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## Investigation of nausea and vomiting of pregnancy

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AN INVESTIGATION OF NAUSEA AND VOMITING OF PREGNANCY

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## AN INVESTIGATION OF NAUSEA AND VOMITING OF PREGNANCY

Nausea and vomiting of pregnancy is truly a "disease of theories". It is the most frequent complaint of the pregnant mother between the second week of gestation and the sixth week post partum, as so called "morning or evening sickness". This occurs in 50% or more of all pregnancies and is so common that it is one of the criteria by which the patient may know herself to be pregnant.

It is interesting to note that "morning or evening sickness" occurs predominantly in women of the Western civilization and/or influence. This is thought to be due to the increased stress of a modern civilization. It is relatively uncommon among the Eskimos, Africans and Orientals, except in industrialized Japan. It more often occurs in the upper class than the lower class. Also, it is not known to occur in lower animals. The age and parity of the pregnant mother are observed not to be predisposing factors to the nausea and vomiting.

Two common observations indicate that it is associated with changes in the biochemical environment of the pregnant mother. It is noticed to accompany pregnancies that progress normally in every respect. And it is known to be conspicuously absent when the product of gestation has succumbed in utero and the pregnancy is to terminate in an abortion. Luikart<sup>1</sup> presented an interesting case substantiating these observations of a 19 year old medical student's wife who was hospitalized with excessive amount of vomiting after

having missed only one menstrual period. The nausea-vomiting was dramatically abrupted the next morning. Pelvic examination at the time revealed definite evidence that the patient was pregnant. During the summer months, she was not followed by Dr. Luikart. Four months later the patient was known to have aborted a 4 cm. intact ovum of mummified twins. The fetal death conceivably corresponds to the time that the vomiting ceased.

An exaggeration of nausea and vomiting in which no food or liquid is retained occurring unrelated to meals and at any time of the day is known as hyperemesis gravidarium. According to Peckham<sup>2</sup> this occurs in 1/150 normal pregnancies and is so severe in 1/400 pregnancies that hospitalization is required for the patient. Why the exaggeration of symptoms occur in some pregnancies and not in others cannot be answered from this paper.

It is the author's intention to present an investigative review of the literature of this subject in an attempt to present the theoretical basis for the various treatments of nausea-vomiting of pregnancy and the more severe form, hyperemesis gravidarium. No attempt has been made to exhaust the literature of this subject but rather the selection of the more pertinent articles from workers recognized in this field. One cannot be partial in the selection of medical literature about a subject in which the author is not a contemporary. But in the perusal of review articles the various workers in the specialty recognize each others contributions. It

is from the bibliographies of their review articles that this subject has been approached. To repeat again, this subject is presented as an investigation of the etiological theories of nausea-vomiting in pregnancy and their respective mode of treatment, with statistical results of most authors.

As previously stated the first symptom is "morning or evening sickness", comprising of mild nausea and an occasional episode of emesis. This may occur as early as the second week of gestation before the mother is suspicious of being pregnant from a missed menstrual period and continue to the sixth week post partum, if the patient has not progressed to hyperemesis gravidarium or has not been relieved by medication.

When the vomiting becomes so pernicious that no food or liquid is retained and occurs unrelated to meals, the diagnosis of hyperemesis gravidarium can be readily made. This usually occurs initially as a mild form and progresses to the more severe form, but occasionally the initial onset may be that of hyperemesis gravidarium with a fulminating type of pernicious vomiting. According to Barnes<sup>3</sup> the diagnosis between the normal and pernicious vomiting is a failure to respond to outpatient ambulatory care. In the severe form the symptoms of the mild form become accentuated. The patient starts vomiting coffee brown material, usually becomes quite irritable and may progress into a comatose condition. The patient experiences a true loss of appetite and associated weight

loss, lassitude and increased fatiguability. Frequently the patient complains of frontal headaches as a predisposing symptom. If fluid and electrolyte therapy is not instituted the patient will soon be in a metabolic "toxemia" due to starvation, dehydration and loss of chloride ions in the vomitus.

Clinically, the patients' condition is comparable to the degree of starvation and dehydration. In the mild form a decreased blood pressure, tachycardia, and a dry furred tongue with an acetonic breathe is noted. With the loss of body fats and fluids, the urine output decreases with a concomitant elevation in N.P.N.. Ketonuria and albuminuria are commonly seen.

After six weeks of rather extensive vomiting with no relief the patient becomes markedly dehydrated with an elevated temperature. In the more severe stage, the eyes become sunken, the skin becomes dry and jaundiced with an increase in pigmentation, the lips and gums become eroded from the excessive vomiting. The blood pressure decreases to below 90 mm. of mercury, the pulse becomes faint with a rate over 120. This is know particularly in this disease as the "pulse of empty arteries". Albumin, acetone, ketone bodies and red blood cell casts are found in progressive amounts in the urine.

Neurological signs may become manifested at this time. The patient may present one or all of several entities. Peripheral neuritis with wrist drop, optic neuritis with retinal hemorrhages, ophthalmoplegia with ocular symptoms and Korsokoff's psychosis. In the last stage, Wernicke's encephalopathy may ensue with con-

vulsions and death.

On post mortem examination the pathology is comparable to a patient succumbing to dehydration and starvation. The only supportive evidence that the patient terminated with hyperemesis gravidarum would be the gravid uterus and evidence of dehydration and starvation. The heart is noted to be atrophic in proportion to the duration of vomiting. The kidneys are grossly noted to have an edematous cortex with the capsule stripping with ease. On microscopic examination, the glomeruli are ischemic and fat is seen in the mitochondrion zone of the first convoluted tubules. The liver will be enlarged and yellowish in appearance from fatty infiltration of mobilized fat due to the starvation. Interspersed in the fatty infiltration, there will be noticed dark blue spots from hemorrhages into the portal triad areas. In the brain, Wernicke's encephalopathy will be seen with marked congestion and many small petechial hemorrhages affecting particularly the hypothalamus and the grey matter of the upper brain stem. But damage to the nerve cells is surprisingly slight.

In the investigation of nausea-vomiting of pregnancy a proven etiology of the disease was not found. There are six main theories that have been advanced by leading authors for the entity and in each of them the treatment varies with the theoretical etiology. It is because of this close allination, that the etiology and associated treatment have been considered together in this paper.



The etiologies are listed for easy reference in the succeeding pages:

- I. Hormonal
- II. Allergic
- III. Nutritional
- IV. Reflex
- V. Toxic
- VI. Psychological

#### I. Hormonal

The decreased function of the adrenal cortex has been indicted as the causative factor in the nausea and vomiting of pregnancy. Some workers believe that the adrenals fail to hypertrophy due to an increased demand during the first trimester of pregnancy. It is known that the adrenal cortex becomes hypertrophic during pregnancy and that the first sign of corticoadrenal insufficiency in adrenalectomized animals is nausea and vomiting. Also, it is well known that in Addison's disease the earliest sign is morning nausea and vomiting, regardless of the sex. The correlation of these disease entities is best noted in the post mortem findings where the pathological picture is much the same in all of them.

Katz and Kaufman<sup>4</sup> treated fifty patients with adrenal cortex and reported most of the cases improved. Although the effect was difficult to evaluate because of the small number of cases with no normals for control, they believe the benefit to be significant.

Carreras<sup>5</sup> believes that the decreased function of the adrenal cortex is indirectly due to the increase of the pituitary gonadotrophin during the first weeks of gestation. In this manner other

pituitary hormones are decreased. This temporary decrease of adrenocorticotrophic hormone causes transitory adrenal insufficiency. He compares the syndrome of general adaptation and the pathologic condition of pregnancy. The alarm reaction phase corresponds to the symptoms of morning nausea and vomiting caused by the transitory adrenal insufficiency to the normal stress of the pregnancy. The resistance phase occurs when the hormones from the placental syncytium, chorionic gonadotrophins, estrogen, and progesterone, increases sufficiently to neutralize the excessive pituitary gonadotrophin. Equilibrium is thus established and all symptoms disappear. If this stimulus is not neutralized the exhaustive phase ensues. The excess adrenocorticotrophic hormone of the pituitary causes excessive secretion and hypertension. The general syndrome of high blood pressure, oliguria, edema and albuminuria is the result of the organism attempting to adapt to the continual stimulus.

Eventually the prolonged hyperfunction of the pituitary and adrenal glands will lead to their atrophy and irreversible shock of the patient. In the author's series of 15 cases, 12 were simple and three were refractory to other treatment. In each case 15 mg. of ACTH was given in 500 cc of 5% dextrose in water daily. In 13 cases, treatment was required for two days before complete relief. In two cases treatment was prolonged for four days before nausea and vomiting were eliminated. In each instance the patients were delivered of normal babies at term.

Van den Bosch<sup>6</sup> had a dramatic result with one patient with severe recurrent vomiting of pregnancy with ACTH. She was known to be refractory to other therapy. A glucose tolerance test of the patient revealed a flat curve fasting value of 94 mg %. With this he assumed the etiology to be a temporary depression of adrenal function. The patient was given 10 mg. ACTH every six hours for two days, followed by 20 mg. every six hours for three days. On the third day all nausea-vomiting stopped and other symptoms subsided. Thereafter ACTH was given intermittently for four weeks. Although one case has no statistical value, the dramatic results with ACTH after other therapy had been tried makes the case worthy of comment.

Although 50-80% of the patients are noted to improve with cortisone, Page<sup>7</sup> is of the opinion that it should not be used because of the adverse effects on the fetus in the first two months of pregnancy.

Guilbeau<sup>8</sup> found five cases of congenital abnormalities in a series of 30 cases of pregnant patients that were treated with an average dose of 50 mg. of cortisone per day. The abnormalities consisted of a club foot, coarctation of the aorta, a premature, a cataract and a hypospadias. In two instances a family history of the abnormality was present.

Some workers believe that the increased secretion of chorionic gonadotrophin occurring in the first trimester is the etiological

agent for "morning sickness". The appearance of gonadotrophin in the serum and urine corresponds to the time of the first symptoms of nausea and vomiting.

Smith and his co-workers<sup>9</sup>, working with the wives of the medical profession found that the appearance of chorionic gonadotrophin in the serum and urine of the pregnant patients to occur five days prior to the expected date of the next period. They noted a constant rise in the levels with a plateau level of 1,000-5,000 International Units per 24 hour specimen of urine between the 25-40th day from onset of last menstrual period. Between the 40-90th day a constant elevation was maintained with the maximum of 450,000 I.U. occurring at the 70th day. By the 90th day the secretion had decreased at a relatively steady state. At the 120th day from last period the gonadotrophin level was hardly detectable. The corresponding levels were obtained in the serum but of a lesser magnitude. The coincidence of nausea-vomiting with the elevated values is perhaps problematic, but it is strong supportive evidence of this theory.

Findley<sup>10</sup> in his work suggested that if chorionic gonadotrophin is the incriminating factor of this disease then nausea-vomiting should be notably present in the patient with hydatid mole. In his series of cases he found 13.5% having excessive vomiting.

Schoeneck<sup>11</sup> in his work found a quantitatively increase in hormonal substances in urine corresponding to an increase in

severity in nausea-vomiting of pregnancy. Although he suggested that the increase may have been due to an increased concentration of the urine due to dehydration of vomiting, he intimated that it could be the initiating factor of vomiting.

Eller and Randall<sup>12</sup> believe that nausea and vomiting must be disassociated to a degree that they are not one and the same symptom. The sensation of nausea may have an organic basis, while vomiting largely depends on the psychosomatic pattern of the patient. Thus some people are prone to vomit easier than others. Any treatment for nausea will alleviate vomiting. They believe that the high concentration of gonadotrophin (cyonin) in the first trimester of pregnancy is the organic basis of nausea. In their series of 68 patients, they treated them with "forced hydration" to lower the serum concentration on cyonin below the nausea threshold by diuresis. Forty seven per cent of their patients were relieved in four days, 60% were notably improved in ten days. They believe their treatment to be the simplest, the most economical and the most effective way of treating nausea and accompanying vomiting.

Luikart<sup>13</sup> in his re-evaluation of the entity believes the etiology to be either an excessive secretion and/or lack of utilization of chorionic gonadotrophin, consequentially diuresis is the most important part of his treatment. Otherwise his treatment varies with the severity of vomiting. In any case a thorough history and physical should not be neglected, particularly

when vomiting occurs in the 4,5,6th months of gestation, to rule out other causes of vomiting besides pregnancy. In mild vomiting his treatment is a conservative regime of fluids in excess between meals, vitamin B intravenously with phenobarbital if necessary. Fat free diet with small amounts of carbohydrates, stilbesterol 25 mg. per day, proper attention to elimination and above all, sincere pre-natal advice to gain the patients confidence. In the more severe vomiting with elevated temperature, jaundice and oliguria, his treatment is more radical. The patient is hospitalized, isolated from all visitors, nothing by mouth for 12 hours after which she may have sips of water, 2000 cc of 5% glucose in water per day with vitamin B complex, stilbesterol, sedation as required, dry foods every other hour and a saline enema every other day. In his series all patients treated with this regime have been notably better in 72 hours.

## II. Allergic

The encouraging results obtained in nausea-vomiting by the use of antihistaminics has lead some workers to believe the etiology to be of an allergic reaction to a foreign protein.

Finch<sup>11</sup> believes that the allergic reaction is due to the secretion of the corpus luteum of pregnancy. And that nausea and vomiting exists as long as the gland is active and diminishes with the diminuation of the gland. The causative agent is thought to be an unidentified hormone. He has been able to desensitize patients with progestin (natural extract in oil), alleviating the

patients symptoms. And with intradermal tests of hormonal extract he has been able to predict those patients that may be prone to become nauseated with pregnancy.

In another approach, Finch<sup>15</sup> was able to induce nausea-vomiting in patients by the administration of synthetic estrogens, (diethylstilbesterol and hexesterol). Following artificially induced symptoms the patient was relieved with antihistaminic treatment. In 29 cases of nausea-vomiting of pregnancy treated with Benadryl and/or Histadyl, 27 were relieved. He concluded that an unidentified hormone, definately not progesterone, from the gravid corpus luteum had induced the nausea and vomiting and that it can be easily treated on an allergic basis.

Dougray<sup>16</sup> hypothesizes that the allergic reaction is from an albumin of ovo-placental origin. The products, peptone, guanidine, and histamine are believed to be liberated in the placenta blood stream by the trophoblast. In his series of 94 cases treated with 25 mg. tablets of Phenergan three times a day, 78 were cured, 4 were improved and 12 failed to respond to the therapy. For side effects of drowsiness 5 mg. of amphetamine sulfate was used successfully.

Cartwright<sup>17</sup> in his study of the antihistaminic Dramamine came to a poor statistical conclusion concerning the benefit of the drug in nausea-vomiting of pregnancy. It is interesting to note that the use of Dramamine in pregnant patients was first

instituted by Navy personnel moving their families across from coast to coast. Previously, it had been accidentally discovered aboard ship to improve motion sickness in seamen who were being treated for allergic conditions. The precise method of action of Dramamine is obscure. In dogs having their vomiting center stimulated with morphine the antiemetic factor of Dramamine was not effective. In Cartwright's series of cases, controls with placebos resembling those of Dramamine were used. In one series Dramamine was first given and later placebos were substituted without the patients knowledge. The patients were started on therapy between the 6-10th week. In half of the cases in which a placebo was administered, relief from symptoms were noted, but the rate and degree of relief was notably greater with Dramamine. Interesting enough, side effects of Dramamine were noted with placebos, after they were substituted for Dramamine. Partial to total relief was obtained in 66% of the patients with side effects noted in 1/3 of them. To the clinician then, the effectiveness of the drug is beneficial in enough cases to warrant its use, even though the value may not be due to its chemical properties.

### III. Nutritional

The deficiency of vitamins has been thought for some time to be the cause of nausea-vomiting of pregnancy, particularly B and C. In the Orient where the diet consists mainly of rice with very little vitamins, beriberi is recognized as a complication of pregnancy. McGoogan<sup>18</sup> in his study of polyneuritis found that the



symptoms of beriberi were similiar to those of polyneuritis of pregnancy and that they develop early in pregnancy in the majority of cases. He noted that pernicious vomiting preceded the later, more severe symptoms. He postulated that the vitamin deficiency is due to the lack of food intake, failure of the retention of food and/or the administration of glucose solution. These conditions may be notably present in a prolonged illness, febrile condition, and pregnancy. In his review of 145 cases, he found that severe pernicious vomiting of pregnancy may result from vitamin B<sub>1</sub> deficiency. He believes that vitamin B<sub>1</sub> should be doubled (from 250 u. to 500 u.) in a pregnant diet and further increased in lactation. And in nausea-vomiting thiamin chloride should be given in doses of 1000 u. orally with adequate amounts of B complex. If it is not tolerated orally the intramuscular route may be used. No particular complications have been noted of large doses. Therapeutic abortion is contra indicated under any circumstances because of the increased mortality rate. The effect of vitamin deficiency on the fetus in utero remains to be investigated.

Weinstein and his co-workers<sup>19</sup> in a series of 78 cases have found 85% relieved from nausea-vomiting with 10-20 mg. tablets of pyridoxine hydrachloride, three to four times a day. In some cases 2500 mg. was given until the patient experienced considerable relief. But in the majority of cases the response was prompt, usually within 48 hours. No side effects were noted. Sedation

and dietary supervision were not neglected.

Hart and McConnell<sup>20</sup> in a series of 100 cases divided their therapy so that 43 patients received pyridoxine hydrachloride, 66 received combined thiamin and pyridoxine. In the first group 50% were completely relieved, 25% partially relieved. In the second series, 75% were relieved, 16% partially relieved. A notably higher incidence of relief was found to occur in primigravidas as compared with multigravidas. Six cases were classified as pernicious emesis, three primigravidas—three multigravidas. All primigravidas were relieved, but only one multigravida was relieved.

Jones<sup>21</sup> in his study of polyneuritis associated with nausea-vomiting of pregnancy, believes that not much improvement can be expected in advanced cases. He stated that involuntary micturition and defecation must be taken as signs of irreparability. And in any instance interruption of pregnancy may hasten the death of the patient.

Watt<sup>22</sup> believes that one should maintain conservative management even after no relief has been obtained in 24 hours for a better over all mortality rate. His treatment consists of isolation, sedation, hydration and high vitamiation. He further limits the intake of protein and fats to eliminate the strain on the liver and kidneys and to prevent acidosis. To eliminate the gastric motility, he places a duodenal tube down and administers fluids high in carbohydrate.

Some workers are of an opinion that a deficiency in carbohydrate reserves may be a factor in nausea-vomiting of pregnancy. Titus<sup>23</sup> believes the depletion is from increased fetal requirements and the low carbohydrate intake of the mother to stay thin. In forty cases of nausea-vomiting, the fasting blood sugars were noted to be low normals of 80-100mg %. It is possible in hyperemesis gravidarum for the blood sugar to be as low as 28mg % without hypoglycemic convulsions because it usually is a relative slow process of long duration. Severe hyperemesis gravidarum may show convulsions comparable to those seen in eclampsia, but in eclampsia the convulsion is due to sudden hypoglycemic reaction. Thus, his theory of low carbohydrate reserve correlates the etiology of toxicosis occurring in early with that of late pregnancy.

Dieckmann<sup>24</sup> believes the period of morning sickness corresponds to the time of deep implantation of the ovum to the differentiation of the placenta. In this same period, the relative rate of growth is greatest. The nutrition for the ovum during this period must come from the surrounding serum of the endometrium. Fats are not available to the embryo in the endometrium. Amino acids require fixing at the fetal side before they can be used. Carbohydrates are available in the serum and are able to pass by osmosis to the embryo. The utilization of only carbohydrates by the embryo requires a large reserve of such by the maternal organ. Thus protein and fat destruction takes place to produce carbohydrate. Until the placenta is differentiated there is a negative

nitrogen balance of the mother as well as acidosis and ketone bodies in the urine. The therapy therefore follows much the same regime with adequate amounts of glucose solution intravenous. Glucose is better utilized by the patient with insulin if over 100 gm. is expected to be given. The general rules of therapy are: initial fasting to rest the stomach, sedation, saturation with glucose and electrolytes in water intravenously and early progressive use of a general diet.

#### IV. Reflex

Some of the earliest etiological theories for the nausea-vomiting of pregnancy were based on the reflex stimulation of the vomiting center. It was thought that "the pelvic condition associated with the retroversion of the pregnant uterus<sup>25</sup> was the initiating factor. Consequently, pessaries were used in the treatment with some success.

Weber and Fetchko<sup>26</sup> believe that the increased gastric motility and secretion plays a role in exciting reflex nausea-vomiting of pregnancy. They selected Banthine for their treatment because of its pronounced parasympathetic and sympathetic ganglion block resulting in reduced gastric secretion and gastro-intestinal motility. They report 74% of 50 patients treated with Banthine, markedly improved.

Anspaugh<sup>27</sup> believes that the hunger reflex alone can produce nausea. In his treatment with dexidrine sulfate he classifies the patient cured if relieved in ten days and no recurrences. In a

series of 165 patients, 148 were completely relieved with 5 mg. tablets of dexidrine before breakfast, dinner, and mid-afternoon. In 13 cases however relief was noted with placebos, so actually only 82 % were cured. The side effects of nervousness was controlled with barbiturates. The effectiveness is said to be due to elevating the mood and curbing the hunger sensation that produces nausea-vomiting.

#### V. Toxic

Merkel<sup>28</sup> postulates that the nausea-vomiting of pregnancy depends on the passage of a "vomiting factor" from the fetal circulation to the expectant mother. He believes that the abnormality is due to an increased capillary permeability of the placenta, particularly the chorionic villi. The increased permeability allows the passage of the vomiting factor from the fetal circulation to the maternal circulation. His treatment consisted of 5 mg. of mensione besulfite (synthetic vitamin K) and 25 mg. ascorbic acid given orally four times per day. In his series of 70 cases, approximately 50% primigravidas-50% multigravidas, 64 were found to have complete remission in 72 hours, 3 relieved of vomiting but remained nauseated and 3 not relieved. In two advanced cases and in pseudocyesis dramatic relief were noted. It was noted that with ascorbic acid alone there was no benefit, but with vitamin K alone 50% of the cases were relieved. In all cases prothrombin and bleeding times were done before and after therapy was initiated and they were noted to remain normal.

It was found that the toxicity of vitamin K was relative low even in doses ten times the therapeutic levels. It was found also, that spontaneous relief was noted to occur in some cases naturally.

Fitzpatrick and his co-workers<sup>29</sup> believe that the "toxin" causing nausea-vomiting in pregnancy is actually absorbed from the gastro-intestinal tract and that the syndrome is a manifestation of histamine intoxication. The toxic substances are breakdown products of bacteria as a result of hypochlorohydrin and delayed emptying time of the stomach. The normal 50-130 min emptying time of the stomach may be prolonged to as much as 5 hours. This is thought to occur because of the change in position, the atony of the musculature and the diminished motility of the stomach during pregnancy. The breakdown products were found to be histamine, tyramine, putrescine and cadaverine. They found that these products induced vomiting when applied to the cerebral center. They also found the enzyme histaminase in the sera of pregnant mothers.

Their treatment consisted of an intestinal absorbent of a polyamine anion exchange resin consisting of synthetic sodium aluminum silicate and magnesium aluminum silicate. "Resion" was found to be ideal as an intestinal absorbent for it inhibits lysozyme, removes the toxic amines, absorbs bacterial metabolites and the essential amino acids, vitamins and minerals are not removed. This product was given in 8cc dosage, four times per day,

on arising, mid-morning, mid-afternoon and at bed time. In their series of 51 patients most were relieved in 48 hours. The medication was continued 2-3 weeks thereafter. The poorest result was found to occur in a group of wives from an Army post. This was believed to be due to the psyche overlay due to their mode of living. No control group was used. They further recommended to their patients: to eat more often in lesser amounts because of the delayed emptying time of the stomach and to eat low fat diets because fats are poorly metabolized during pregnancy. For the anxious patient sedation was prescribed.

#### VI. Psychological

In each of the succeeding theories of nausea-vomiting presented, reservation is made for the psychogenic aspect of the entity. With the multiplicity of theories, one is easily prone to label the disease of psychosomatic origin and treat the patient on this basis. When the proof of an etiology remains obscure and unrelated therapies produce good statistical results, one cannot eliminate the patient's psyche as a factor in the causation of the disease.

Robertson<sup>30</sup> in his study of nausea-vomiting of pregnancy believed it due to a "rejection dyspepsia" syndrome. He believed the "dyspepsia" was due to a combination of three predisposing factors. The first factor was previous dyspepsia before marriage. This is the inherent vomiting threshold of the patient and remains

fixed throughout her life. The second factor he ascribes to mother attachment acquired by the patient during adolescence. This is the feeling of shame that the patient has because she is pregnant. This factor tends to decrease as the patient remains detached from her mother. The third factor is associated with disturbed sexual function during pregnancy due to the loss of sex interest and/or the increase in demands of her spouse. This is acquired after marriage as an adult and varies with each pregnancy. The feelings of shame towards her mother and sense of duty to the increased demands of her spouse become manifested by a feeling of disgust associated with nausea and vomiting. The treatment suggested is therefore isolation from the environmental factors of her husband and mother. In a series of series of cases with a control group he was able to demonstrate statistically that these factors do play a role in the dyspepsia of pregnancy. In successive pregnancies, the same factors modified by time and husband behavior were noted to be present.

Bernstein<sup>31</sup> in his series of 20 cases half with symptoms and half without, noted no essential difference in attitudes of the patients towards important aspects of their lives (pregnancies, delivery, family, children or spouse). Whether pregnancy was planned or not seemed to have no bearing on the nausea and vomiting. He explained the vomiting of the one group and not of the other on their different vomiting threshold and on the handling of their feeling of rejection through other channels of symptoms



or acting out behavior. He concluded that the emotional factor, the feeling of rejection, causing nausea and vomiting can be effectively treated by suggestion. And that the labeling of the patients as neurotics is unjust for the neurosis is transitory.

Harvey and Sherfey<sup>32</sup> in their psychiatric interview of 20 patients with nausea and vomiting found that their life histories revealed a ready pattern to gastro-intestinal disturbance in response to stress. All presented serious disorders of sexual life with frigidity as its consistent expression. Also, immaturity of personality was notably common among the group. They found through the Rorschach test that the guilt towards the mother was the most important psychodynamic factor in their nausea-vomiting during this time of increased anxiety and tension.

Associated with the treatment by suggestion and isolation, Kroger and DeLee<sup>33</sup> used hypnosis on 21 patients and found that 19 were completely relieved. Most of the patients were hospitalized and were refractory to other types of therapy. One case was so severe that therapeutic abortion was indicated. The therapy of hypnotic suggestion was thought to raise the vomiting threshold of the patient and/or establish a block in the nervous pathway between the gastro-intestinal tract and the vomiting center.

Most authors agree that psychotherapy in some form or other plays a major role in the treatment of nausea-vomiting of pregnancy. But Page<sup>71</sup> believes that psychotherapy in any form is too slow for the present pregnancy. But that it is more significant in the

prevention of pernicious emesis in the next pregnancy of the patient and in the pregnancies of the patient's daughters.

Without a proven etiology of the nausea-vomiting occurring in pregnancy the present trend is to treat the entity symptomatically with medical management. Each patient is individualized and treated according to her presenting symptoms. Prognosis is usually good and only in a very small percentage of cases are radical measures contemplated. According to Page<sup>7</sup>, the presence of scleral jaundice with associated coffee ground vomiting, tachycardia, retinal hemorrhages and weight loss despite treatment is the one indication for the interruption of the pregnancy by a therapeutic abortion. But if generalized jaundice is present, the interruption is contra-indicated because the condition has become irreversible.

Barnes<sup>3</sup> and others<sup>13,22,24</sup> similarly agree on the medical management for the ambulatory patient with mild nausea-vomiting. In every case a thorough history, physical and psychological evaluation is done to eliminate other factors that cause nausea-vomiting in the adult female. They believe that a diet of four to five small dry meals with fluids taken between meals is important. Further therapy consists of intravenous vitamins, particularly the B complex and C, given each day for five days or more. For sedation, phenobarbital is given three to four times per day. The elimination is considered and when indicated an enema is given as often as every other day. Barnes also uses

the antihistaminic Thorazine routinely as an adjunct in his medical therapy to control the vomiting in both the mild and severe forms.

For the patients whose symptoms are becoming progressively worse on ambulatory care, isolation is required. The patient is confined to a hospital bed in a darkened, quiet room with no relatives or visitors allowed. The patient is heavily sedated until gastric equilibrium is maintained. The stomach is initially rested and nothing is given by mouth for the first 12-24 hours, after which dry meals and progressive sips of water are given as tolerated. In the first 24 hours, 3000 cc of fluids are given intravenously partially in glucose and in saline solution with vitamins being added. In the second 24 hours, the same is given and increased if the urinary output is below 1500 cc, with 500 cc of a protein solution being added. Enemas are given when indicated. Psychotherapy in the form of a careful explanation of the nausea-vomiting and reassurance to the patient is added.

The recent use of Thorazine has been investigated by other workers. Moyer<sup>34</sup> treated 78 patients and obtained complete relief in 55 cases. Only four cases were complete failures. Benaron and associates<sup>35</sup> found the complete to almost complete cessation of symptoms in approximately 1-5 days without any apparent harmful effect on the mother or child.

The appearance of obstructive type jaundice in a small number of patients receiving Thorazine has discouraged its

routine use in the mild form of nausea-vomiting of pregnancy. Its use at present is reserved for the more persistent form which is unrelieved by other therapy.

Some recent antiemetic preparations with and without pyridoxine HCl (Bonamine and Bonadoxin), have been used in the treatment of mild nausea-vomiting of pregnancy with some success. Pyridoxine HCl is believed to help restore normal carbohydrate metabolism and to improve the hepatic function by the formation of choline. It is also essential for the transamination of many of the amino acids. The antiemetic property is due to meclizine HCl present in the preparations. Meclizine HCl is a piperazine derivative and exerts its antiemetic action probably at the vomiting center. It may also act peripherally by an anticholinergic effect at the gastric and other levels. The usual dosage is one tablet at bedtime. The side effect of drowsiness is minimized by adjusting the dosage. Single trials have proven beneficial in some instances, but no statistical clinical evidence is available for a large number of cases.

#### Conclusion

The symptom of nausea-vomiting is one of the most frequent complaint of the pregnant mother. There is no adequate evidence presented in this paper for a true etiology of the entity. The unrelated theories and associated treatments noted in this review indicates that the subject remains to be investigated further.

The occurrence of the disease more often in a modern civili-

zation indicates that it may be associated with the increased stress of our environment. The absence of symptoms in other pregnant mammals is perhaps explained on the basis of diminished stress in their habitat. The majority of workers investigated recognize stress as a factor in the perpetuation of the nausea-vomiting cycle once it has been established, but few believe it to be the initiating factor.

The reaction to stress varies with different organisms and once established it easily becomes accentuated in various symptoms such as the nausea-vomiting in pregnancy. This best explains the occurrence of symptoms in some women and not in others. The stress reaction is manifested by the sympathetic and parasympathetic nervous systems and associated adrenal function. The apparent time for the symptoms is either on arising when the stress of the new day's activities are superimposed on the resting state of the individual or in the evening when the patient is fatigued and the stress of the evening household duties over balance the nausea-vomiting threshold. In some instances the return of the spouse psychologically initiates the rejection dyspepsia.

The known cessation of symptoms when the fetus succumbs in utero and the recorded instances of vomiting before the time of the first missed period are strong indications that the unknown initiating factor of vomiting is of an organic basis rather than psychological. It is the author's suspicion that the initiating

factor when isolated, will be on a true hormonal basis with predisposing factors of stress and avitaminosis. There are essentially four periods in the life of the female when her endocrine system undergoes delicate balancing, at puberty, post conception, post partum, and post menapausal. It is at these times that she may easily show outward symptoms of the inward change. Perhaps a correlation of the symptoms at each of these periods in a series of post menapausal patients would be a rewarding project.

The known cessation of symptoms when the fetus succumbs in utero also indicates that therapeutic abortion, although rarely indicated, does have a place in the treatment of severe pernicious vomiting. From the literature reviewed for this paper and from personal communication with some of the local obstetricians the subject of therapeutic abortion in severe hyperemesis gravidarium was treated with considerable hesitancy and vagueness. The criteria for the interruption of the pregnancy was found to be quite variable. In most instances therapeutic abortions seemed to be contra-indicated even if the symptoms were progressing with so called conservative medical management. Yet, each year maternal deaths are recorded that are attributed to pernicious vomiting of pregnancy, that could perhaps be saved with a therapeutic abortion done before it was irreversible. This is unfortunate in present day therapeutic knowledge. The criteria for the interruption of the pregnancy should be established by a panel

of obstetricians with clinical experience in the subject.

It is the author's conclusion from this review that therapeutic abortions should be taken under consideration in progressive pernicious vomiting of pregnancy when it fails to respond to other therapy and accompanied by the presence of scleral jaundice, persistent weight loss, coffee ground vomitus and retinal hemorrhages. With the before mentioned present, consultation should be asked of an internist, a psychiatrist and one other obstetrician, all being in agreement before the abortion is truly indicated. With the adherence to these qualifications the mortality rate from hyperemesis gravidarum should be reduced.

The therapy for the entity should be on a psychological, antiemetic and nutritional basis to adequately treat and to prevent the progression of symptoms. In the mild ambulatory care of the patient frequent dry meals with fluids between meals and intravenous vitamins, particularly the B complex group and C, is quite important. The patient should be evaluated psychologically at the onset of the disease. She should be acquainted with the symptoms and assured of a good prognosis. The use of one of the recent antiemetic agents greatly assists in the controlling the vomiting centrally. The routine use of Thorazine however is contra-indicated because of the obstructive type jaundice noted in a few cases.

In the more severe form of nausea-vomiting the patient is

required to be hospitalized. The patient should be given complete reassurance by the attending physician and a psychiatrist, but extensive psychotherapy should not be attempted. The elimination of the environmental factors by isolation is the most important aspect of the psychological therapy in this stage of the entity. The stomach should be initially rested for the first 24 hours. The importance of fluid and electrolyte therapy with proper attention to the urine output can be easily understood. A protein solution and vitamins, C and B complex, particularly pyridoxine HCl should be added. The patient should be heavily sedated until gastric equilibrium is maintained. After the first 24 hours, the patient should be started on frequent dry meals and progressive sips of water as tolerated. Enemas should be given as indicated. If the patient is unrelieved and persistent vomiting continues into the second day, Thorazine should be given to eliminate the vomiting centrally as an adjunct to the therapy of hydration, isolation, sedation and high vitamination. With the further progression of symptoms a therapeutic interruption should be considered when the necessary indications and qualifications are present.

The major emphasis on the use of B complex vitamins, particularly pyridoxine HCl in the treatment of nausea-vomiting of pregnancy is not without merit. It is well known that the symptoms of nausea-vomiting in pregnancy are similar to those of avitaminosis, particularly beriberi and that a number of



patients have improved with the use of pyridoxine. Recently it has been combined with an antiemetic agent and used quite successfully.

The action of pyridoxine is known to improve specifically the hepatic function by the formation of choline. In the literature reviewed for this paper no investigation has been made into the possibility of using choline and/or other lipotropic agents per se in the treatment of nausea-vomiting of pregnancy. Perhaps an investigation of lipotropic agents would prove them to be an additional therapeutic entity especially in the more resistant forms.

#### Summary

This paper is an investigative review of the literature on the subject of nausea-vomiting of pregnancy and the severe form, hyperemesis gravidarum. The symptoms were found to vary from simple nausea in the morning or evening, to persistent vomiting with its resultant disturbance in the physio-metabolic mechanism. It was found to occur in 50% or more of all pregnancies, some beginning as early as the second week of gestation and rarely, (mild forms), extending into the sixth week of the post partum period. It is known to be conspicuously absent when the fetus succumbs in utero.

The entity more often occurs in women of the Western civilization and/or influence. This is thought to be due to the increased stress of our mode of living.

In the investigation, the disease was found to be truly a disease of theories. In the past, the treatment was based on the theoretical etiological factor. Six main etiological theories and their associated treatments are reviewed, hormonal, allergic, nutritional, reflex, toxic and psychological.

Without a proven etiology of the entity, the present trend is to individualize the patients and treat symptomatically with psychotherapy, fluid and electrolyte therapy, sedation and high vitamination. Recent antiemetic preparations have been used to treat the disease at the vomiting center.

It is the author's opinion that the initiating factor when isolated will be a true hormonal substance with avitaminosis and stress as predisposing and perpetuating factors. Treatment therefore should be on a psychological, nutritional and antiemetic basis, with therapeutic abortion reserved for the patient in severe distress.

The criteria for the interruption of the pregnant patient with hyperemesis gravidarum was found to be quite variable from this review. This unfortunate situation needs to be rectified by a panel of qualified obstetricians.

The use of pyridoxine HCl in the treatment of the symptoms was emphasized. The action of pyridoxine is known to improve the hepatic function by the formation of choline. Possibly an investigation into the use of choline and/or other lipotropic agents in the treatment of nausea-vomiting of pregnancy would prove it to be an additional therapeutic entity.

I wish to acknowledge my sincere appreciation to Dr. William C. Boelter M.D., for his personal guidance and consideration in the investigation and correlation of the subject.

I wish also to dedicate this thesis to my wife whose symptoms in the first trimester of pregnancy initiated my personal interest in this subject.

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