PERNICIOUS VOMITING OF PREGNANCY.

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General History. Slight degrees of nausea and vomiting in the early months of pregnancy have probably occurred from time immemorial, but, according to Guéniot and Anquétin, the more severe forms of the affection were first described by Oribasius and Paul of Ægina, who, however, appeared to have no idea that it might end fatally. Similar views were held by Guillemeau, Mauriceau and the obstetricians of the seventeenth and the greater part of the eighteenth centuries. Indeed, Dionis and many others considered vomiting a favorable sign, and thought that women subject to it were usually exempt from serious complications at the time of labor, or, as Rigby expressed it, nearly one hundred and fifty years later, "a sick pregnancy is a safe one."

In 1789 Vaughan reported a case which he considered was saved from a fatal termination only by the employment of rectal feeding, so that it would seem that it was not until the latter part of the eighteenth century that it began to be recognized that vomiting of pregnancy might occasionally be so persistent as to lead to death from inanition.

As far as I can learn, Simmons, in 1813, was the first to induce abortion for its relief, an example which was soon followed by Davis, Chailly-Honoré, Churchill and others. The justifiability of the procedure, however, was first brought prominently to the attention of the profession by a

discussion before the Academy of Medicine of Paris, in March, 1852, upon which occasion Dubois and Danyau contended that the induction of abortion was not only justifiable, but urgently demanded in severe cases; while Cazeaux held that interference was unnecessary, and even hastened death in some instances.

Dubois supported his contention by his own experience in 14 severe cases, 10 of which died without operation, while abortion was induced in the other 4. Only one of the latter recovered; in two the vomiting persisted until death; while the fourth patient died from infection. Notwithstanding this apparently poor result, which he held was due to the fact that interference had been delayed so long that death was practically inevitable, no matter what line of treatment was adopted, Dubois contended that abortion was the rational treatment, and should be induced before the patient's condition became absolutely hopeless, and was urgently indicated under the following conditions: 1. When the vomiting is incessant. 2. When emaciation is rapid and the patient so weak as to be obliged to keep her bed. 3. When she faints upon the slightest exertion. 4. When pronounced alterations occur in her features. 5. When there is marked and continuous fever and an excessive acidity of the breath, which cannot be relieved by treatment.

The next important contribution to the subject was the monograph of Guéniot, in 1863, in which the author collected from the literature 118 cases of pernicious vomiting, with 46 deaths, and carefully analyzed them from the point of view of etiology and treatment. Concerning the former, his conclusions were not very satisfactory, but on the other hand he taught that the induction of abortion was the treatment par excellence in severe cases, and should be resorted to as soon as medicinal treatment proved unavailing and the patient was perceptibly losing ground.

The work of Dubois and Guéniot greatly stimulated the

interest in the subject, concerning which an immense literature gradually developed; but unfortunately the contradictory statements of the various writers simply served to accentuate the fact that their knowledge concerning the etiology of the condition was very fragmentary and imperfect; while the manifold recommendations as to treatment indicated that they either were practically worthless, or that several types of vomiting, with varying clinical histories, had been grouped together in a single category.

OBJECT OF ARTICLE. In this paper it is my object to bring together the more important contributions to the literature of the subject, and, guided by my own experience, to set up certain well-defined types of the disease, in the hope of establishing more satisfactorily its etiology and laying down more definite rules for guidance in its treatment.

Leaving out of consideration all cases in which the vomiting is dependent upon conditions which have nothing to do with pregnancy, and limiting our attention only to those cases in which it is apparently due solely to the pregnancy itself or to some lesion of the generative tract—in other words, adopting the distinction of Matthews Duncan between the vomiting in and the vomiting of pregnancy—I hope to be able to show that the evidence at present available seems to justify the differentiation of three distinct types of vomiting of pregnancy—namely, reflex, neurotic, and toxemic—each of which is dependent upon different etiologic factors and demands especial methods of treatment.

FREQUENCY. It is difficult to give definite figures as to the frequency of serious vomiting of pregnancy, since even the statements concerning the incidence of the ordinary morning sickness vary greatly. Thus, Gardner states that the latter occurs in only 15 per cent. of pregnant women, while Giles, Gerst, and Horwitz noted it in 47.8, 66.66, and 84 per cent. of their cases, respectively. In my private practice it was present in slightly more than one-half of the

patients. According to Pick and Lwow, the pernicious type occurs about once in 1000 cases; but as their conclusions were drawn entirely from hospital experience, they do not necessarily give a correct idea as to its incidence in private practice, in which it would seem to be much more frequent. This is clearly shown by my own experience at the Johns Hopkins Hospital, where only 2 out of 4500 clinical cases suffered from serious vomiting of pregnancy; while I have seen 10 cases during the past two years in my private and consultation practice.

It would also seem, as Horwitz first pointed out, that there is a marked variation in its incidence in different countries, as it occurs much more frequently in France, England, and America than in Germany and Russia; a fact which may possibly be explained by the greater frequency of neurotic conditions among the inhabitants of the former countries. Indeed, many competent German authorities, such as Hohl, Lomer, Frank, and Strassmann, have stated that they have never seen a case of vomiting of pregnancy end fatally; while in this country there is hardly a general practitioner of extensive experience who has not had one or more cases in his own practice. It is likewise interesting to recall the fact that Anquétin stated that the condition apparently became more frequent in France after the abandonment of universal venesection.

ETIOLOGY. 1. *Reflex Vomiting.* This variety of vomiting may be due to the presence of abnormalities of the generative tract or ovum, which existed prior to the onset of pregnancy, or are coincident with it. Among such conditions may be mentioned: (*a*) Abnormalities of the uterus, particularly displacements. (*b*) Certain cases of endometritis. (*c*) Ovarian tumors. (*d*) Abnormalities of the ovum, such as hydramnios, hydatidiform mole, and certain cases of twin pregnancy.

The reflex character of the vomiting of pregnancy was

recognized at an early period, and Mauriceau attributed it to a sympathy between the uterus and the stomach, as he believed that distinct nervous connections existed between the two organs, by which abnormal stimuli originating in the diseased uterus were readily transmitted to the stomach.

That uterine displacements may occasionally be the cause of the condition is clearly demonstrated by the fact that the vomiting sometimes ceases immediately upon the replacement of a retroflexed uterus. This conception of the etiology of the condition was particularly elaborated by Graily Hewitt, who published extensive monographs upon the subject in 1871, 1885, and 1888, in which he clearly demonstrated that certain cases at least were due to displacements of the uterus and could be cured by restoring the organ to its normal position. At the same time he probably erred when he concluded that anteflexion had a much more deleterious influence than retroflexion.

Owing to his extensive contributions, Hewitt is generally regarded as the father of this theory, although several writers who preceded him held similar, but not so pronounced, views; among whom may be mentioned Busch and Moser, Stolz, Brian-Moreau, Ulrich and others. Following the publication of Hewitt's last monograph, his view has never lacked supporters, as is evidenced by the teachings of Guéniot, in 1889, and Lwow, in 1900.

From my own experience, I can state without hesitation that a retroflexed uterus may occasionally be the exciting cause of the condition, and in such cases vomiting ceases immediately after its replacement. At the same time it must be admitted that this is only exceptionally the case, since in the vast majority of patients with retroflexion of the pregnant uterus, even when symptoms of incarceration are present, vomiting is lacking, or at least no more severe than in women with perfectly normal genitalia.

Dance, in 1827, in one of the earliest autopsies performed

upon a woman dying from hyperemesis, noted an abnormal thinness of the uterine wall; and ever since then occasional advocates have been found for the belief that the vomiting is due to undue distention of the uterus, a view which was held in part by Schroeder. While it cannot be denied that such an explanation may occasionally hold good, as is apparently demonstrated in some cases of hydramnios and twin pregnancy, it must, nevertheless, be admitted that it is not of universal application, and even in those cases in which it appears most probable conclusive evidence cannot be adduced in its favor.

Horwitz in 1883 pointed out that in certain cases the vomiting appeared to be due to imflammatory conditions of the muscular wall of the uterus, which in several of his cases was associated with peritoneal involvement. Whether these lesions were really the cause of the condition, or should be regarded merely as accidental complications, cannot be decided, but the evidence at present available makes the latter probable. Tuszkai, in 1895, rehabilitated the theory of peritoneal irritation, with only partial success. At the same time there can be no doubt that abnormal conditions of the uterus certainly favor the occurrence of vomiting, as was clearly shown in one of Davis' cases, in which severe vomiting accompanied an intramural pregnancy, and ceased immediately after its removal by operation.

The uterine origin of vomiting was likewise advocated by Martin in 1904, who stated that in the majority of cases the condition should be attributed to hyperemia of the uterus and its impaction in the pelvic cavity; while Evans, of Montreal, taught that the ordinary morning sickness was probably connected with the rhythmical contractions of the organ.

In 1849 J. H. Bennett, in his work on inflammation of the uterus, directed attention to the part which he believed was played by inflammatory conditions of the cervix in the production of the vomiting of pregnancy, and ever since then

this view has had numerous adherents; and he himself, in 1875, stated that more extended experience had only served to confirm his original views.

A little later Copeman invoked the influence of the cervix in another manner, and assumed that the vomiting was due to irritation resulting from its abnormal rigidity, particularly in the region of the internal os, and held that it could be cured by dilating the cervix. This view and the procedure dependent upon it was accepted by Rosenthal and many others, and enjoyed considerable vogue for some years, but has gradually fallen into disrepute; though, even as late as 1896, Kehrer reported a case which he considered demonstrated the correctness of such teachings. Cervical catarrh has likewise been considered to play an important etiological part, and Lwow stated that 75 per cent. of the women suffering from vomiting of pregnancy presented this abnormality.

As far as I am able to ascertain, the causal relation between abnormalities of the cervix and the severe forms of vomiting of pregnancy has not been conclusively demonstrated, nor do I think that it will be in the future; as it seems to me that a palpably accidental condition has been erroneously considered as causal. This contention is well exemplified by a case of Davis, in which several small cysts in the cervix were considered as the etiological factor, while autopsy showed marked lesions in the liver and kidneys; and still more forcibly by a case of Lang, in which inflammation of the cervix was considered the essential factor, while autopsy demonstrated the presence of acute yellow atrophy of the liver.

Ever since 1827, when Dance, at autopsy upon two patients dying from vomiting of pregnancy, found suppurative changes in the decidua, it has been considered that endometritis may play an important part in the production of the condition, a view which in modern times has been particularly insisted upon by Veit, Jaffé, Jaggard, Flaischlen,

Goldspohn, and many others. Nevertheless, it does not appear that its advocates have adduced conclusive evidence in its support, and it seems probable that endometritis, when it occurs, should generally be regarded as an accidental complication, rather than an important etiological factor. At the same time it must be admitted that it may tend to exaggerate what might otherwise be only a minor complaint.

There can be no doubt that in exceptional instances the presence of tumors of the ovaries may accentuate or even cause serious vomiting. Such a connection was clearly demonstrated in a case of Krassowsky's, in which very severe vomiting ceased immediately after the removal of a small ovarian tumor; and in one of my own cases a similar result followed the removal of a small fibromyoma of the ovary.

Clinical observation apparently shows that both hydramnios and twin pregnancy predispose to excessive vomiting, though whether this is the result of the mere overdistention of the uterus or whether it is associated with some toxemic condition has not yet been demonstrated.

Hydatidiform mole likewise has a similar effect, and Bué has reported three cases in which the vomiting ceased immediately after the evacuation of the mole, and has collected a large number of similar cases from the literature. Likewise, in one of my cases the spontaneous expulsion of the mole occurred just in time to prevent the induction of abortion for the relief of vomiting. But in this condition, as well as in twin pregnancy and hydramnios, the exact interpretation of the effect of the abnormality is not easy; as it is possible, on the one hand, that the vomiting may be merely the result of overdistention of the uterus, while on the other it may quite as readily be attributed to a toxemic condition, which may be due to abnormal metabolism on the part of the mother or fetus, or to the formation of syncytiotoxins resulting from the presence of unusually large amounts of

fetal elements in the maternal blood. The latter conception has been particularly elaborated by Veit and Behm, and will be considered in detail under toxemic vomiting.

Chorioepithelioma has likewise been invoked as a cause of the condition by Davis and Harris, although in their case it is questionable whether the vomiting was due to the presence of fetal tissues in the growth itself, or merely to the mechanical action of the cerebral metastases which were found at autopsy.

2. *Neurotic Vomiting.* Although the effect of pregnancy upon the mental, moral, and nervous equilibrium had long been recognized, and Anquétin, Tisserand, Duncan, Rosenthal, Ahlfeld and others had pointed out that many cases of severe vomiting were neurotic or hysteric in origin, it was, nevertheless, not until Kaltenbach read his paper upon the subject before the Berlin Obstetrical Society in 1890 that general attention was directed to this phase of the subject.

On that occasion he pointed out the necessity for narrowing the conception of the pernicious vomiting of pregnancy, and confining it strictly to those cases in which there was no disease of other organs or of the generative tract to which it might be attributed. At the same time he emphasized the great paucity of positive autopsy findings, and commented upon the contradictory character of the lesions noted.

In this restricted sense he held that the severe cases of hyperemesis were the result of an abnormal condition of the nervous system, by which the reflex irritability was heightened and the reflex control lessened. This being the case, it could readily be understood how the irritation might be increased by diseased conditions on the part of the generative tract on the one hand or of the stomach on the other. Accordingly he concluded that the vast majority of cases of vomiting of pregnancy were due to a neurosis, more or less allied to hysteria; although he was compelled to admit that many of

the patients presented no evident manifestations of the latter condition, and therefore assumed that in many instances a hysteria, which had previously been larval, might become manifest under the influence of pregnancy. In view of its neurotic nature, he insisted upon the value of suggestion and the rest cure in the treatment of the condition, and held that if they were intelligently carried out, the field for the induction of abortion would be greatly limited, if not entirely obliterated.

This paper immediately gave rise to considerable discussion, and a number of authors, among whom may be mentioned Ahlfeld, Chazan, Rosenfeld and others, claimed that they had antedated Kaltenbach's views by a number of years. As has already been indicated, this is undoubtedly true; but, nevertheless, it would seem that the credit rightly belongs to Kaltenbach, since he was the first to insist upon the importance of neurotic influences in their entirety. At the same time it is interesting to note that two years later Mettler, of Chicago, enunciated almost identical views, apparently without knowledge of Kaltenbach's work.

The neurotic origin of the condition was enthusiastically accepted by a number of writers, among whom may be mentioned Luez, Klein, and Graefe. Klein published histories of a number of cases and insisted upon the curative value of an absolute rest cure and attached less importance to the action of suggestion. He stated that the vast majority of cases could be promptly cured by putting the patient to bed, keeping her absolutely quiet, prohibiting all intercourse with her family and friends, and at the same time administering small quantities of iced milk at frequent intervals, and if this were not well borne, to resort entirely to rectal feeding. If, however, such a course did not lead to the desired result within three or four days, he advocated the removal of the patient to a well-regulated hospital, where she could be placed under ideal conditions for a very

strictly conducted rest cure. Graefe expressed similar views in his original article in 1900 and reiterated them more strongly in 1904.

To anyone who has had considerable experience with this class of cases there can be no doubt that the vomiting must frequently be attributed to some neurotic condition, as is manifested by the remarkable cures which sometimes follow all sorts of unphysiologic procedures, as well as the mere threat to induce abortion, or a feigned attempt to bring it about. Only upon such an hypothesis can one explain the results obtained by Muret, Damany and others. Thus the former observed a patient who had lost forty-nine pounds in weight as the result of incessant vomiting, which ceased immediately upon a single lavage of the stomach. In Damany's case equally satisfactory results were obtained by the use of an electric battery, which was later found to be entirely out of order. Moreover, it is more than probable that the vast majority of cures following the application of leeches to the epigastrium or cervix, the dilatation of the latter by Copeman's maneuver, or the application to it of various drugs are susceptible of a similar explanation.

At the same time it should be borne in mind that it is possible that the underlying cause of the neurosis may be a mild toxemia, but at present satisfactory evidence cannot be adduced in support of such a view.

When Graefe's first paper was read before the Leipzig Obstetrical Society, in 1900, Winscheid stated in the discussion that the tendency to attribute all cases to neurasthenia or hysteria was too extreme, as he did not believe that such conditions could give rise to the extreme emaciation and cachexia which characterized the severe cases. To my mind, however, this objection does not necessarily hold good, as I have in several instances seen women, who had become markedly emaciated and were apparently dying from starvation, immediately cease vomiting after a vigorous lecture

or the threat of inducing abortion, after I had unduly magnified its dangers.

3. *Toxemic Vomiting.* According to Mauriceau, one of the earliest theories concerning the production of the vomiting of pregnancy was that it was due to the excretion by the stomach of humors resulting from the suppression of the menstrual function. As far as I have been able to ascertain, Fischl, in 1884, was the first modern writer to suggest the toxemic nature of the condition, being led to this conclusion after observing a woman who was admitted to the hospital in a torpid condition with slight fever, with the history of severe continuous vomiting, and was immediately cured by the evacuation of a densely impacted colon. As the result of his experience he classified the causes of vomiting of pregnancy as essential and symptomatic, and held that the former would become more and more rare as the cases were more carefully investigated.

The following year (1885) Jolly reported two cases of paralysis which occurred in pregnant women suffering from the vomiting of pregancy, and attributed the former condition to a neuritis, which was probably caused by the circulation of some toxic substance peculiar to pregnancy. Similar cases were soon described by Moebius, Whitfield, Desnos, Joffroy, Pinard and others, who expressed a similar belief concerning the interrelation of the two conditions, but did not adduce absolute proof as to its correctness.

In 1892 Lindemann reported the autopsy findings upon a patient of Solowieff's who died from multiple neuritis complicating hyperemesis, and found histologic signs of parenchymatous neuritis, as well as fatty degeneration and cloudy swelling of the liver and kidneys. As similar lesions were present in the organs of the fetus, he was inclined to believe that he had adduced direct proof of the toxemic nature of the condition, as the presence of the lesions in both

the mother and the fetus could be due only to the circulation of some toxic substance.

Following Lindemann, a considerable number of cases of neuritis, associated with vomiting, were reported by Eulenberg, Stembo, Mader, Kühne, Kreutzmann, Bar and others. Eulenberg gave a tabulated list of the cases occurring up to the time of his report, but no one up to the present time has advanced irrefutable proof in favor of the toxic nature of the two conditions, although each succeeding observation has rendered such an origin more probable.

Additional support in favor of the toxemic nature of the vomiting of pregnancy is afforded by its occasional association with jaundice. As early as 1879, Matthews Duncan suggested that the underlying factor in certain of the fatal cases, at least, was acute yellow atrophy of the liver, and supported his contention by autopsy in one case. This view was likewise advocated by Roughton in 1885, but obtained little if any recognition; though it is interesting to note that Lomer, in his article upon icterus in pregnancy, likewise suggested that possibly some connection existed between hepatic disturbance and the production of vomiting.

The toxemic theory was also advocated in a modified form by Holladay, who, in 1886, suggested that when the vomiting persisted after the fourth month of pregnancy it was probably due to a suppositious secretion from an abnormally persistent corpus luteum.

Following these suggestions, there was a lull in the advocacy of the toxemic nature of the condition, and it was not until the last years of the nineteenth century that other writers began to insist upon its possibility, when Allbutt and Bacon, in 1896 and 1897, respectively, expressed themselves in its favor upon purely theoretic grounds.

In 1898 Bouffe de Saint Blaise, in a long article upon the autointoxication of pregnancy, which was based in great

part upon Pinard's hepatotoxemia theory, made a tolerably clear case for eclampsia and the pre-eclamptic toxemia, but when he attempted to apply the theory to the other complications of pregnancy, the outcome was much less satisfactory; while his arguments in favor of the toxemic nature of vomiting were especially inconclusive.

With the exception of the positive autopsy findings of Lindemann, and several isolated cases of acute yellow atrophy of the liver, it was not until 1901 that Champetier de Ribes and Bouffe de Saint Blaise reported definite hepatic lesions in vomiting of pregnancy. In a communication to the Society of Gynecology, Obstetrics, and Pediatrics of Paris, they briefly described the autopsy findings in a woman dying in convulsions at the end of pregnancy, who had suffered from vomiting throughout its entire course, and reported the presence of lesions in the liver which they considered identical with those observed in eclampsia, and therefore concluded that the anatomical substratum was the same in both conditions. Unfortunately, the promised report of the microscopic examination of their specimens has not yet appeared.

Since then an abundant literature has developed concerning the toxemic nature of the condition, and four main theories have been advanced as to the source of the toxic materials giving rise to it: 1. Gastrointestinal tract. 2. The ovum and its appendages. 3. Ovarian secretion. 4. Hepatic lesions.

1. *Intestinal Origin.* The most consistent advocate of the intestinal origin of the condition is Dirmoser, who in 1901 summed up his observations in a monograph, and two years later reiterated his experience in another article. He pointed out that in women suffering from the vomiting of pregnancy examination of the urine showed an increased amount of uric acid, indoxyl, skatoxyl, aromatic sulphates, phenols, and nucleoalbumins; while the following abnormal substances

were frequently noted: acetone, diacetic acid, peptone, urobilin, etc. From these observations he concluded that one had to deal with the absorption of toxic materials derived from the decomposition of carbohydrates in the stomach and proteids in the intestinal tract, which, circulating in the blood, brought about the neurosis, which in turn caused the vomiting. Moreover, he believed that the results of treatment still further substantiated this view, in that the administration of intestinal antiseptics and the copious employment of rectal irrigation frequently led to cure, or at least to a marked improvement in the condition of the patient. In his article of 1903 he added another link to his chain of evidence by demonstrating that the intestinal contents of such patients were more toxic than in normal individuals, as indicated by the fact that their administration to mice and rabbits was promptly followed by death, while control experiments gave negative results.

2. *Fetal Origin.* In 1902 and 1903 Veit, taking advantage of the fact that portions of the periphery of the ovum—chorionic epithelium and even portions of the villi—are constantly gaining access to the maternal circulation during pregnancy, enunciated an hypothesis along the line of Ehrlich's side-chain theory, which he believed capable of affording a satisfactory explanation for most of the abnormalities of pregnancy. He held that, under normal conditions, the fetal products gaining access to the maternal blood were readily rendered innocuous, but that when excessive amounts were introduced Nature was no longer able to fulfil her task, and consequently cytotoxins were developed, which brought about lesions in the maternal organs, and likewise led to hemolytic changes in the blood.

Veit attempted to demonstrate the correctness of his theory by experimental work, and injected into rabbits varying quantities of an emulsion of human placentæ; and, upon finding degenerative changes in the kidneys and the

presence of albumin in the urine, contended that his point was proven. His conclusions naturally evoked the greatest interest, and similar experiments were promptly undertaken by Weichardt, Liepmann, Wormser and others, with the result that considerable discredit was cast upon the syncytiotoxin theory; and at present the general consensus of opinion seems to be that his conclusions were based upon imperfect methods of experimentation, and that equally positive results would have followed the introduction of beefsteak or any other heterogeneous animal material. At the same time there is no doubt concerning the almost universal occurrence of "placental deportation," and, accordingly, it would seem rash to conclude that it may not give rise to abnormal conditions in some instances; but at the present time it would seem inadvisable to accept Veit's theory until further experimental contributions conducted along proper lines demonstrate its correctness.

Veit's theory has received a certain amount of support from the observation of hemoglobinemia and hemoglobinuria, associated with the jaundice and vomiting of pregnancy, by Hirschberg, Schaeffer, Fellner, Brauer, von der Velden and others. And it must be admitted in all such cases that the abnormal condition of the blood must be due to the action of some hemolytic agent; but whether this is derived from fetal cells or from other sources has not as yet been determined.

Shortly afterward Behm reported to the Berlin Obstetrical Society that he had obtained excellent results in several cases of hyperemesis by the employment of abundant rectal injections of salt solution, and held that his results clearly indicated the toxic origin of the vomiting. He then accepted Veit's syncytiotoxin theory in its entirety, and stated that the beneficial results following the use of saline solutions could be readily explained by supposing that it served to wash out of the system the toxic agents, which were produced after

the entrance of abnormal amounts of fetal tissues into the maternal blood.

While there can be no doubt as to the correctness of Behm's actual observations, the objections which have already been made to the acceptance of Veit's theory can be urged still more strongly against the theoretic deductions of the former. Moreover, it is interesting to note that the use of salt infusions in this connection was not original, as they had been employed by Condamin for many years prior to the appearance of Behm's communication. Following the teaching of Veit and Behm not a few authors, among whom may be mentioned Clivio, Jardine, and Kehrer have adopted more or less similar views.

3. *Ovarian Origin.* Reference has already been made to the views of Holladay concerning the part played by the secretion of abnormal corpora lutea in the production of vomiting in the latter months of pregnancy. Pierrehughes in 1902, basing his observations upon six cases, concluded that it was more than probable that in many cases at least the vomiting of pregnancy was due to some abnormality in the ovarian secretion. His argumentation was not at all conclusive, and would apply equally well to abnormal products from the thyroid, liver, or other organs. It is interesting to note, however, that his conclusions were based in part upon metabolic observations by Meillère, who demonstrated in all his cases a decrease in the amount of chlorides in the urine and a diminished urea coefficient.

At the same time, Pierrehughes and Meillère made the interesting observation that while the amount of urea was found to be diminished when determined by accurate chemical methods, that the urine, nevertheless, decomposed an amount of sodium hypobromite sufficiently large to indicate the presence of a normal urea content. The practical bearing of this observation will be dwelt upon when the differential diagnosis of the several varieties of vomiting is considered.

Somewhat similar views were advanced by Turenne in 1905, who held that the less severe types of vomiting were due to the suppression of the ovarian secretion during pregnancy, and that the condition might be alleviated or cured by supplying the deficiency by the administration of ovarian extract. He reported 24 cases in which excellent results were obtained by this means.

4. *Hepatic Origin.* Reference has already been made to the views expressed by Matthews Duncan, Roughton, and Lomer concerning the possible part played by the liver in the production of vomiting, as well as the autopsy findings of Lindemann, Champetier de Ribes, and Bouffe de Saint Blaise. The hepatic origin of the condition, however, was first brought prominently forward by Stone in 1903, who reported the autopsy findings in a fatal case of vomiting, in which the liver presented the lesions of acute yellow atrophy, in that the entire central portion of each lobule had undergone complete necrosis, while the peripheral portion showed signs of fatty degeneration, and only a few cells remained perfectly normal.

Stone's observations were confirmed by Ewing, who, within the past few months, reported finding similar changes in the livers of four women dying from the vomiting of pregnancy, one of whom had a convulsion immediately before death. As the result of his experience, Ewing concludes that both vomiting of pregnancy and eclampsia are closely allied conditions, and are associated with similar hepatic lesions, and therefore should be grouped together under a common heading—toxemia of pregnancy.

Edgar has advanced similar views, which are based upon Ewing's findings, and not upon personal observation. While there can be no doubt as to the correctness of the observations of Stone and Ewing concerning the association of lesions characteristic of acute yellow atrophy of the liver, with certain cases of vomiting of pregnancy, I cannot accept their con-

clusions as to the identity of eclampsia and vomiting, as will be brought out more fully farther on.

My own experience with the toxic type of vomiting of pregnancy dates from May, 1903, when I lost a patient after the induction of abortion at the third month. (Case I., at end of article.) At the time the operation was undertaken her condition was fairly satisfactory and gave promise of a successful outcome. The operation itself was not difficult, and the vomiting ceased for eighteen hours immediately following its completion, after which the patient began to eject at frequent intervals, large quantities of dark, coffee-ground-like material without apparent effort. She gradually passed into a torpid condition, and later became comatose, and died fifty-four hours after the abortion.

At the autopsy, which I was fortunate enough to obtain, we found changes in the liver identical with those observed by Stone and Ewing, associated with intense degeneration of the secretory portion of the kidneys.

This case made a deep impression upon me, as the patient clearly seemed to succumb to an intoxication rather than to starvation, as is usually stated. But at that time I did not fully appreciate the significance of the hepatic lesion, for whose production I attempted to account by invoking one of the more common explanations, and finding none, was inclined to regard it merely as an accidental complication.

Further experience, however, soon led me to change my opinion, for within the next year I saw five other cases of severe vomiting of pregnancy, in all of which I felt compelled to resort to the induction of abortion. Two patients died: one just as the case mentioned above, and the other at the seventh month, with clinical symptoms characteristic of acute yellow atrophy. The three remaining patients were seriously ill, but recovered. Unfortunately I was unable to obtain an autopsy in the fatal cases, but in two of the cases which recovered (Cases II. and III. at end of article) I was able

to make accurate metabolic observations, both before and after the induction of abortion. The results obtained were so surprising as to place the matter in an entirely new light, and to force me to conclude that the hepatic changes certainly played a most prominent part in the fatal issue. Since then I have had an opportunity to observe a fourth toxemic case, as well as several neurotic ones, in which accurate metabolic observations were made, and which served to confirm me more fully in the view just mentioned.

In the three toxemic cases (Cases II., III., and IV.) I found that the total nitrogen output was practically normal, while the urea nitrogen was considerably diminished and the amount of nitrogen excreted as ammonia greatly increased, so that the so-called ammonia coefficient, instead of representing 3 to 5 per cent. of the total nitrogen of the urine, reached 32, 38, and 46 per cent., respectively. This condition clearly indicated a marked disturbance in metabolism, and can readily be brought into relationship with the hepatic changes.[1]

Since observing my case of acute yellow atrophy of the liver accompanying hyperemesis I have carefully searched the literature for similar observations, and have found the following autopsy reports: 1 case each reported by Duncan, Roughton, Hirschberg, Lang, Beatty, Stone, Zaborski, and 4 cases by Ewing, which, together with my own, make a total of 12 observations. Moreover, in 5 other cases reported, respectively, by Schmorl, Erismann, Lindemann, Davis, and Zaborski, marked fatty degeneration of the liver and kidneys was noted.

When one contrasts the extremely contradictory results obtained at autopsy upon women dying from the vomiting of pregnancy with the uniformity of the lesions observed

[1] Since the meeting in May I have seen three other cases of pernicious vomiting, all of which presented an abnormally high ammonia coefficient, and recovered after the induction of abortion.

in the 17 cases just mentioned, one cannot fail to suspect that the association between the two conditions cannot be merely accidental, but that they must bear some direct connection to one another. Likewise it seems very probable to me that many similar cases must have been overlooked in the past, for the reason that the majority of the autopsies were not performed in hospitals, but in private houses, and frequently by persons little skilled in pathological technique, and who, while searching diligently for lesions of the generative or intestinal tract, would very likely overlook so unexpected a change in the liver.

Moreover, when one studies the clinical history of acute yellow atrophy one cannot fail to be impressed with the marked relationship which that condition and the allied states of icterus gravis, typhoid icterus, etc., bear to pregnancy. According to Lebert, Kerkring, in 1706, was the first to report the death of a pregnant woman from icterus gravis, and since that time everyone who has studied the condition has laid stress upon the association, as is indicated by the writings of Horaczek, Ozanam, Budd, Rokitansky, and all subsequent investigators. Thus, Thierfelder stated that 62 per cent. of the 143 cases of acute yellow atrophy of the liver which he collected from the literature affected pregnant women, while Quincke estimates that more than 60 per cent. of all cases occur in women, a majority of whom are pregnant.

Of course, it is well known that acute yellow atrophy of the liver usually occurs in the second half of pregnancy, and particularly after the seventh month; while the fatal cases of vomiting of pregnancy are much more common in the first half of gestation. At the same time, however, exceptions occur in both directions. Beatty and Le Masson having reported cases of acute yellow atrophy at the sixth and eighth weeks, respectively, while occasionally death results from vomiting in the second half of pregnancy.

If it should eventually be demonstrated that toxemic vomiting and acute yellow atrophy are really manifestations of similar toxic processes, it would seem difficult to explain their varying behavior, though it might be assumed that so serious a lesion may be characterized by vomiting in the first and by jaundice in the second half of pregnancy.

From our knowledge of the liver, it would seem that it is in a state of particular susceptibility during pregnancy, and is much more prone to abnormal processes than at other times. Thus, Tarnier in his graduation thesis in 1857, stated that fatty degeneration of the liver was a usual concomitant of pregnancy, and his contention was confirmed by Blot. Unfortunately, these findings were made in women dying from puerperal infection; and as similar observations upon normal pregnant women made in recent years are not at hand, it must remain doubtful for the present whether this condition of the liver is a characteristic accompaniment of pregnancy, or merely a sequel of fatal puerperal infection.

At the same time there is no doubt that the liver in pregnancy offers a locus minoris resistentiæ, as is clearly shown by the occurrence of epidemics of catarrhal jaundice at that time. Thus within the past one hundred years numerous such epidemics have been reported, in which large numbers of the inhabitants in certain localities were affected; the disease running its ordinary course in men and in non-pregnant women, whereas in pregnant women it was remarkably fatal, as more than one-half the pregnancies ended in abortion or premature labor, and many of the women died in coma, and occasionally in convulsions. The most important of these epidemics were reported by Kercksig. in Lüdenscheid, 1794; Charpentier, in Rubaix, 1854; Bardinet, in Limoges, 1859; Saint Vel, in Martinique, 1861; Meunier, in Paris, 1871; Smith, in St. Paul, Minn., 1873; Klingelhoefer, in Heusenstamm, 1876; and Young, in 1898.

In this connection it is interesting to recall the fact that pregnancy itself sometimes appears to be the etiological factor concerned in the production of jaundice, as is well illustrated by the fact that certain individuals suffer from jaundice in every pregnancy. Such cases have been reported by Beking, Benedict, Schaeffer, Brauer, von der Velden and others, in several of which it recurred in from four to six successive pregnancies, and was frequently associated with hemoglobinemia and hemoglobinuria. In Benedict's case the same tendency was noted in two sisters.

Moreover, it should be borne in mind that other functions of the liver are more or less seriously interfered with during pregnancy. Thus, Payer has pointed out that alimentary glycosuria is readily produced in 80 per cent. of all pregnant women. And the investigations of Strauss have shown that the ease with which such a condition can be produced in non-pregnant individuals affords a valuable index as to the degree of hepatic insufficiency. Likewise, Charrin and Guillement have demonstrated that the liver cells of pregnant guinea-pigs contain an unusually large amount of glycogen, thereby apparently indicating that less of it is consumed during pregnancy than at other times. They consider that such a condition renders more difficult the storing of additional quantities of glycogen, so that a considerable portion of the sugar ingested is promptly eliminated, instead of being converted into glycogen and stored for future use. If their supposition proves correct, it would afford a satisfactory explanation for the production of alimentary glycosuria.

When one attempts to explain the significance of the changes in metabolism noted in my toxemic cases, one finds that it is difficult to do so satisfactorily. Ever since Schmiedeberg and Schroeder pointed out that ammonia was a forerunner of urea, and was converted into it in the liver, it has been assumed that any condition which interferes with complete oxidation would tend to bring about an increase in the

amount of ammonia excreted and a corresponding decrease in the urea output. Minkowski went a little farther and showed that the actual precursor of urea was ammonium carbamate, which, by oxidation, was readily converted into urea. At first glance it would therefore seem permissible to suppose that the necrotic lesions observed in the liver would interfere with a complete oxidation of nitrogenous materials, and thus lead to a marked increase in the ammonia coefficient at the expense of the urea. Moreover, such a conclusion would apparently harmonize with the urinary findings in acute yellow atrophy of the liver and acute phosphorus poisoning; since in both conditions there is marked destruction of liver tissue, associated with a considerable increase in the ammonia coefficient, though, according to Neuberg and Richter, the latter does not reach so high a figure as in the cases of vomiting here reported.

On the other hand, it is possible that the relation between the liver changes and the high ammonia coefficient is not so direct, and that the increased ammonia output is not necessarily a manifestation of the destruction of liver tissue, but rather indicates that an excessive amount of acid material has been set free in the circulation, and whose neutralization is absolutely essential if life is to continue. Thus Münzer believes that such an explanation holds good for both acute yellow atrophy and phosphorus poisoning, and, reasoning by analogy, there is no inherent reason why it should not apply to certain cases of toxemic vomiting of pregnancy as well. Unfortunately, it is extremely difficult at present to formulate a well-defined expression of opinion in this regard, as the entire doctrine of acid intoxication seems to be still *sub judice*. Thus, while diabetes is considered the classical example of intoxication with oxybutyric acid, and the increased ammonia coefficient accompanying it merely a manifestation of an attempt to neutralize the excess of acid, it must nevertheless be admitted that our knowledge of the ultimate factors

concerned in the excessive production of the acid is still very fragmentary.

Another example of excessive ammonia output is found in certain cases of gastroenteritis in children, to which Czerny and Keller directed attention in 1897. They pointed out that in such cases the ammonia coefficient frequently rose as high as 30 to 52 per cent., and were in doubt whether it was a manifestation of an acid intoxication, or was directly due to some disturbance in the function of the liver, probably resulting from absorption of toxic material from the intestines. Pfaundler, on the other hand, contended that neither view was correct, and held that the high ammonia output was due almost entirely to the presence of excessive amounts of fat in the food, which was decomposed in the intestines into its component acids, which were readily absorbed and required prompt neutralization. Plausibility is lent to his contention by the fact that the ammonia coefficient can be promptly lowered by simply decreasing the amount of fat taken with the food.

Moreover, Schittenhelm has shown that in adults a considerable increase in the ammonia coefficient may be brought about by arbitrary variations in the character of the diet and by other artificial conditions. Thus, he observed that an increase in the amount of fat ingested, or the administration of dilute hydrochloric acid, would readily bring about such a condition, which would promptly disappear upon the administration of an alkali or a change in the character of the food. At the same time he showed very clearly that various abnormal conditions of the liver were likely to lead to a similar change, and considered that variations in the ammonia coefficient of the urine would afford a fairly reliable index of the extent to which the hepatic function had become impaired.

That the absorption of toxic materials from the intestines may lead to changes in the ammonia output was shown by

the experiments of Glaessner. This investigator, finding that none of the methods usually employed brought about prolonged constipation in dogs, exsected a portion of the intestine and replaced it in the reverse direction, so that its peristaltic movements were opposed to those of the rest of the bowel. This operation had the desired effect and the dogs remained constipated for ten days to two weeks, at the end of which time an abundant stool would be passed, to be followed by another period of constipation. Careful study of the metabolism immediately following evacuation of the bowels showed that it was of the ordinary type; whereas, as the constipation became more marked, the ammonia coefficient increased to double its usual value.

To still further complicate the interpretation of the matter, Folin and Möner have shown that in individuals obtaining an insufficient amount of food, or who are actually starving, there is a marked increase in the ammonia coefficient, which in the cases studied by them reached 26.79 and 40 per cent., respectively. Moreover, the former investigator showed that the substitution of a purely vegetable for a mixed diet was attended by a marked decrease in the urea and an increase in the ammonia coefficient; while some of the nitrogenous substances, such as kreatinin, underwent a still more marked distortion.

From the considerations just adduced, it would therefore seem evident that an increase in the ammonia coefficient may or may not afford conclusive evidence of the existence of an acid intoxication, and that in the present state of our knowledge it would be inadvisable to dogmatize too strongly concerning its significance. This is particularly the case in my own observations, as I unfortunately made no attempt to determine the presence of acetone, diacetic or oxybutyric acid and allied substances in the urine, though leucin and tyrosin were absent in the two cases in which they were

searched for.[1] Likewise, I did not attempt to determine the alkalinity of the blood, although it is hardly likely that notable changes would have been detected, even though an underlying acid intoxication were present, since an excess of acid would immediately have been neutralized by an increased production of ammonia, and thus withdrawn itself from observation.

Accordingly, it seems to me that even had we been able to determine the presence of abnormal acids in the urine, the existence of an acid intoxication would not necessarily have been demonstrated, and while we might seriously consider its possibility, we should nevertheless have been unable to advance a satisfactory explanation for its production. This being the case, I feel at present that I must remain content with demonstrating that in certain cases of toxemic vomiting of pregnancy there is a marked disturbance in metabolism, which is manifested by a great increase in the ammonia coefficient, and that it must be left to future investigations to determine whether the change is directly due to the inability of the diseased liver to effect complete oxidation, or whether it is a manifestation of an acid intoxication. Moreover, we are absolutely ignorant concerning the nature of the toxic material concerned, and whether it is derived from the fetus or mother.

SYMPTOMS. It is difficult to give a satisfactory definition of the pernicous vomiting of pregnancy, for the reason that the gradations between the ordinary morning sickness and the more severe forms of vomiting are often so gradual as to render it difficult to predict in a given case whether the condition may continue without injury to the health of the patient, or will pass into pernicious vomiting. Generally speaking, it may be said that vomiting should be regarded as pernicious in character when it occurs so frequently as

[1] In the three additional recent cases none of these substances were present, nor could the presence of lactic acid be detected.

to interfere seriously with taking food, or leads to marked emaciation.

We are indebted to Dubois for the classical clinical picture of pernicious vomiting, which he divided into three stages:

In the first stage the constant vomiting is associated with considerable emaciation, and frequently with a troublesome dribbling of saliva. At the same time the urine becomes scanty and high colored and the pulse somewhat accelerated. In the second stage the vomiting becomes still more severe, the emaciation more pronounced, and the breath assumes a peculiar acid and fetid odor. As the patient becomes worse the pulse increases in frequency, and eventually there may be a slight rise in temperature. Finally, in the third stage there occurs for a short time an apparent amelioration in the symptoms, the vomiting sometimes ceases, and the patient and her friends become encouraged as to the outcome. Unfortunately, this is merely a transient condition, as the patient usually soon passes into a delirious or torpid condition, and dies in coma or convulsions. During the last period there is no hope for recovery, which is not out of the question in the preceding stages.

My own experience has led me to believe that the clinical picture drawn by Dubois cannot always be followed at the bedside, as pernicious vomiting may occur either in an acute or a chronic form, of which the latter is the more frequent.

In the acute type, which according to my experience is always toxemic in character, death may occur within ten days or two weeks after the onset of vomiting. In such cases the patient, who was formerly perfectly well, or simply suffering from what appeared to be ordinary "morning sickness," suddenly begins to vomit everything she ingests, and soon presents signs of considerable prostration. The condition is usually associated with but little elevation in the pulse rate, and fever is absent. After it has persisted for a number of days the patient begins to eject at frequent inter-

vals and apparently with but little effort considerable quantities of dark, brownish, coffee-ground-like material, and soon passes into a torpid condition, and later dies in coma, which is sometimes disturbed by convulsions. (Cases I. and IV.) This variety of vomiting is not necessarily associated with great emaciation, as one of my patients (Case IV.) died while apparently still well nourished, and with a pulse of 96.

In the early stages of this form of vomiting the ordinary tests show that the urine is apparently perfectly normal, though naturally it is diminished in quantity on account of the small intake of fluids. In the last stages of the disease, however, it contains albumin, blood, and various varieties of tube casts, though this may not be noted until only a few hours before death. As a rule the temperature is not materially elevated; but occasionally, shortly before death, it may reach a considerable height, and in one of my cases, not reported in this article, it registered 108 immediately before the fatal outcome. Occasionally in the last stages of the disease the patient may present an icteric discoloration of the conjunctivæ, or even a decided icterus, though the latter is exceptional.

In the chronic form, on the other hand, which may be toxemic or neurotic in variety, the vomiting may continue for weeks or months, during which the patient becomes more and more emaciated, apparently entirely as the result of the ingestion of insufficient amounts of food. Under such circumstances she gradually becomes too weak to pursue her ordinary avocations, and eventually is forced to take to bed. At the same time the pulse slowly increases in frequency, fever is usually absent, and the black vomit of the acute variety is lacking until the very last stages of the disease. Consciousness is preserved until shortly before death, which is to be attributed in great part to inanition; while in the acute cases it is manifestly the result of an intoxication.

That inanition is the usual cause of death in the chronic variety has been generally recognized from the time of Dubois, and its importance was particularly insisted upon by Sutugin. Moreover, Frank, in 1893, reached a similar conclusion from the study of the metabolism, as he found that in such a case the quantity of nitrogen excreted by the urine was far greater than that taken in by the mouth. This is particularly interesting, since it was noted in the first metabolic study undertaken in this condition.

In none of the cases which I have observed have the patients complained of disturbances in the olfactory sense —the so-called hyperosmia—upon which Horwitz laid so much stress; though his observations in this regard are both interesting and significant.

The outline of the clinical history which I have just given applies particularly to cases of pernicious vomiting, occurring in the first half of pregnancy. On the other hand, when it continues into the second half of pregnancy or originates in that period, the recognition of the significance of the condition becomes more difficult and the symptoms are frequently attributed to the typical pre-eclamptic toxemia.

Moreover, when the affection is associated with jaundice, it usually presents the typical clinical picture of acute yellow atrophy; while, if icterus is absent and the patient is only seen after she has passed into a comatose condition, it is quite natural to mistake the condition for eclampsia, especially as examination of the urine would show the presence of albumin, casts, and frequently blood.

DIAGNOSIS. Hyperemesis, as indicated above, should be diagnosticated whenever the vomiting becomes so constant that the patient is unable to retain any considerable quantity of food, or presents considerable emaciation. Much more important, however, than the mere diagnosis of pernicious vomiting is the determination as to whether one has to deal

with its reflex, neurotic or toxemic variety, since upon this point depends the treatment to be pursued.

Accordingly, whenever a woman suffers from serious vomiting, even though it may not be absolutely pernicious in type, a careful vaginal examination should be made for the purpose of detecting any abnormality of the generative tract or ovum. The existence of a displaced uterus, an ovarian cyst, or a pelvic inflammatory mass is readily detected by the usual methods; while an increase in the size of the uterus out of proportion to the supposed duration of the pregnancy should arouse suspicion as to the existence of a hydatidiform mole or hydramnios.

On the other hand, it is extremely difficult to diagnosticate decidual endometritis with certainty; although its existence should be suspected when it is known that the patient suffered from endometritis before conception, or when a dark brownish or brick-dust-colored discharge flows from the cervix. In the latter event the occurrence of a spontaneous abortion may be expected.

If no abnormalities can be detected on the part of the generative tract or ovum, the diagnosis must lie between the neurotic or toxemic types of vomiting. Unfortunately, as far as my experience goes, they cannot be differentiated positively by clinical symptoms, except at the terminal period of the affection, when it is too late to institute effective treatment, and therefore our only resource lies in a thorough chemical examination of the urine, and the determination of the ammonia coefficient.

In order to make such a determination, the entire amount of urine passed during the twenty-four hours should be collected, care being taken to place enough chloroform in the vessel to prevent decomposition. Then the total nitrogen should be determined by the Kjeldahl method, and the amounts of urea and ammonia by the methods of Schöndorf and Schloessing, respectively. In normal pregnancy, and

even in neurotic vomiting, the ammonia coefficient varies from 3 to 5 per cent. (Cases V. to VII.); but in the toxemic type of vomiting it may attain immense proportions, being 32, 38.5, and 46 per cent. in Cases II., III., and IV.

Thus far my experience with the toxemic type of vomiting has not been sufficiently extensive to permit me to lay down definite rules as to the extent to which the ammonia coefficient may rise without particular danger to the patient; but at present it would seem that its increase to 10 per cent. would justify the diagnosis of toxemic vomiting, and would afford an urgent indication for the prompt termination of the pregnancy. In Case IV. the ammonia coefficient was only 16 per cent. when I first saw the patient, who did not appear to be seriously ill; and, while it enabled me to make a diagnosis of the toxemic variety of vomiting, I felt justified in delaying interference and testing the efficacy of medicinal treatment. The outcome of the case, however, showed that I was in error, as the patient died in coma forty-eight hours after the induction of abortion with an ammonia coefficient of 46 per cent.

In addition to the determination of the total nitrogen and the urea and ammonia coefficients, it is, if possible, advisable to determine the other nitrogen subdivisions, as their study may possibly throw still further light upon the nature of the condition. The urine should be likewise examined for the presence of leucin and tyrosin, which were absent in my cases, but were present in several of those examined by Ewing.

Unfortunately the determinations just mentioned cannot be undertaken by the practising physician in his office, but demand the services of a well-trained chemist. In this connection it is extremely important to note that a rough estimate of the amount of ammonia cannot be made by determining the amount of urea by the Doremus apparatus, and assuming that a decrease in its amount indicates an

increased ammonia coefficient, for the reason that with this test the ammonia, as well as the urea, is decomposed by the sodium hypobromite; so that it might indicate the presence of a normal amount of urea, when in reality it was markedly diminished and its place taken by ammonia. This fallacy was exemplified in Case I., in which a normal urea output, as determined by the Doremus method and the absence of albumin and casts, caused me to overlook the toxemic nature of the condition until too late. A similar observation was made by Pierrehughes, who stated that in certain cases apparently normal amounts of urea were indicated by the sodium hypobromite method, when in reality more accurate chemical methods showed that the urea coefficient was markedly diminished.

Another complication is that the determination of ammonia by the Schloessing method requires the best part of forty-eight hours, so that the result cannot be known for two days after the urine has been placed in the hands of the chemist. It is therefore to be hoped that the method of distilling the ammonia in vacuo will prove thoroughly satisfactory, as under such circumstances the determination can be made within a few hours. At present, however, this is a matter for decision on the part of the professional chemist, and need not detain us here.

In connection with the question of diagnosis it is important to direct attention to the condition of the pulse, as it is generally stated that some idea of the severity of the case can be obtained from its character and frequency. My experience, however, has led me to believe that this is not necessarily true, since in Case IV. the patient died with a pulse of 96. Moreover, a rise in temperature is not nearly so common as was believed by the early observers, and many patients die without any manifestation of fever. The occurrence of the black vomit, on the other hand, is a sign of great value, and indicates a most serious condition; and, while it cannot be

said that its occurrence is necessarily indicative of death, it must nevertheless be regarded as of most ominous prognostic import.

In view of what has been said concerning the connection between acute yellow atrophy of the liver and the toxemic type of vomiting, the occurrence of jaundice in pregnant women suffering from hyperemesis should always be regarded as ominous, and as indicating some serious derangement of the liver, rather than as a manifestation of a simple catarrhal jaundice.

When discussing the symptoms of the vomiting of pregnancy, particularly in the latter months, it was pointed out how readily it might be mistaken for eclampsia, especially if the patient were comatose; and Ewing has gone a step farther and stated that he considers both acute yellow atrophy of the liver and eclampsia as manifestations of one and the same toxemia. This conclusion, however, is so absolutely opposed to my own experience, which has taught me that the two diseases differ radically, whether considered from a clinical, chemical, or histological point of view, that I cannot allow it to pass unchallenged.

Clinically eclampsia is nearly always preceded by a characteristic pre-eclamptic toxemia, which is usually associated with pronounced general symptoms and early evidence of serious disturbance in the renal and circulatory functions, scanty urine, containing albumin and casts, and œdema. In vomiting, on the other hand, the urine is practically normal in amount until shortly before death, or at least is in direct proportion to the quantity of fluid ingested; whereas in the pre-eclamptic toxemia it is always considerably diminished, notwithstanding the administration of diuretics and of large quantities of fluid by the mouth or rectum. Moreover, in vomiting, albumin and casts usually appear only in the terminal stage of the disease, while œdema is never present.

From a chemical point of view the difference is even more striking. In eclampsia there is usually a marked decrease in the total amount of nitrogen excreted, and while there may be a considerable diminution in the urea coefficient, pronounced variations do not occur in the ammonia coefficient, though occasionally it may rise to a slight extent. In vomiting, on the other hand, the total amount of nitrogen may be quite normal, while the ammonia coefficient becomes unusually high. (Compare Charts I. to III. with IV. to VI.) My own experience would seem to indicate that an increase in the ammonia coefficient is of favorable prognostic import in eclampsia; whereas its significance is just the reverse in the vomiting of pregnancy.

From a pathologic point of view, the lesions in the two conditions differ so markedly that I do not see how it is possible for anyone who has once observed them to consider that they are at all related. In eclampsia, as was first pointed out by Jürgens, Schmorl and others, the lesion consists in necroses occurring in the portal spaces, dependent upon thrombotic processes in the smaller portal branches. At first they are sharply limited to the portal spaces, but as they enlarge they invade the lobules from the periphery toward the centre, and are so characteristic that their mere presence justifies the diagnosis of eclampsia without any knowledge of the clinical history of the case. On the other hand, in the acute yellow atrophy accompanying the toxemic vomiting of pregnancy the changes are purely degenerative in character, and begin about the central vein of the lobule and gradually extend toward its periphery. These differences are clearly shown in Figs. 1 and 2, and to my mind make it incredible that they could be confounded with one another.

After reading Ewing's article I wrote to Schmorl, who has had the most extensive experience in the study of the liver lesions of eclampsia, and inquired whether he had ever seen

the eclamptic lesions beginning in the centre of the lobules. He replied in the negative, and stated that they always began in the tissues about the periphery and only invaded the lobule itself secondarily. Moreover, Opie, in his article upon zonal necroses of the liver, which was based upon material studied in the Pathological Laboratory of the Johns Hopkins University, stated that the lesions in eclampsia were highly characteristic, as it was only in that disease that they began at the periphery of the lobule, while in acute yellow atrophy the central or midzonal areas were the first to become involved.

Therefore, from my own experience, as well as that of Schmorl, I cannot understand how it is possible for one to confound the lesions in the two conditions. Moreover, when one takes into consideration the difference in the clinical history and metabolism of the two diseases, the case becomes absolutely convincing. From the evidence at present available it would therefore seem that we have to deal with at least two varieties of toxemia of pregnancy, one giving rise to eclampsia or the pre-eclamptic toxemia, and the other to the vomiting of pregnancy and acute yellow atrophy, though it is quite within the range of possibility that further research will demonstrate the existence of still other varieties.

PROGNOSIS. Generally speaking, it may be said that the prognosis is excellent in the reflex and neurotic forms of vomiting, provided they are properly treated. At the same time it must be admitted that patients suffering from them may succumb to inanition if proper measures are not instituted in good time.

In toxemic vomiting, on the other hand, in view of the serious organic lesions and changes in metabolism, the prognosis is most grave, and it seems safe to say that death will be the usual outcome if the toxemia is pronounced, unless the pregnancy is promptly interrupted. Thus far six examples of the toxemic type have come under my obser-

vation (Cases I., II., III., and IV., and two others not mentioned in this article), in all of which I felt obliged to induce abortion, but notwithstanding this, death occurred in four instances; a mortality of 66⅔ per cent. Of course, these figures are not sufficiently large to justify one in drawing very general conclusions, but at the same time they clearly demonstrate the great gravity of the condition.

TREATMENT. The treatment to be pursued in a given case of vomiting of pregnancy depends entirely upon the variety with which one has to deal. It is assumed that medicinal treatment has been tried without avail before the medical adviser comes to regard the case as at all serious.

If any abnormality of the generative tract or ovum be found it should be remedied as far as possible; the retro-displaced uterus should be replaced and held in position by a properly fitting pessary; ovarian tumors should be removed and inflammatory masses treated by appropriate antiphlogistic measures. On the other hand, if hydramnios or hydatidiform mole be diagnosticated, the pregnancy should be promptly terminated.

If the toxemic variety of vomiting be diagnosticated abortion should be induced as soon as its nature is fully recognized, as it would seem to offer the only chance of saving the patient, since the lesions associated with it are apparently incompatible with life, if far advanced, and especially as there is no reason to suppose that they can be materially influenced by medicinal or dietetic treatment. In view of the tendency of chloroform in some cases to give rise to degenerative changes in the liver, it would appear more rational to employ ether as an anesthetic in this variety of cases. After the uterus has been emptied the patient should be given abundant rectal or subcutaneous saline injections. The stomach should be washed out occasionally with a weak solution of sodium bicarbonate if the vomiting persists. No attempt should be made to feed the

patient by mouth, and even ice should be withheld until the vomiting ceases, all reliance being placed upon the salt infusions and enemata and the employment of rectal feeding.

On the other hand, if the neurotic variety of vomiting is diagnosticated the treatment should depend to a considerable extent upon the impressionability of the patient. In certain exceptional cases a good moral lecture may prove all that is necessary. In other instances the patient should be assured that her condition will not terminate fatally nor require the induction of abortion, and that it will probably yield to intelligent treatment. She should then be given some harmless remedy and receive the most minute directions as to the character of her food and the manner in which it should be taken. If such mild methods do not suffice, the patient should be put to bed in charge of a sensible nurse and the family and friends excluded from the room; all feeding by the mouth should be stopped and its place taken by the administration of saline and nutritive rectal enemata. Occasionally it may be necessary to add small quantities of laudanum to the enemata or to give an occasional hypodermic of morphine.

If, however, such treatment is not followed by improvement within three or four days the patient should be threatened with removal to a hospital, and, if the threat does not prove effectual, it should be actually carried out and the patient placed in a private room in a well-regulated hospital, where a rigorous rest cure can be instituted upon the most approved plan. In my experience such drastic measures are rarely necessary, as the modified rest cure, as outlined above, will usually be followed by the cessation of vomiting within a couple of days, and the vast majority of patients will be on the high road to recovery within a week. (See Cases V., VI., and VII.)

Of course it is possible that exceptional cases may not

be amenable to such treatment, and under such circumstances it may become necessary to resort to the induction of abortion in order to prevent death from starvation; though I believe with an accurate diagnosis and sufficient assurance on the part of the physician that such a resort will become less and less frequently necessary and that the operation should be reserved almost entirely for the cases of toxemic vomiting.

HISTORY OF CASES.

CASE I.—Mrs. H. T. P. I first saw the patient on April 22, 1903, when she desired to ascertain whether she was pregnant. She was a tall, thin, delicate-looking woman, aged twenty-eight years, who had been married two years and had never been pregnant. Her last menstrual period occurred on February 10th and lasted five days, but in March and April there was a slight flow at the regular time, but much less abundant than usual. Prior to seeing me she had suffered a good deal from nausea.

On examination the uterus was found to be enlarged to the size of a two months pregnancy and softened, so that there was little doubt about the diagnosis.

A few days later I saw the patient again, when she was complaining intensely of nausea and vomiting, for which I regulated the bowels and ordered some capsules of pepsin and nitrate of silver. As these were without effect, various other remedies were employed, with the same result. Gradually the nausea and vomiting became so intense that the patient was unable to retain anything at all, so that on May 6th I ceased all attempts to administer food by the mouth and resorted to rectal feeding. From this time she received two nutritive enemata daily, consisting of twelve ounces of pepsinized milk and two eggs, as well as a third enema of 750 c.c. of salt solution. They were borne extremely well, but nevertheless the patient still suffered severely from

vomiting, and grew weaker and more emaciated. Her pulse, which was 70 when I first saw her, slowly rose to 92.

On May 15th I asked her physician, Dr. W. F. Lockwood, to see her in consultation. At that time she was suffering intensely from profuse salivation and was constantly vomiting small quantities of a dark, brownish-looking fluid, and complaining of intense pain in the epigastric region. In spite of the comparatively low pulse, it was decided that the prompt induction of abortion was indicated, which was done on the afternoon of the 16th.

The cervix was dilated without great difficulty by means of Goodell's and Hegar's dilators sufficiently to permit the introduction of one finger into the uterus. The ovum was then detached from the uterine wall and broken up into small pieces, which were readily removed by means of ovum forceps. A douche of sterile salt solution was then given. During the attempt to introduce the finger into the uterus the outlet was considerably torn, so that it was necessary to repair it with three silkworm-gut sutures.

The patient stood the operation well and was put back to bed in good condtion.

During the first eighteen hours following the operation her condition improved markedly and the nausea and vomiting ceased entirely. At the end of that period they reappeared, and the patient constantly vomited small amounts of a coffee-ground-like material, with almost no effort. This could be checked only by the hypodermic administration of morphine, which was continued throughout the 17th and 18th; but before its administration her condition became torpid and she gave the impression of suffering from a profound toxemia.

Gradually the pulse became quicker, and in spite of the administration of nutritive enemata, subcutaneous salt infusions and the hypodermic use of digitaline and strychnine, it become more and more rapid. On the morning of the

19th it reached 120, and slowly increased in frequency until she died, at 9 P.M. The temperature was perfectly normal until the morning of the day of death, when it reached 101.5°. During the last twelve hours of life the patient was absolutely unconscious and died without an effort.

The urine was examined several times during her illness, and the day before the induction of abortion the twenty-four-hours' specimen amounted to 750 c.c. and contained 30 grams of urea, as estimated by the Doremus ureometer, and no albumin. Microscopic examination was negative, except for the presence of amorphous urates. As no examination was made after the operation, it cannot be said whether albumin was present or not, though, from the condition of the kidneys at autopsy, its absence would have been surprising. Unfortunately a chemical examination of the urine was not made in this instance.

ABSTRACT OF AUTOPSY PROTOCOL (No. 2110. Dr. H. T. Marshall). *Anatomical Diagnosis.* Recent laceration of the vagina, with infiltration into adjacent tissues. Lacerated cervix. Portion of placenta adherent to and growing into uterine wall. Uterus of early pregnancy. Fatty degeneration, areas of necrosis and bile staining of liver. Fatty degeneration and bile staining of kidneys. Chronic adhesive pleurisy, left side. Old latent tuberculosis of two-thirds of upper lobe of left lung. Scar at right apex.

Body of a well-built, sparely nourished woman. No œdema; no jaundice; pupils equal. Slight postmortem discoloration of dependent parts. Subcutaneous fat slight in amount.

Peritoneal cavity negative.

Thorax. Pleural cavities dry. The right cavity is clear; on the left side dense adhesions between upper lobe and chest wall. Pericardial cavity clear.

Heart. Apparently normal; valves clear. Myocardium is soft, opaque, yellowish, and apparently bile-stained.

Lungs. Upper lobe of left lung greatly reduced in size. Contains a few calcified and caseous foci. Small apical scar in right lung.

Liver. Weighs, 1000 grams; is small and of a bright-yellow color, with smooth surface and soft consistence. On section it presents a very fatty, bile-stained appearance, with areas of degeneration and necrosis evident to the naked eye. The capillaries stand out very prominently between the fatty and yellow strands. Except that the degeneration is not so extreme, the section suggests acute yellow atrophy. No nodules in liver. Gall-bladder normal.

Stomach. Is small and contains about 500 c.c. of dark fluid, containing blood cells, bile, and debris. Mucosa normal.

Intestines, spleen, pancreas, and *thyroid* normal.

Kidneys. Both kidneys present an identical appearance and are considerably enlarged. The capsule strips off readily, leaving a bile-stained, opaque, yellow surface, with no vessels showing. On section the cortex measures 7 to 8 mm., is very yellow, opaque, and granular, and slightly raised above the level of the pyramids. No structures, vessels, or glomeruli can be made out. The pyramids are pale and their periphery shows lines and areas of fatty appearance, which is particularly marked in their outer third. The renal pelves are normal.

Genitalia. Bladder normal. Tubes and ovaries normal. Uterus appears normal and measures 11 cm. from fundus to cervix, and 8 cm. between the insertions of the tubes. The external os is roughened and shows some superficial necrosis. On section the uterine cavity appears clear and normal, except that on the posterior wall near the fundus there is a rough, shaggy, reddish area, which projects 6 to 7 mm. above the general surface, and extends to the right cornu. On section it presents a soft and somewhat friable appearance and extends some distance down into the muscular

wall. It appears to be decidedly infiltrating, but no sign of it can be found outside of its original boundaries.

Microscopic Examination. Under the low power, sections of the liver stained with hematoxylin and eosin present a remarkably mottled appearance, about one-half of the area of the section being occupied by rounded or irregularly shaped areas, which stain bright pink with eosin and are separated from one another by less brightly staining tissue. Upon closer examination it is seen that these areas correspond to the central portions of the liver lobules, all of which are involved in the process. The individual lobules are sharply marked off from one another, and the interlobular spaces present a normal appearance, with connective tissue, bloodvessels, and bile-ducts. Nowhere is there any hemorrhage into the portal spaces, nor any trace of thrombosis of their vessels.

In each lobule three distinct zones may be distinguished: peripheral, midzonal, and central. The peripheral zone consists of one or two layers of practically normal liver cells, with brightly staining nuclei and a faintly granular protoplasm. In places even this narrow zone of normal cells is imperfect, so that the cells of the midzonal layers of adjacent lobules abut directly upon one another. The midzonal portion of the lobules varies in thickness, but in general occupies one-half of the distance between the central vein and the periphery. It is made up of large, irregularly shaped cells, whose nuclei stain fairly well and whose protoplasm is almost entirely replaced by a number of vacuole-like structures nearly as large as the nuclei. These probably represent the location of fat droplets, which were dissolved out by the hardening fluids, but as osmic acid specimens were not available, positive statements cannot be made in this regard. In this layer there is considerable engorgement of the intralobular capillaries. The connective-tissue elements are well preserved, and in places appear somewhat

increased in number. No leukocytes are present. The central portion of each lobule, which occupies at least one-half of its total area, is marked off from the midzonal layer by an irregular, wavy line, though in places it is perfectly apparent that the two portions merge into one another. The central portion stains brightly with eosin, and in many lobules is entirely made up of absolutely necrotic cells with a coarsely granular structure, no nuclei of any kind being visible. In others an occasional connective-tissue nucleus can be distinguished, while in rare instances the degenerated nuclei of some of the liver cells take on an indistinct stain with hematoxylin. In some of the lobules there is a well preserved central vein; in others its location is indicated by a mass of nuclei, while in still others all trace of it has disappeared.

Kidneys. Sections through the kidneys show that the glomeruli present practically a normal appearance. The secretory portion of the renal tubules, on the other hand, is almost entirely necrotic, and their cells are converted into irregular, coarsely granular, vacuolated masses, which contain only an occasional faintly staining nucleus. In many places the lumina of the tubules are obliterated, while in others they are more or less completely filled with granular material, which occasionally contains red blood cells. The collecting tubules, on the contrary, appear to be perfectly normal, and their cells stain in the typical manner. The connective-tissue portion of the kidneys appears unchanged.

Uterus. Sections through the projection at the fundus, which was noted at autopsy, show that it is composed almost entirely of fibrin, but immediately adjoining the uterine wall it encloses a few chorionic villi, which present a normal appearance. The decidua presents its characteristic structure, except that it appears richer in fetal cells than is usually the case.

Placenta. Sections through the placenta removed at the time of operation present the appearance characteristic of early pregnancy. The villi are covered by two layers of epithelium—syncytium and Langhans layer—and present a myxomatous stroma, which contains but few bloodvessels. Many giant cells are present in the intravillous spaces and occasional trophoblastic islands are seen.

CASE II.—*Toxemic Vomiting.* Mrs. E. J. A. (Chart 1). The patient was seen October 26, 1903, in consultation with Dr. James Bosley, from whom I obtained the following history: Twenty-nine years old, married seven years, but has never been pregnant; has always been perfectly healthy, although of a somewhat nervous disposition. The last menstrual period occurred on August 1, 1903. On September 9th she began to suffer from nausea and vomiting, which gradually became worse in spite of vigorous treatment. For the past two weeks the patient has been unable to retain food and has vomited almost constantly. She has lost approximately twenty pounds in weight. The day before I saw her she had been seen in consultation by Dr. I. E. Atkinson, who recommended the induction of abortion.

Examination showed a very emaciated patient, with eyes sunken far back in their orbits. She complained of intense pain in the epigastric region, and stated that she vomited almost constantly. At the side of the bed was a basin containing a quantity of coffee-ground-like material which she had recently vomited. The patient looked extremely ill; the pulse was 132, and temperature normal. The heart and lungs were normal. There was apparently a slight diminution in the liver dulness, whose lower edge was two fingers' breadth above the costal margin. On palpation the fundus of the uterus could be felt just above the pubis.

In view of the serious condition of the patient it was determined that abortion should be induced the following day.

This delay was for the purpose of allowing the collection of a twenty-four-hour specimen of urine. A trained nurse was procured and instructed to administer two rectal enemata of 500 c.c. of salt solution during the next twenty-four hours. As soon as the first specimen of urine, which amounted to 500 c.c., had been collected the operation was proceeded with.

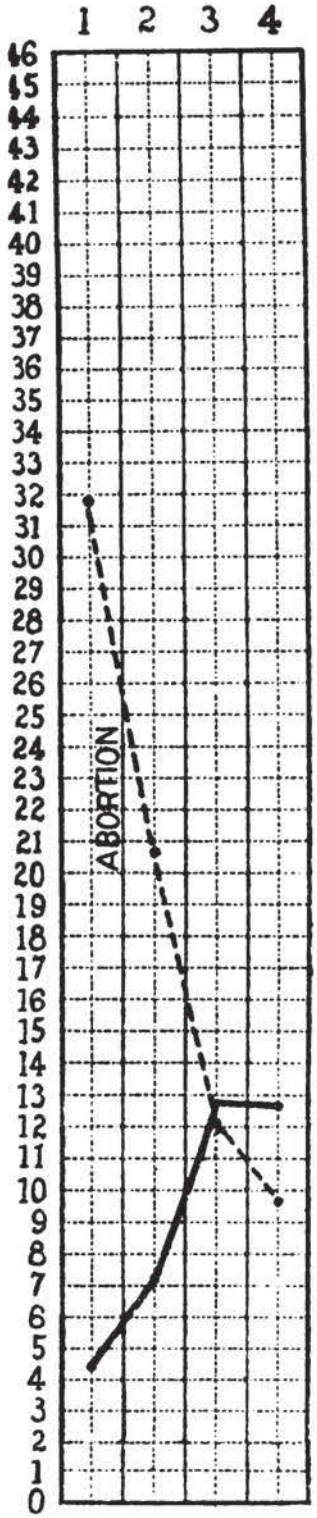
Examination at that time showed that the vagina was short and the external os small, hard, and virginal. The cervix was dilated by means of Goodell's and Hegar's dilators until the index finger could be readily introduced into the uterus, which required about twenty-five minutes. The ovum was then separated from its attachment by the finger, and its fragments removed by means of an ovum forceps. A uterine douche was then given and the uterus packed with gauze. The patient stood the operation well and was put back to bed in good condition, with a pulse of 124.

She began to improve almost immediately, and within twenty-four hours the pulse had become slower, the nausea had practically ceased, and a marked change in her general appearance was noted. After this convalescence was so rapid that it was unnecessary for me to see her after the fourth day. The pulse reached 72 on the sixth day after operation, and the highest temperature was 100.4° on the second day.

Chart I. gives a graphic idea of the condition of the urine, which for the twenty-four hours immediately preceding the operation presented an ammonia coefficient of 32 per cent. Albumin or casts were at no time present. A specimen of urine examined one month later was perfectly normal, with an ammonia coefficient of 4 per cent.

Case III.—*Toxemic Vomiting.* Mrs. C. C. (Obstetrical No. 1710, Johns Hopkins Hospital. Chart II.) The patient was seen on February 25, 1904, in consultation with Dr. George B. Reynolds, when I obtained the following history: Thirty-seven years old, married fourteen months. One

CHART I



Toxemic vomiting. Mrs. E. J. A.
Solid line represents total nitrogen of urine expressed in grams.
Broken line represents percentage of total nitrogen excreted as ammonia.
Determinations made from twenty-four-hour specimens

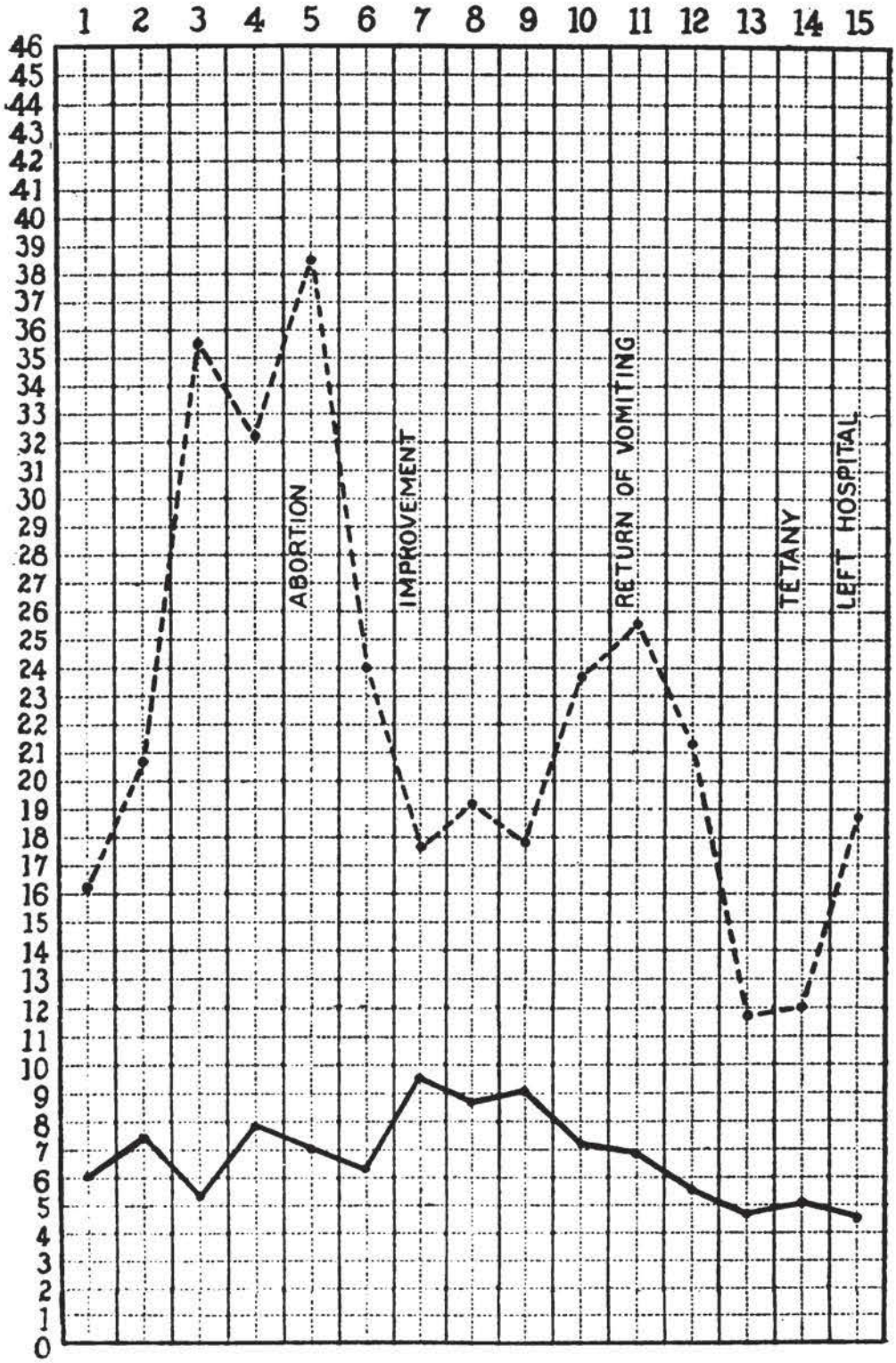
miscarriage at two months eight months previously. Was in excellent health prior to the present illness. The last menstrual period began December 13, 1903. Four weeks later the patient began to suffer with indigestion, which was soon followed by nausea and vomiting, accompanied by violent pain in the epigastric region. For the past three weeks the nausea and vomiting has been intense, no solid food being retained for the past two weeks, and for the last two days even the blandest fluids cause immediate vomiting. During this period she has suffered almost constantly from severe headache, and has lost fifteen to twenty pounds in weight.

On examination the patient was found to be a small, emaciated woman, with a pale and haggard face. The lips and mucous membranes were without color and the tongue thickly coated. She was vomiting small quantities of clear fluid at frequent intervals. Auscultation revealed no abnormalities; pulse 120 and weak, temperature normal. The liver dulness was normal. The abdomen was not distended or painful on pressure. The fundus of the uterus could not be felt above the symphysis pubis. Vaginal examination negative, except for an eight to ten weeks' pregnant uterus.

On account of her surroundings, the patient was immediately transferred to the Johns Hopkins Hospital, where she was kept under observation for four days and nourished almost exclusively by the rectum and given copious saline enemata. During this period the fluid intake and output was carefully measured, and the amount of total nitrogen and the ammonia coefficient determined. At the end of this time her condition was worse rather than better, and, as seen from the accompanying chart, the ammonia coefficient reached 35.5 per cent. on the third day.

In view of her condition it was thought best to attempt the induction of abortion by a bougie, which was readily introduced without anesthesia, at noon February 29th, when her temperature was 99.2° and pulse 112. As the bougie

CHART II



Toxemic vomiting. Mrs. C. C.
Solid line represents total nitrogen of urine expressed in grams.
Broken line represents percentage of total nitrogen excreted as ammonia.
Determinations made from twenty-four-hour specimens.

did not bring on uterine contractions, it was removed the following morning, and the uterus emptied by means of the finger and ovum forceps. The patient stood the operation well and was put back to bed in good condition.

Following the operation the patient improved slowly, until March 5th, when she became torpid and drowsy and gave the impression of a person profoundly intoxicated. At the same time the nausea and vomiting, which had almost ceased, increased in severity. As seen by the chart, this was accompanied by a rise in the ammonia coefficient from 18 to 25 per cent. Following this there was improvement for several days, until March 9th, when the nausea and vomiting reappeared and the patient developed a tetany, which continued for two days. During this period the nausea and vomiting were very severe and the patient impressed one as being desperately ill, though the pulse varied between 88 and 100, and was of poor volume. By March 11th her condition had improved considerably and the nausea had disappeared, so that she was able to take two meals of solid food during the day. As the patient had become very dissatisfied with the hospital, she was allowed to go home at this time, although far from well.

She eventually made a good recovery, and on returning to the hospital the following May, had so improved in appearance that she was not recognized. The urinary examination at that time showed an ammonia coefficient of 4 per cent.

At no time during the illness were albumin or casts present in the urine. The highest temperature was 100° on the day of abortion. Chart II. gives a good idea of the relation between the total nitrogen and the ammonia coefficient.

Case IV.—*Toxemic Vomiting.* Mrs. H. H. S. (Obstetrical No. 2116. Chart III.) The patient was seen on March 20, 1905, in consultation with Dr. A. K. Bond, from whom I obtained the following history. Thirty-three years of age, married October, 1904, no previous pregnancies. No serious

illness, except typhoid fever five years ago. He was first consulted on March 13th, when the patient stated that she believed that she was two months pregnant, having menstruated last January 13, 1905. The next day she complained considerably of nausea and vomiting, which had begun February 20, 1905, and asked that something be done to relieve it. Simple remedies were administered without effect. Three days later, March 17th, the vomiting had become so distressing that nothing could be retained by the stomach. The vomited matter consisted either of recently ingested food or of a clear, colorless, odorless, and tasteless fluid. The only thing that seemed to give relief was morphine, administered hypodermically. The bowels were constipated and resisted the strongest purgatives.

The patient is a large, well-nourished woman, with a bright complexion and anxious expression, who is lying in bed and making almost constant efforts to vomit, but expelling only small quantities of clear fluid.

On examination the heart and lungs presented no abnormality; the pulse was 68 and of good volume. The liver dulness was apparently normal. No tenderness of abdomen on palpation. No jaundice. Vaginal examination showed a nulliparous outlet, the cervix virginal and quite hard; the uterus in normal position, soft in consistency and enlarged to the size of an eight to ten weeks' pregnancy. Appendages normal.

I advised stopping all attempts at feeding by the mouth, and the daily administration of four high saline enemata of 400 c.c. each. A trained nurse was obtained and directed to save a twenty-four-hour specimen of urine. The first specimen measured a little over 500 c.c. and contained 7.5 grams of total nitrogen, with an ammonia coefficient of 15.8 per cent., and no albumin. Microscopic examination was negative, except for the presence of amorphous urates.

A diagnosis of toxemic vomiting was made on the strength of the high ammonia coefficient, but in view of the apparently satisfactory general condition of the patient, it was thought that immediate interference was not indicated.

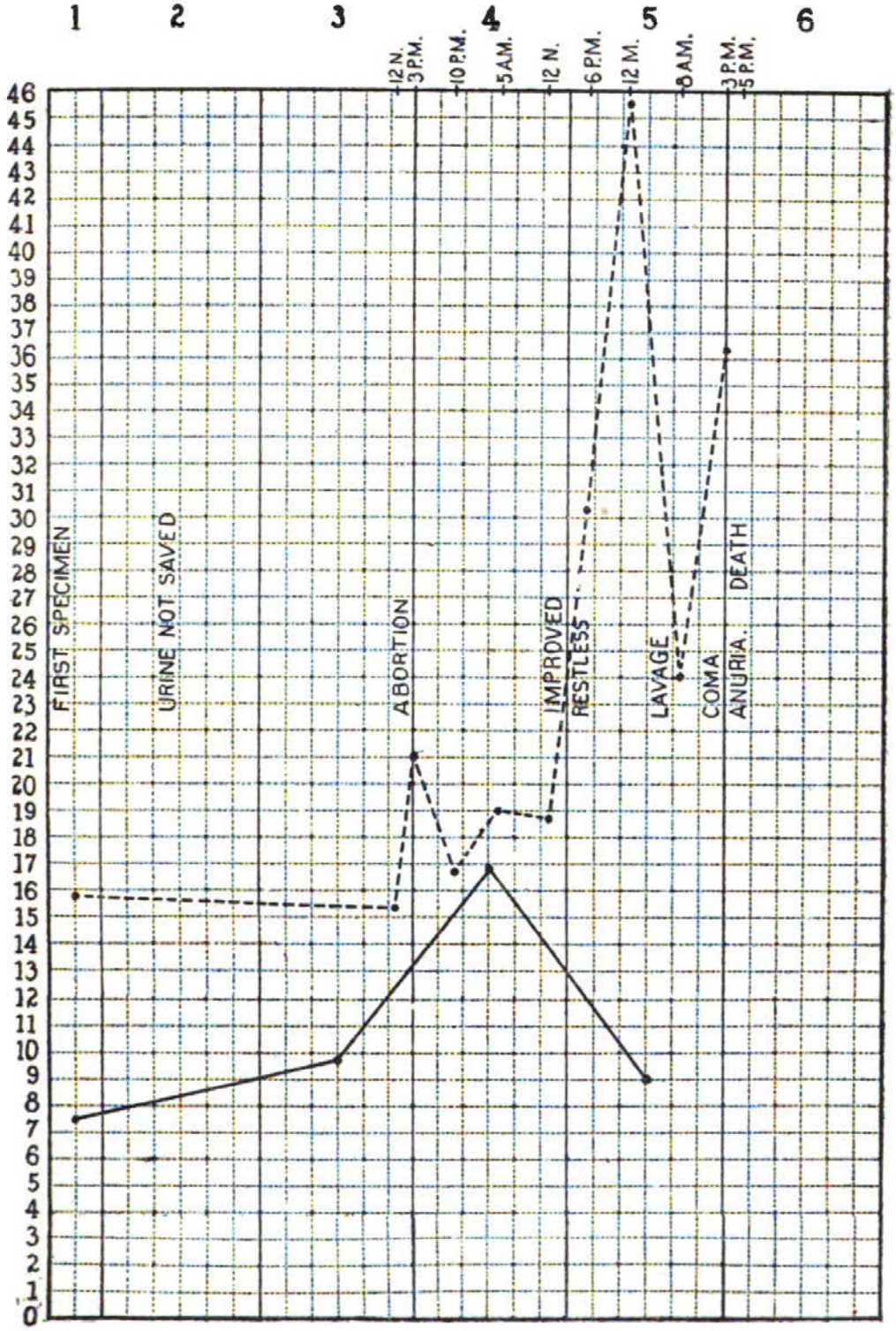
Her condition continued the same on the 22d, but unfortunately the urine was not saved. On the 23d the vomiting became more intense, and the matter vomited changed from a clear mucus to a dark-greenish or brownish-fluid material. The ammonia coefficient was 15.3 per cent. When I saw the patient on the morning of the 24th I recommended her removal to the hospital for the immediate termination of pregnancy, in view of the change in the appearance of the vomit and the continued high ammonia coefficient. Urine drawn by catheter just before the operation presented an ammonia coefficient of 21.3 per cent.

The patient was anesthetized by chloroform, and after the usual preparations the cervix was dilated with Wathen's instrument, followed by Hegar's bougies. It was so resistant, however, that only a No 17 bougie could be introduced, after which the uterus was cleaned out with a dull curette and ovum forceps, followed by a hot intrauterine saline douche and a pack of iodoform gauze. The patient stood the operation well and was put back to bed in good condition.

The following night the patient improved considerably, vomited but little, and was very comfortable. When I saw her at 2 P.M. on the 25th she was looking better than before the operation, was in excellent spirits, and stated that she had not vomited since ten o'clock the previous evening.

During the afternoon she became more uncomfortable and suffered so extremely from nausea that her stomach was washed out with a weak solution of sodium bicarbonate at 6.45 P.M., and a considerable amount of dark-brown material removed, after which considerable relief was obtained. The patient passed a restless night, in spite of the administration of two hypodermics of $\frac{1}{8}$ grain of mor-

CHART III



Toxemic vomiting. Mrs. H. H. S.

Solid line represents total nitrogen of urine expressed in grams.

Broken line represents percentage of total nitrogen excreted as ammonia.

Total nitrogen determined from twenty-four-hour specimens. Ammonia coefficient for first three days from twenty-four-hour specimens, afterward from each specimen as catheterized.

phine. She became very restless about 3 A.M., March 26th, when her stomach was again washed out and a large amount of apparently blood-stained material siphoned off.

When I saw her at 11 A.M. her condition had changed markedly, as compared with the previous day. She was very torpid and the pupils were quite tightly contracted. The pulse was more rapid than the day before and of poor volume, but did not exceed 100. The liver dulness was unchanged and there was no great tenderness over the lower abdomen. At this time a slight yellowish coloration of the conjunctivæ was noted. The stomach was again washed out and the material removed contained large quantities of brownish reddish flakes, which, under the microscope, were found to be composed of blood cells. During the afternoon the patient became irrational and restless and tossed wildly in bed; shortly afterward she became comatose, and remained so until she died, at 6 P.M.

Prior to 3 P.M., as shown by the urinary chart, urine was excreted freely, but catheterization at that time yielded only 150 c.c. of blood urine, and at 5 P.M. only 4 c.c. of apparently pure blood was obtained.

From the time I first saw the patient nothing was administered by the mouth, but large quantities of salt solution were given by the rectum, as well as occasional nutritive enemata after her admission to the hospital.

Before admission to the hospital the entire twenty-four-hour specimens of urine were examined; but after the operation she was catheterized regularly and the ammonia coefficient determined in each specimen, though the total nitrogen was estimated from the total twenty-four hours' output.

From the accompanying chart (Chart III.) it is seen that ammonia coefficient remained between 15 and 16 per cent. for several days, but rose to 21.3 per cent. just prior to the induction of abortion, while the total nitrogen was practically normal. The high total nitrogen after the abortion was

probably due, in part at least, to the involution of the uterus. As the patient became worse the ammonia coefficient rapidly rose and reached 45.5 per cent. forty-six hours after the abortion. The sudden drop immediately after this was probably due to the lavage with sodium bicarbonate, as it had risen to 36.5 per cent. in the specimen obtained three hours before death.

It is interesting to note that albumin was not present until the day of death, its first trace being noted at 8 A.M., together with a few hyaline and granular casts. Seven hours later albumin was present in large quantity and casts were extremely numerous; while the last catheterized specimen consisted only of 4 c.c. of blood. Leucin and tyrosin were not present.

At no time during the illness did the patient show any signs of emaciation, and just before death presented the appearance of a well-nourished woman, with a ruddy complexion.

The temperature at no time was elevated, its highest point being 99.2°. The pulse remained persistently low, and shortly before death, after it could no longer be felt at the wrist, was found to be 98 on auscultation.

CASE V.—*Neurotic Vomiting.* Mrs. W. J. C. (Chart IV.). I first saw the patient November 14, 1904, when I obtained the following history. Twenty-eight years old, married nine years, two children and one miscarriage. The labors were difficult, but not instrumental. General health excellent, except in last and present pregnancy. The last menstrual period occurred September 5, 1904. Almost immediately after missing the October period vomiting began, which, after a couple of weeks, became so frequent and intense that she was hardly able to retain food of any description, and as a consequence had lost considerably in weight. Heart, lungs, liver, and genitala normal. Pulse, 96; temperature normal.

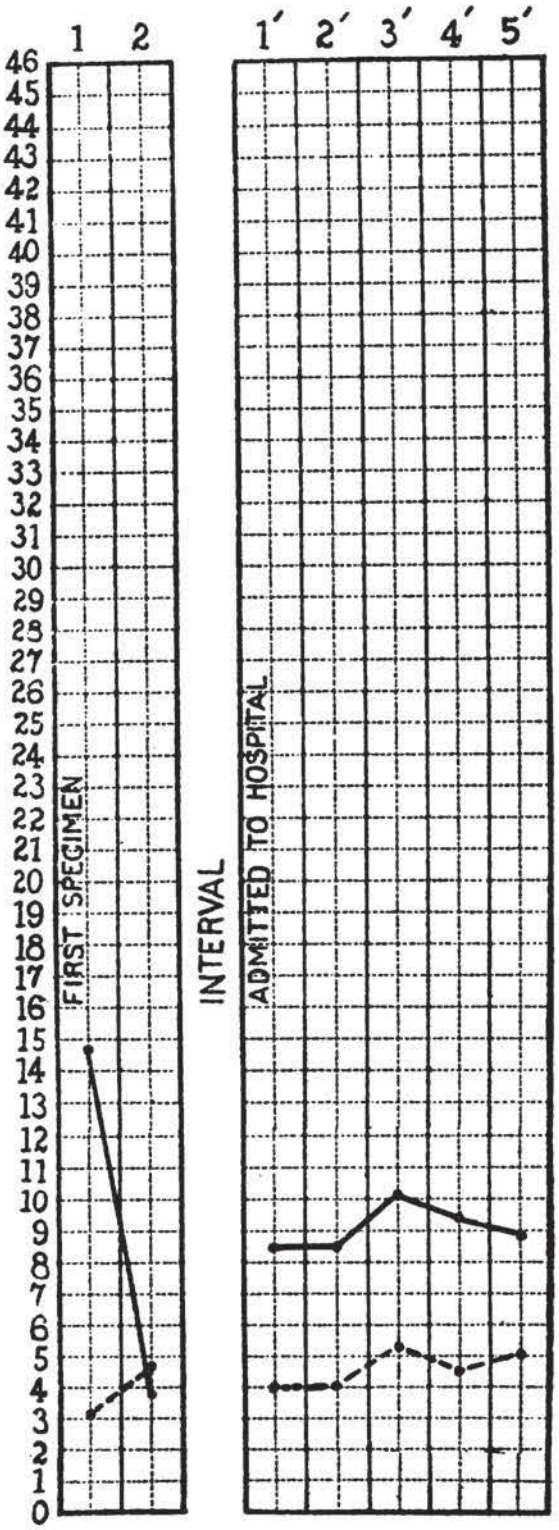
As shown by Chart IV., two twenty-four-hour specimens of the urine examined at this time presented a normal ammonia coefficient. Shortly afterward a slight, bloody discharge appeared, and the patient believed that abortion was imminent. As long as this continued she did not vomit, but as soon as the hemorrhage ceased the vomiting reappeared with its original intensity, so that I was urged to induce abortion, as the various remedies which I prescribed were without avail.

In the latter part of November the patient had a number of severe asthmatic attacks, similar to those from which she suffered throughout the second half of her last pregnancy. On December 1st her condition became so serious that she was transferred to the hospital. When I saw her shortly after admission she was sitting propped up in bed and gasping for breath, with labored respiration and a marked inspiratory tug, and with loud rales over both lungs. The pulse was 116 and the temperature normal. She was considerably emaciated, with the eyes sunken far back in their orbits, and gave the impression of being desperately ill.

From the examination of the urine and the history of the case, I felt convinced that a large part at least of the symptoms were neurotic in origin, and accordingly placed her under the care of a competent trained nurse and ordered a diet of measured quantities of water, milk, and egg albumen, and the saving of all urine. She was told that her vomiting was not of such a character as to necessitate abortion, and would undoubtedly yield to treatment. As a result the vomiting ceased within forty-eight hours, while the asthmatic attacks became less frequent and severe. Improvement was so rapid that at the end of five days she was able to retain a more liberal diet, and left the hospital on the tenth day greatly improved. The second part of Chart IV. shows the condition of the urine during the first five days of her stay in the hospital.

The vomiting did not reappear after her return home,

CHART IV



Neurotic vomiting. Mrs. W. J. C.
Solid line represents total nitrogen of urine expressed in grams.
Broken line represents percentage of total nitrogen excreted as ammonia.
All determinations made from twenty-four-hour specimens.

but within a short time the asthma grew worse, and gradually became so severe as to appear to menace her life. Accordingly, after consultation with her physician, Dr. Cary B. Gamble, she was once more removed to the hospital and abortion induced on December 29th. With the exception of two days one week after the operation the asthmatic attacks ceased with the administration of the chloroform. The convalescence was uneventful and the patient returned home in excellent condition.

CASE VI.—*Neurotic Vomiting.* Mrs. H. B. McN. (Chart V.). I first saw the patient February 12, 1905, when I obtained the following history: Twenty-five years old, married three years, no children; one abortion at two months shortly after marriage. Last menstrual period December 21, 1904. She was perfectly well until February 1, 1905, when she began to suffer intensely from nausea and vomiting; for the past week she has vomited everything she has taken and has lost considerably in flesh and is extremely nervous.

Physical examination showed no abnormalities and the genitalia were normal, except for the pregnancy. Pulse, 100; temperature normal. In spite of the administration of a number of remedies, the vomiting grew worse rather than better. Accordingly a twenty-four-hour specimen of urine was saved on the 18th and 19th and found to be normal, as shown in Chart V.

Having diagnosticated neurotic vomiting from the normal condition of the urine, I told the patient that there would be no necessity for interfering with the pregnancy, and that she would be promptly cured if she would implicitly follow my directions. I then put her to bed and gave very minute directions as to the character of her food and how it should be taken.

When I saw her again on the 27th her condition had not improved. I accordingly told her that there was no doubt about her ultimate recovery, but that if she did not cease

CHART V

Neurotic vomiting. Mrs. H. B. McN.
Solid line represents total nitrogen of urine expressed in grams.
Broken line represents percentage of total nitrogen excreted as ammonia.
Determinations made from twenty-four-hour specimens.

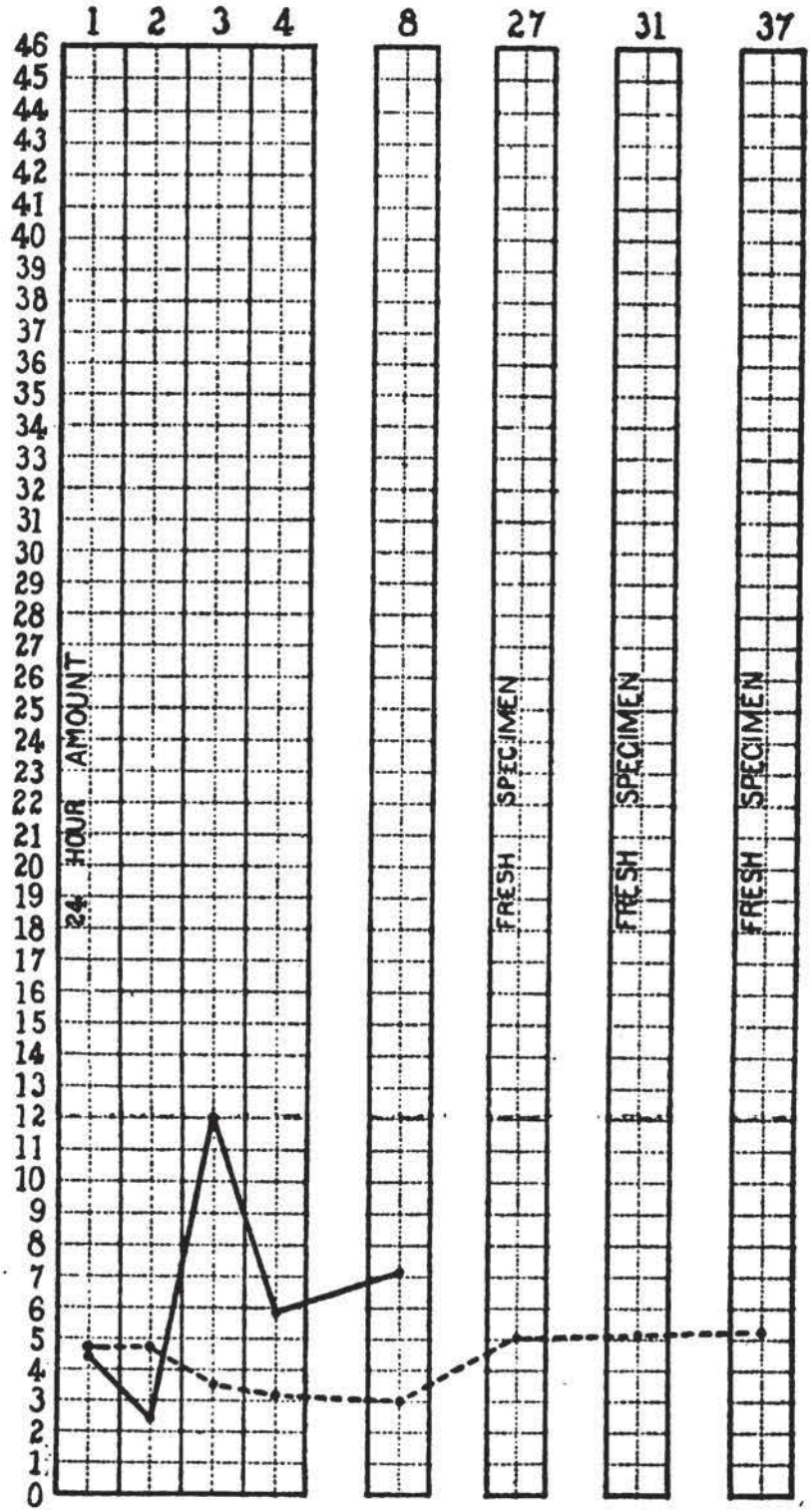
vomiting within three days I should take her to the hospital, put her under a trained nurse, not allow her to see her family, and institute a rigid rest cure. Upon calling three days later to learn the effect of my threat, I found that the patient had not vomited since my last visit, and had been able to eat three meals a day with great comfort ever since.

The vomiting did not recur and the patient improved markedly in appearance, so that one month later she was stouter than ever before in her life. She told me later that I could not have made a more fearful threat, as she had an abnormal horror of a hospital and would have done anything to escape going to one.

CASE VII.—*Neurotic Vomiting.* Mrs. W. T. W. (Chart VI.) I first saw the patient April 12, 1905, in consultation with her husband, who is a physician. She was twenty-one years old, married sixteen months and had not been pregnant. The last menstrual period occurred February 5, 1905. She began to suffer from nausea and vomiting just after missing her March period. At first the vomiting occurred at regular intervals, but for the past three weeks it has occurred after every meal, sometimes at once and at other times not for several hours. Several days ago she fainted while vomiting. A week before I saw her she had gone to the seashore, but was not benefited by the trip. She has lost considerably in weight and complains of pain in the epigastric region. She is very nervous, and told me that her mother had suffered in all of her pregnancies with intense nausea, which on several occasions was so severe that the induction of abortion was considered.

Examination showed a small, thin woman, with no jaundice or œdema. The heart and lungs were normal; pulse, 120; temperature normal. The abdomen was scaphoid and the liver dulness seemed slightly diminished, terminating 5 cm. above the costal margin in the mammary line. The genitalia were normal and the uterus enlarged to the size of a seven to eight weeks' pregnancy.

CHART VI.



Neurotic Vomiting. Mrs. W. T. W.

Solid line represents total nitrogen in grams.

Broken line represents percentage of total nitrogen excreted as ammonia.

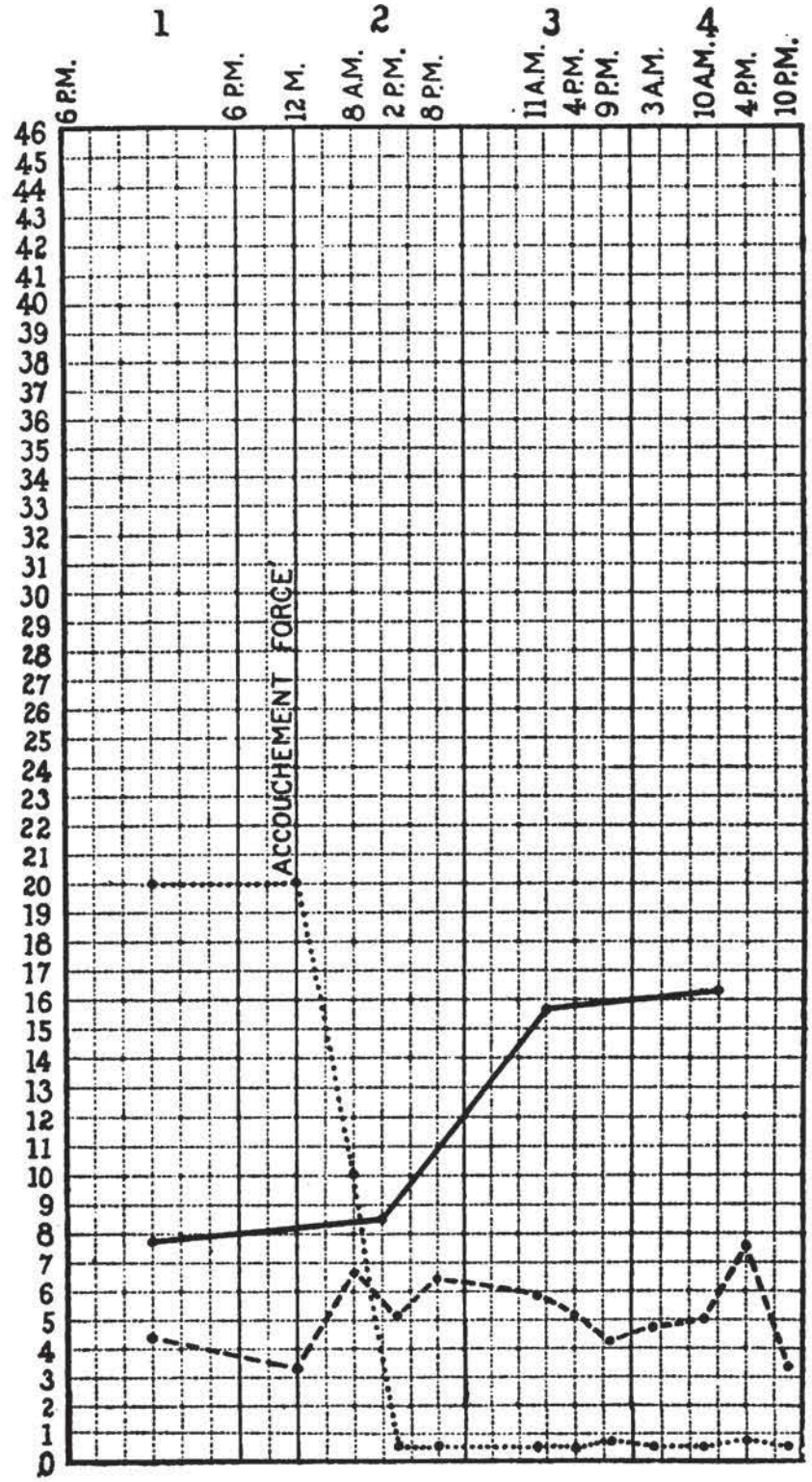
First five determinations made from twenty-four-hour specimens, the last three from single fresh specimens.

The patient was put to bed and a twenty-four-hour specimen of urine collected, which, as shown by Chart VI., presented a normal ammonia coefficient. Accordingly a diagnosis of neurotic vomiting was made. The patient was assured that she would recover promptly if she followed my directions, and a trained nurse was obtained and ordered to allow no one in the room but the husband, and then only for a few minutes a day. She received several saline enemata each day, but no food for the first twenty-four hours, and only albumin and water afterwards. Within two days the vomiting ceased, and two days later small amounts of food were given by the mouth, and by the end of the week the patient was able to go about in comfort.

Her condition continued satisfactory for nearly three weeks, when the vomiting returned and soon became more severe than before. The patient rapidly emaciated, and her husband felt that the only hope for her recovery lay in the induction of abortion. A more rigorous trained nurse was secured, the patient put back to bed and nourished only by the rectum, and told that she could not see her friends nor receive anything by the mouth until the vomiting ceased, and that if that did not occur within a few days she would be taken to the hospital and completely isolated. On this occasion recovery was slower, but within forty-eight hours the nausea became less violent, and the vomiting ceased two days later, although the patient still complained of great depression and felt that her recovery was merely temporary. Shortly afterward she was allowed small quantities of solid food and began to move about the room. After this improvement was rapid, and a few days later, when I telephoned to inquire how she was, I found the was dressing to go to the horse show. She rapidly regained her loss in weight and has since been in excellent condition.

Case VIII.—*Pre-eclamptic Toxemia.* Mrs. W. F. C. (Chart VII.) Induction of premature labor. Typical clinical

CHART VII.



Pre-eclamptic toxemia. Mrs. W. F. C.
Solid line represents total nitrogen expressed in grams.
Broken line represents percentage of total nitrogen excreted as ammonia.
Dotted line represents number of grams of albumin per liter of urine
Total nitrogen determined from twenty-four-hour specimens.
After first day ammonia coefficient and amount of albumin determined

history. This chart is given for comparison with Charts I. to III. from cases of toxemic vomiting, and clearly demonstrates the differences in metabolism in the two conditions.

I am under many obligations to my associate, Dr. J. M. Slemons, for the chemical examination of the urine in the cases here reported.

CONCLUSIONS. 1. The pernicious vomiting of pregnancy is not due to a single etiological factor, and occurs in one of three varieties—reflex, neurotic, and toxemic.

2. The reflex type is dependent upon the existence of abnormalities of the generative tract or ovum, and may be cured by their correction or removal.

3. The neurotic type is dependent upon the existence of a neurosis without demonstrable lesions, and is more or less allied to hysteria. It is the most frequent variety of serious vomiting, and can be cured by suggestion or modified rest cure.

4. The toxemic type is associated with characteristic changes in metabolism and, in fatal cases at least, with lesions in the liver analogous to those observed in acute yellow atrophy. It may occur in an acute or chronic form, the former causing death in ten days or less, while the latter may persist for weeks, or even months.

5. In reflex and neurotic vomiting there are no manifest changes in the urine, while the toxemic variety is characterized by a marked decrease in the amount of nitrogen excreted as urea and a characteristic increase in the amount excreted as ammonia. The so-called ammonia coefficient rising from 3 to 5 per cent. to as high as 46 per cent. in one of my cases.

6. The toxemic type is diagnosticated by the examination of the urine, the reflex by careful bimanual examination of the genitalia, and the neurotic after the exclusion of the other two varieties.

7. The prognosis is excellent in reflex and neurotic vomiting, provided appropriate treatment is instituted, so that the

termination of pregnancy is rarely indicated. In toxemic vomiting, on the other hand, a fatal issue can be averted only by the prompt induction of abortion, and even then the prognosis is dubious.

LITERATURE.

Ahlfeld. Hyperemesis gravidarum, Ptyalismus, Hysterie. Centralbl. f. Gyn., 1891, pp. 329–330.

Allbutt. Albuminuria in Pregnancy. Lancet, 1897, i. pp. 579–82.

Anquétin. Les vomissements incoercibles pendant la grossesse. Révue médicale, 1865, ii. pp. 205–17, 275–89, 336–49, 398–407 and 467–78.

Bacon. The Vomiting of Pregnancy. American Journal of the Medical Sciences, 1898, cxv. pp. 683–98.

Bar. Des polynévrites et des mononévrites gravidiques. Bull. de la Soc. d'obst. de Paris, 1894, vii. pp. 180–85.

Bardinet. De l'ictére épidémique chez les femmes encientes. L'union médicale, 1863, xx. pp. 260–63.

Beatty. A Case of Acute Atrophy of the Liver. New York Medical Record, 1895, xlviii. pp. 274, 275.

Behm. Ueber Hyperemesis gravidarum mit Aufstellung einer neuer Intoxikationstheorie vom Wesen der Krankheit. Archiv. f. Gyn., 1903, lxix. pp. 410–30.

Beking. Icterus gravidarum. Ref. Centralbl. f. Gyn., 1897, p. 1432.

Benedict. Zur Kenntniss des Schwangerschafts-Ikterus. Deutsche med. Wochenschr., 1902, xxviii. pp. 296, 297.

Bennett. On the Obstinate Sickness During Pregnancy. British Medical Journal, 1875, i. p. 769.

Blot. De l'ictére épidémique chez les femmes enceintes. Bull. de l'acad. imp. de méd., Paris, 1864–65, xxx. pp. 55–66.

Bouffe de St. Blaise. Les autointoxications gravidiques. Annales de gyn. et d'obst., 1898, l. 342–72.

Brauer. Ueber Graviditäts-Hemoglobinurie. Münchener med. Woch. enschr., 1902, xliv. pp. 825, 826.

Brauer. Ueber Graviditäts-Ikterus. Centralbl. f. Gyn., 1903, pp. 787–89.

Brauer. Eine Graviditäts-Toxonose des Zentralnervensystems. Münch. med. Wochenschr., 1904, li. pp. 1142–45.

Brian-Moreau. Note zur une cause peu connue des vomissements des femmes enceintes. Gazette hebdomadaire, 1856, iii. pp. 514, 515.

Budd. On Diseases of the Liver. Third American edition, 1857, pp. 250–98.

Bué. Des vomissements incoercibles et du curettage dans la mole hydatidiforme. La presse médicale, 1897, v. pp. 29, 30.

Busch and Moser. Handbuch der Geburtskunde, Berlin, 1843.

Cazeaux. Traité théoretique et pratique de l'art des accouchements. 3me. ed., Paris, 1850, 286–89.

Chailly-Honoré. Bullétin gen. de therap., 1844, October, 288.

Champetier de Ribes et Bouffe de St. Blaise. Note sur un cas de vomissements incoercibles avec autopsie. Comptes rend. de la Soc. d'obst., de gyn. et de paed. de Paris, 1901, iii. pp. 95–97.

Charpentier de Rubaix. Du danger de l'ictére chez les femmes encientes. Révue med-chir. de Paris, 1854, xv. pp. 268–70.

Charrin et Guillement. Le glycogéne hépatique pendant le grossesse. Compte rend. de l'acad. de sciénces, 1900, cxxx. pp. 673–76.

Chazan. Ueber Hyperemesis gravidarum. Centralbl. f. Gyn., 1891, p. 541.

Chazan. Zur Frage der Hyperemesis gravidarum. Centralbl. f. Gyn. 1896, pp. 849–51.

Churchill. Induction of Premature Labor on Account of the Presence of Certain Diseases Caused by or Connected with Pregnancy. The Theory and Practice of Midwifery. Second edition. London, 1850, pp. 247–48.

Churchill. Nausea and vomiting. On the Diseases of Women. New Am. Ed. by Condie, 1852, 446–60.

Clivio. Das unstillbare Erbrechen der Schwangaren. Rassigna d'ost. e gin., 1901 (Ref. Centralbl. f. Gyn., 1902, pp. 1037–38).

Condamin. Note sur un nouveau traitement des vomissements incoercibles. Lyon médicale, 1902, xcviii. pp. 145–148.

Copeman. A Novel Treatment of Obstinate Vomiting in Pregnancy. British Medical Journal, 1875, i. pp. 637, 638.

Czerny u. Keller. Zur Kenntniss der Gastroenteritis im Sänglingsalter. Jahrbuch f. Kinderheilkunde, 1897, xliv. pp. 15–52, and lxv. pp. 274–81.

Damany. Observation de vomissements incoercibles au début d'une grossesse. Gazette méd. de Paris, 1896, lxvii. p. 208.

Dance. Vomissemens opiniatres survenus au commencement de la grossesse, et paraissant dépendre d'un état morbide de l'utérus et du produit de la conception. Arch. gen. de méd., Paris, 1827, xiv. pp. 245–52.

Danyau. Vomissemens opiniatres. L'union médicale, 1852, vi. pp. 125, 126.

Davis, D. D. Elements of Obstetric Medicine. Second edition, London, 1841.

Davis, E. O. Fatal Nausea and Vomiting of Pregnancy. Transactions of the American Gynecological Society, 1894, xix. pp. 110–118.

Davis and Harris. Syncytioma Malignum and Ectopic Gestation causing Pernicious Nausea. Transactions of the American Gynecological Society, 1900, xxv. pp. 364–81.

Desnos, Joffroy et Pinard. Sur un cas d'atrophie musculaire des quatres membres à évolution trés rapide, survenue pendant la grossesse et consécutivement à des vomissement incoercibles. Bull. de l'acad. de méd. de Paris, 1889, 3me. ser. xxi., pp. 44–51.

Dionis. Traité general des accouchmens, Paris, 1718, 143–47.

Dirmoser. Den vomitus gravidarum perniciosus. Wien, 1901.

Dirmoser. Ein Weiterer Beitrág zur Autointoxikationstheorie bei Hyperemessi gravidarum. Wienerklin. Wochenschrift, 1903, xvi. pp. 405–409.

Dubois. Quelques considerations sur l'avortment dans les cas de vomissements. Bull. de l'acad. de méd., Paris, 1851–52, xvii. pp. 557–83.

Duncan, Matthews. Clinical Lecture on Hepatic Diseases in Gynecology and Obstetrics. London Medical Times and Gazette, 1869, i. pp. 57-59; also Clinical Lectures on the Diseases of Women, third edition, 1886, 293–305.

Edgar. Practice of Obstetrics, second edition, 1904, pp. 336–44.

Edgar. Hepatic Lesions in Obstetric Practice. Journal of the American Medical Association, 1905, xliv. pp. 1077–80.

Erismann. Beiträge zur Lehre von Hyperemesis gravidarum. D. I. Basel, 1890.

Eulenberg. Ueber Puerperale Neuritis and Polyneuritis. Deutsche med. Wochenschr., 1895, pp. 118–21 and 140–46.

Evans. On the Etiology of the Nausea and Vomiting of Pregnancy. American Gynecological and Obstetrical Journal, 1900, xvi. pp. 45–51.

Ewing. The Pathology, Anatomy and Pathogenesis of the Toxemia of Pregnancy. American Journal of Obstetrics, 1905, li., pp. 145–55.

Fellner. Die Beziehungen Innerer Krankheiten zu Schwangerschaft-Geburt und Wochenbett. Liepzig u. Wien., 1903, pp. 116–20.

Fischl. Zur Genese der Hyperemesis gravidarum. Prager med. Wochenschr., 1884, ix., pp. 22–24 and 229–31.

Flaischlen. Ueber Hyperemesis gravidarum. Zeitschr. f. Geb. u. Gyn. 1890, xx. pp. 81–92.

Frank. Ueber Hyperemesis gravidarum. Prager med. Wochenschr. 1893, xviii. pp. 11–12 and 24–26.

Frank. Ueber Hyperemesis gravidarum. Centralbl. f. Gyn., 1898, pp. 448, 449.

Folin. Laws Governing the Chemical Composition of the Urine. American Journal of Physiology, 1905, xiii. pp. 66–115.

Gardner. The Diagnosis of Early Pregnancy. American Journal of Obstetrics, 1897, xxxv. pp. 54–63.

Gerst. Contribution à l'étude des vomissements de la grossesse. Thése de Paris, 1903.

Giles. Observations on the Etiology of the Sickness of Pregnancy Transactions of the London Obstetrical Society, 1893, xxxv. pp. 303–33.

Glaessner. Experimentelles über der Obstipation. Wiener klin. Woch enschr., 1904, xvii. pp. 1205, 1206.

Goldspohn. A Unique Case of Circumscribed Infection of the Placenta and Excessive Vomiting. American Journal of Obstetrics, 1904, l. pp. 712–19.

Graefe. Ueber Hyperemesis gravidarum. Sammlung zwangloser Abhandlungen, a. d. Gebiete der Frauenheilkunde und Geburtshilfe, 1900, iii. Heft 7.

Graefe. Zur Frage der Etiologie der Hyperemesis gravidarum. Monatsschr. f. Geb. u. Gyn., 1904, xx. pp. 23–39.

Guéniot. Des vomissements incoercibles pendant la grossesse. Thèse de Paris, 1863, p. 128.

Guéniot. Etiologie et traitement des vomissements incoercibles de la grossesse. Archives de tocologie, 1889, xvi. pp. 745–769.

Guillemeau. Du vomissement qui vient aux femmes grosses. De la grossesse et accouchement des femmes. Paris, 1620.

Hewitt. The Vomiting of Pregnancy: Its Causes and Treatment. Transactions of the London Obstetrical Society, 1871, xiii. pp. 103–17.

Hewitt. On the So-called Uncontrollable Vomiting of Pregnancy. Transactions of the London Obstetrical Society, 1885, xxvi. pp. 273–324.

Hewitt. On the Severe Vomiting of Pregnancy. Transactions of the American Gynecological Society, 1888, xiii. pp. 218–58.

Hirschberg. Drei Fälle von acuten Gelben Leberatrophie. D. I. Dorpat., 1886.

Hohl. Das Erbrechen der Schwangeren. Lehrbuch der Geburtshülfe, II. Aufl. 1862, pp. 222–25.

Holladay. Vomiting in Pregnancy. Lancet, 1897, i. 579–82.

Horaczek. Die gallige Dyscrasie mit acuten gelber Atrophie der Leber. Wien., 1843.

Horwitz. Ueber das unstillbare Erbrechen der Schwangeren. Zeitschr. f. Geb. u. Gyn., 1883, ix, pp. 110–90.

Jaffé. Ueber Hyperemesis gravidarum. Volkmann's Sammlung klin Vorträge, No. 305.

Jaggard. Notes on the Pernicious Vomiting of Pregnancy. Transactions of the American Gynecological Society, 1889, xiv. pp. 441–61.

Jardine. Three Cases of Pernicious Vomiting of Pregnancy. Journal of Gynecology and Obstetrics of the British Empire, 1903, iv. pp. 272–77.

Jolly. Ueber Paraplegie in der Schwangerschaft. Neurologisches Centralbl., 1885, iv. p. 305.

Jürgens. Fettemboli und Metastase von Leberzellen bei Eclampsie. Berl. klin. Wochenschr., 1886, p. 519.

Kaltenbach. Ueber Hyperemesis gravidarum. Zeitschr. f. Geb. u. Gyn., 1891, xxi. pp. 200–208.

Kehrer. Gazetamponade des Mutterhalses zur Stillung der Hyperemesis gravidarum. Centralbl. f. Gyn., 1896, pp. 393–400.

Kehrer, E. Die physiol. u. path. Beziehungen der weiblichen Sexualorgane zum Tractus intestinalis. Berlin, 1905, pp. 92–160.

Kercksig. Von einer epidemischen Gelbsucht. Hufeland's Journal der pract. Arzneikunde, 1799, vii. 3tes Stück., pp. 94–109

Klein. Hyperemesis gravidarum. Zeitschr. f. Geb. u. Gyn., 1898, xxxix. pp.75–97.

Klingelhöfer. Beitrag zum Icterus epidemicus. Berl. klin. Wochenschr., 1876, xiii. pp. 76, 77.

Krassowsky. Les vomissements incoercibles de la grossesse. Annales de gyn. et d'obst., 1894, xli. p. 37.

Kreutzmann. Ein Fall von Hyperemesis gravidarum gefolgt von Polyneuritis in graviditate. New Yorker med. Monatschr., 1900, xii. pp. 101–108.

Kühne. Beitrag zur Lehre von der Hyperemesis gravidarum. Monatsschr. f. Geb. u. Gyn., 1899, x. pp. 432–36.

Lang. Sur un cas de vomissements incoercibles à 4 mois de la grossesse. Mort de la parturient. Archives de tocolog. et de gyn., 1893, xx. pp. 620–28.

Lebert. Ueber Icterus typhoides. Virchow's Archiv., 1854, vii. 343–96 und viii. pp. 147–91.

Le Masson. Les ictérus et les coliques hépatiques chez les femmes en etat de puerpéralité. Thése de Paris, 1898, p. 317

Lindemann. Zur. path. Anatomie des unstillbaren Erbrechens der Schwangeren. Centralbl. f. allg. Path. u. path. Anat., 1892, iii. pp. 625–30.

Liepmann. Ueber ein für menschliche Placenta specifisches Serum. Deutsche med. Wochenschr., 1902, pp. 911–12; 1903, 80–81 and 283–85.

Lomer. Ueber die Bedeutung des Icterus gravidarum für Mutter und Kind. Zeitschr. f. Geb. u. Gyn. 1886, xiii. pp. 169–85.

Luez. Traitment des vomissements de la grossesse, benins et graves reconnue d'origine nerveuse. Thése de Paris, 1893.

Lwow. Hyperemesis gravidarum. Deutsche Medizinal Zeitung, 1900, xxi. pp. 1013–15, 1025–27, 1037–39, 1049–51, 1061–63, 1073–75, 1085–87 and 1097–1100.

Mader. Zur Polyneuritis peripherica puerperarum et gravidarum. Wiener klin. Wochenschr., 1895, viii. pp. 537–39 and 555–59.

Martin. On the Vomiting of Pregnancy. British Medical Journal, 1904, ii. pp. 1569–71.

Mauriceau. Traité des maladies des femmes grossesse. 6me ed., 1721, i. pp. 128–34.

McClintock. The Excessive Vomiting of Pregnancy. Dublin Journal of the Medical Sciences, 1873, lv. pp. 462–73.

Meillére. Sur quelques cas de retention des chlorures. Comptes rendus de la soc. de biologie., 1902, liv. pp. 1135, 1136.

Mettler. The Nervous Element in the Vomiting of Pregnancy. Journal of the American Medical Association, 1892, xviii. pp. 16–64.

Meunier. Essai critique zur l'ictére des femmes encientes à propos l'epidémie de Paris, 1871–72. Thése de Paris, 1772.

Minkowski. Störungen des Stickstoffumsatzes in der Leber. Lubarsch-Ostertag. Ergebnisse der allg. Path. u. path. Anat., 1895, ii. Jahrgang, pp. 726–31.

Möner. Quoted by Folin.

Münzer. Der Stoffwechsel des Menschen bei akuter Phosphorvergiftung. Deutsches Archiv. f. klin. Med., 1892, lii. p. 199.

Münzer. Die Harnstoffbildende Funktion der Leber. Arch. f. exp. Path. u. Pharm., 1894, xxxiii. p. 164.

Muret. Hyperemesis gravidarum und Hysterie in Allgemeinen. Deutsche med. Wochenschr., 1893, xix. pp. 123–25.

Neuberg and Richter. Ueber das Vorkommen von freier Aminosäuren in Blute bei akuter Leberatrophie. Deutsche med. Wochenschr., 1904, xxx. pp. 499–501.

Opie. Zonal Necrosis of the Liver. Journal of the Medical Research, 1904, xii. pp. 147–67.

Ozanam. De la forme grave de l'ictére esséntiel. Thése de Paris, 1849.

Payer. Ueber den Einfluss des Zuckers auf den Stoffwechsel der Schwangeren. Monats. f. Geb. u. Gyn., 1899, x. pp. 559–580 und 784–800.

Pick. Ueber Hyperemesis gravidarum. Volkmann's Sammlung klin. Vorträge, N. F., 1902, Nos. 325 and 326.

Pfaundler. Zur Frage der Säurevergiftung, etc. Jahrbuch f. Kinderheilkunde, 1904, lx. pp. 719–50.

Pierrehughes. Etude critique zur les vomissements incoercibles de la grossesse. Thése de Paris, 1902.

Quincke. Acute Leberatrophie. Nothnagel's specielle Pathologie u. Therapie, 1899, xviii. pp. 294–315.

Rigby. A System of Midwifery. Philadelphia, 1841, pp. 101–103.

Rokitansky. Die acute Schmelzung der Leber. Lehrbuch der path. Anatomie, 3te Auf., 1861, iii. pp. 269–72.

Rosenthal. Ueber das Copeman'sche Verfahren zur Beseitigung des hartnäckigen Erbrechens Schwangerer. Berl. klin. Wochenschr., 1879, xvi. pp. 388–91.

Roughton. Pernicious Vomiting of Pregnancy. Lancet, 1885, ii. pp. 425, 426.

Saint Vel. Note sue une forme d'ictére grave chez les femmes enceintes. Gazette des hôpitaux, 1862, xxxv. pp. 538, 539.

Schaeffer. Ein Beitrag zur Etiologie des wiederkehrenden Icterus. Monatsschr. f. Geb. u. Gyn., 1902, xv. pp. 907–20.

Schittenhelm. Zur Frage der Ammoniakausscheidung im menschlichen. Urin. Deutsches Arch. f. klin. Med., 1903, lxxvii. pp. 517–39.

Schmiedeberg. Ueber das Verhalten des Ammoniaks zur Harnstoffbildung in Tierkörper. Arch. f. exp. Path. u. Pharm., 1877, viii. p. 1.

Schmorl. Path. anat. Untersuchungen über Puerperal-Eklampsie. Leipzig, 1893.

Schmorl. Zur Lehre von der Eklampsie. Archiv. f. Gyn., 1902, lxv. pp. 504–529.

Schroeder. Die Bildungsstätte des Harnstoffes. Arch. f. exp. Path. u. Pharm., 1882, xv. p. 364.

Schroeder. Lehrbuch der Geburtshilfe. 12te Auf., 1893, p. 434.

Simmons. Quoted by Danyau.

Smith. A Synopsis of Ten Cases of Jaundice Occurring in Pregnant Women. Northwestern Med. and Surg. Journ., 1873–74, iv. pp. 436–40.

Solowieff. Ueber einen Fall von Hyperemesis gravidarum, begleitet von Neuritis multiplex. Centralbl. f. Gyn., 1892, pp. 492–97.

Stolz. Quoted by Hewitt, 1885.

Stone. Toxemia of Pregnancy. American Gynecology, 1903, iii. pp. 518–50.

Strauss. Zur Funktionsprüfung der Leber. Deutsche med. Wochenschr., 1901, pp. 757–59 and 786, 787.

Sutugin. Hyperemesis gravidarum. Das übermässige Erbrechen der Schwangeren, Berlin, 1883.

Tarnier. Recherches sur l'etat puerpéral, etc. Thése de Paris, 1857.

Thierfelder. Acute Atrophy of the Liver. Ziemssen's Cyclopedia of the Practice of Medicine. American edition. 1880, ix. pp. 242–305.

Tisseraud. Du vomissements nerveux. Thése de Paris, 1865.

Turenne. Traitment rationnel de la toxémie gravidique précoce, et en particulier des vomissements simples de la grossesse. Annales de gyn. et d'obst. 1904, 2me Ser. i. pp. 657–85.

Tuszkai. Zur Frage der Hyperemesis gravidarum. Verh. der deutschen Gesell. f. Gyn., 1895, vi. pp. 766–87.

Tuszkai. Ueber Indication der Einleitung der Geburt bei Hyperemesis. Berl. klin. Wochenschr., 1903, xl. 803–05.

Ulrich. Lethaler Fall von Vomitus gravidarum. Monatsschr. f Geb., 1858, xi. pp. 92–97.

Vaughan. Case of Vomiting in Pregnancy Successfully Treated. Memoirs of the Medical Society of London, 1789, vol. ii. pp. 125–32.

Veit. Ueber Endometritis decidua. Volkmann's Sammlung klin. Vorträge, 1885, No. 254.

Veit. Ueber Albuminurie in der Schwangerschaft. Berl. klin. Woch., 1902, pp. 513 und 540.

Veit and Scholten. Syncytiolyse und Hämolyse. Zeitschr. f. Geb. u. Gyn., 1903, xlix. pp. 210–32.

Von den Velden. Icterus gravidarum. Hegar's Beiträge zur Geb. u. Gyn., 1904, viii. pp. 448–64.

Weichardt. Experimentelle Studien über der Eklampsie. Deutsche med. Wochenschr., 1902, pp. 224–26.

Winscheid. Ueber Hyperemesis gravidarum. Centralbl. f. Gyn., 1900, 806–08.

Whitfield. Puerperal Neuritis due to the Vomiting of Pregnancy. Lancet, 1889, i. pp. 627, 628.

Wormser. Zur moderner Lehre von den Eklampsie, 1904, li. pp. 7–10.

Young. Simple and Malignant Jaundice of Pregnancy. Medical News, 1898, lxxviii. pp. 618–21.

Zaborski. Hyperemesis gravidarum. Monatsschr. f. Geb. u. Gyn., 1904, xx. pp. 39–47.