen with Dr. Frost on July 15, 1931, she was within one month of term. She has been in bed in the hospital for six weeks on account of pernicious vomiting. She required daily intravenous infusions of 5% glucose and could tolerate only a liquid or semi-solid diet. Her blood picture was that of a severe secondary anemia. At this time, she was given one cc of liquid extract of suprarenal cortex (Armour) intravenously with
with no reaction of any kind. Twelve hours later she felt much better and was given another intravenous injection. She felt very markedly improved after the second injection and her appetite returned for the first time in six weeks. Unfortunately, she was allowed to satisfy her appetite to the fullest extent. The result was inevitable. She had a gastric upset and refused further suprarenal therapy. The result was inevitable. She had a gastric upset and labor was induced and she was delivered a few days later.

Case III

In case 3 and case 4, J. Mann (46) illustrates the treatment as carried out at the Burns' Department, Toronto General Hospital and developed by Doctors Harding and Van Wyck.

The patient M. R., was admitted on June 30, 1931; para 1; gravida 2; Pregnant 2 months. She has been quite well until 5 weeks before admission to the hospital. During this time her nausea and vomiting had increased in severity until she became acutely dehydrated and emaciated with severe ketosis. The temperature was 100.2 degrees C; pulse 120; respirations 24. She was given the routine treatment on admission, including a bed bath, simple enema and later chloral hydrate and sodium bromide per rectum.

Urinalysis on admission: Colour - deep amber; specific gravity 1.026; ketones 4 plus; urobilin, albumin and microscopic tests negative.

Blood analysis - hemoglobin 80%; sedimentation time - 80 minutes; total serum protein - 7.2%.

During the first 24 hours in the hospital she was given 4,300 cc of fluid in the form of 3,000 cc of 10% glucose in normal saline intravenously; 1,000 cc normal saline intravenously; 300 cc by mouth. The urinary output was 830 cc; specific gravity 1.030; ketones 4 plus. The temperature and pulse became
normal. The patient cooperated well and was very quiet with the sedative administrations and there was very little vomiting.

During the second 24 hours in the hospital the total fluids administered was 5,740 cc as 3,000 cc of 10% glucose in normal saline intravenously; 1,000 cc normal saline intravenously; 1,740 cc of water by mouth, of which 1,000 cc returned as vomitus. The urinary output for the same period was 2,850 cc with a specific gravity of 1.018; sugar 2 plus; trace of ketones.

On the third day, the patient showed marked improvement. There was no vomiting and the fluid intake by mouth was 2,500 cc fruit juices. The urinary output was 1,900 cc; specific gravity 1.013; sugar, ketones, bile and urobilin absent.

On the fourth day, the patient continued to improve. There was no vomiting and the fluid intake was 3,200 cc. The urinary output was 2,500 cc; specific gravity 1.006. Diuresis was definitely established. From this point on the patient was given solid foods and all the fluids she could take, and she made a rapid recovery. The vomiting was limited to once daily during the 4 weeks in the hospital.

Case IV

The patient M. P. was admitted on February 6, 1931; gravida 1; 3 months pregnant. She had been well until 3 weeks before admission. In the last 2 of these 3 weeks the vomiting was severe, and she showed no response to treatment at home. On admission, the patient was moderately dehydrated, but not emaciated, and there was no obvious ketosis. There was almost continuous vomiting of bile stained material. The temperature was 99 degrees C; pulse 100; respirations 30; There were no other significant physical findings.
Urinalysis: - Volume 3.3; colour - dark amber; specific gravity - 1.025; albumin - sugar, ketones, bile, urobilin, microscopic negative.

Blood analysis - Hemoglobin 75%; total serum albumin protein 7.5%; white blood cells - 8.5; sedimentation time - 50 minutes; CO₂ combining power 65.

The general physical condition was good and the laboratory findings, apart from oliguria, were negative. The mental attitude was bad; the patient was a recent Irish immigrant, homesick and lonesome, and not desirous of having a child. She was restless and irritable and did not cooperate. Routine admission treatment was carried out, and for the first few hours and effort was made to reassure the patient and make her comfortable. The initial rectal sedative was chloral hydrate, 30 grains and sodium bromide 60 at 3:00 P.M. This was repeated at 10:00 P.M. and at 11:30 P.M., morphia grains 1/4 and codeia, grain 1/2 "H", were given and at that the patient only slept for short intervals during the night. By 7:00 o'clock the following morning, 15 hours after admission, her intake was only 80 cc of fruit juice and the output was 150 cc with a specific gravity of 1.025. The sedative had practically controlled the vomiting.

During the next 24 hours the total fluid intake was 4,050 cc as 1,600 cc 10% glucose in normal saline intravenously; 2400 cc fruit juice and water by mouth. The vomitus was clear fruit juice, occasionally containing a little bile; the total amount was less than 100 cc. During this time she was very restless and hard to manage and the fluids by mouth were administered with difficulty. The rectal sedatives were promptly expelled. 1/2 strength H.M.C. tablets and codein "H" were used as alternatives. The urinary output was only 100 cc; specific gravity 1.026 and the urine was negative for sugar, ketones,
bile, and urobilin.

On the third day, in an effort to produce diuresis intravenously glucose was resumed; rectal sedatives were again unsuccessful, and we had to continue with hypodermic sedatives to control the extreme restlessness. The fluid intake for the 24-hour period was 5,900 cc as 3,000 cc 10% glucose in normal saline intravenously; 2,900 cc of fruit juice by mouth. The urinary output was 1,400 cc with a specific gravity of 1.028. Urinalysis showed sugar 1 plus, otherwise negative. The total vomitus was 250 cc consisting of bile-stained fruit juice.

The patient did not look dehydrated, but it was evident that a normal tissue balance (water) had not yet been obtained and intravenous glucose was continued in an attempt to bring about the readjustment, waiting for a free diuresis as an indication that this had been accomplished.

By 5 P.M. on the 4th day she had received 3,100 cc of fluid, as 1,900 cc of 10% glucose in normal saline intravenously; 1,200 cc of fruit juice by mouth. The urinary output up to this time was 1,000 cc; specific gravity 1.028; the total vomitus was 650 cc of bile-stained fruit juice. At this point a noticeable edema developed in the face and the eyelids became quite puffy. There was no edema elsewhere. All fluids administered was discontinued. At 6:00 P.M. the temperature was 102.6 degrees C; pulse 120; respirations 22. By the end of this 24-hour period the urinary output had increased another 1,800 cc to a total of 2,800 cc at a specific gravity of 1.011.

On the following day the patient was feeling better than she had since admission. Her mental attitude improved and she became quite reasonable. Hunger returned and she requested food. This was granted and was well tolerated. There was no vomiting through out the day. The total fluid intake for this day was 1,230 cc by mouth and the output was 2,100 cc at a specific gravity of 1.008. A very definite diuresis had been established. From this point on the patient was given a full diet. The relationship between intake and output showed a
return water balance.

The total fluid administered in this case was obviously beyond a desirable therapeutic limit. The large amount of water and fruit juice by mouth should under ordinary circumstances promote a diuresis before edema develops. The kidneys apparently had a normal threshold for glucose.

Case V

M. T. Harrison gives this case of hyperemesis with necropsy findings.(30).

On December 5, 1930. I was called to see a colored woman aged 26, who previous to her marriage 2 years before was a graduate nurse. Her appendix was removed in 1924, tonsils in 1927 and on July 4, 1930 when 6 weeks pregnant an abortion was induced because of uncontrollable vomiting. Following the abortion on July 4th she menstruated once. She missed her monthly period expected early in September and during the last week in September became nauseated. She called her family physician who diagnosed the condition as the nausea of pregnancy. She did not respond to his treatment and on November 19 was transferred to an Atlanta hospital.

She was placed on limited fluid intake, alkalis and a carminative prescription by mouth. Glucose 2% in normal saline was administered daily by rectum. Her room was quiet, visitors were restricted and she was given mild sedatives with an occasional small dose of morphine and scopolamine. The first week she vomited almost every liquid taken by mouth. On the 26th she vomited very little and apparently enjoyed what nourishment she was given. Until December 4th there seemed to be slight daily improvement. On the morning of this day the nurse detected a rapid pulse and made the following notation on the chart, "Patient acts queerly at times". Her physician was notified. He ordered 1 cc of digitoxin 1/4 4 hours and calomel grains 4. Normal saline was given under skin and by rectum.
Her temperature ranged from 97 - 99.8 degrees F with an average close to normal. Her pulse had varied from 88 - 122, with an average between 90 and 100. The most notable observation was obstinate constipation. In fact not one entirely satisfactory bowel movement was recorded.

Examination on December 5 at 1:30 A.M. disclosed an emaciated, colored woman who answered questions rather slowly and who seemed more or less dazed. The skin was dry and felt cold. Her blood pressure was 100/88; T 97.8; P 140 R 26; The lips were dry and fissured. There was no glandular enlargement in the neck. The lungs were clear and other than a rapid rate the heart appeared normal. The abdomen was distended. The percussion note was tympanitic. Above the symphysis could be felt the upper border of an oval mass. The cervix was soft and approximately 15 cm in diameter. The clinical diagnosis was hyperemesis gravidarum with a very discouraging outlook. Intensive supportive measures were instituted. For about 12 hours there was some improvement after which she began to decline and died about 24 hours later.

Three hours after death, a necropsy was performed by Dr. J.C. Norris whose report follows: - The heart was not enlarged. The right side was soft and dilated. The liver was normal in size, but pale and flabby. The cut surface had a greasy appearance. The spleen was soft and was slightly enlarged. The kidneys were swollen and showed cortical petechiae. There was a moderate nephritis. The uterus was soft 16 cm in diameter and contained a 4 month fetus. The placenta overlies the internal os.

The anatomical diagnoses were: (1). Generalized toxemia. (a). Toxic myocarditis with dilatation. (b). Congestive pneumonitis (c) Toxic hepatitis (d) Toxic splenitis (e) Toxic nephritis (2). Dehydration. (3). Anemia. (4). Pregnancy at 4 months with placenta previa.
Case VI.

J. P. Gardiner illustrates the treatment he is using in the following case report.

Mrs. L., a seconipara, whose first pregnancy was uneventful except for light nausea for a week or two, became nauseated in the present pregnancy about the 4th week and by the 6th week the nausea was severe. There was vomiting immediately after the taking of food or liquid. Before I saw the patient she had been treated with corpus luteum without any apparent effect. She was a well nourished woman (though she asserted that she had lost weight,) with a slight fullness of the thyroid, and the chest and abdomen were normal. The urine was normal. The uterus was enlarged indicating a 2 1/2 month pregnancy. The bowels were constipated moving only by enema. The pulse ranged from 100 to 110 and the blood pressure was 120 systolic and 70 diastolic. The patient was weak and hardly able to sit up. The routine treatment was instituted. The foot of the bed was elevated and she was urged to lie face downward. Morp ine 0.016 gm and scopalamine 0.004 gm were given and the bowels were saturated by the drip method with physiologic saline containing 1% sodium bicarbonate plus 15% dextrose. The vomitus reduced fehling solution. The vomitus grew less the second day and by the third day it was only occasional. One 3 of cold milk was given q hour and phenobarbital of sodium 0.09 gm was given q 12 hours. She was instructed to lie face down at intervals at night for the following 2 weeks. Recovery was complete.
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