

**A further report on the relation of thyroidism to the toxæmia of pregnancy
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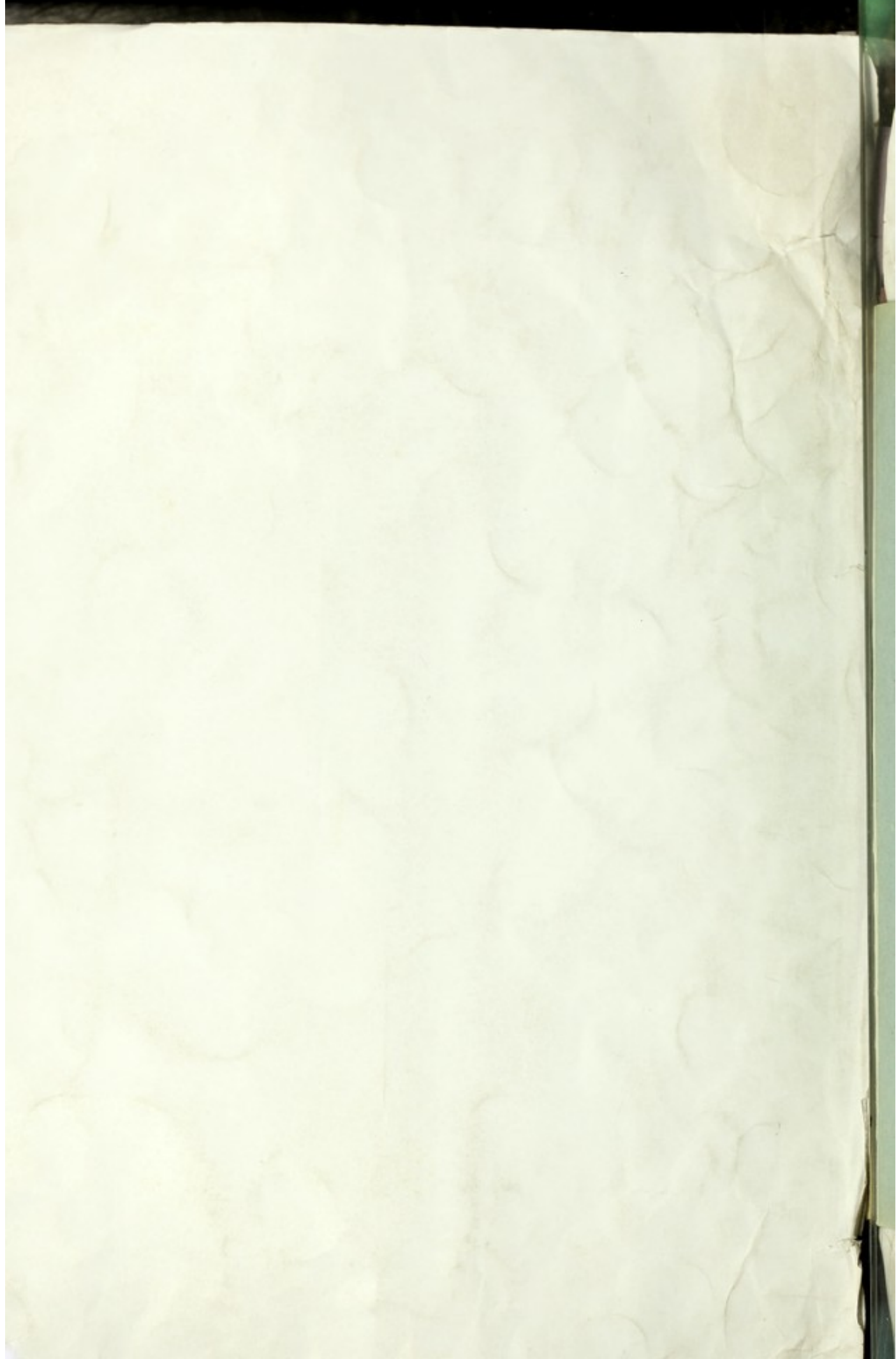
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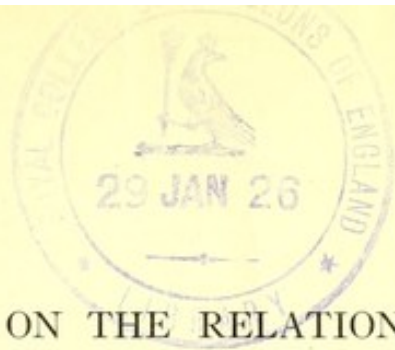
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A FURTHER REPORT ON THE RELATION OF THYROIDISM TO THE
TOXÆMIA OF PREGNANCY

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A FURTHER REPORT ON THE RELATION OF THYROIDISM TO THE TOXÆMIA OF PREGNANCY¹

By GEORGE GRAY WARD, JR., M. D., NEW YORK CITY

IN April, 1909, I presented a study of the relation of the thyroid gland and thyroidism to the toxæmia of pregnancy (1) as a thesis for Fellowship in this Society, and after reviewing some of the research work that had been done up to that time and the deductions to be drawn therefrom, I reported two cases that had come under my observation which were illustrative of the subject and seemed to bear out clinically some of the conclusions of the laboratory.

The conclusions in my paper were as follows:

1. The thyroid gland is, in all probability, concerned in promoting nitrogenous metabolism.

2. There is considerable evidence that the thyroid gland normally hypertrophies during pregnancy, and plays an important part in the increased nitrogenous metabolic processes incident to that state.

3. It is very probable that the toxæmia of pregnancy is largely dependent upon faulty metabolism; at least, insufficient metabolism is an accompaniment which greatly adds to the seriousness of the condition.

4. Failure of the thyroid gland to hypertrophy during pregnancy is probably followed by insufficient metabolism, and may result in the various forms of toxæmia of pregnancy.

5. Graves' disease, by materially altering the quantity and quality of the thyroid secretion, has an important influence upon metabolic processes; therefore, if associated with pregnancy, owing to the increased metabolism incident to that state, it becomes a grave complication.

6. When there is a failure of the normal hypertrophy of the thyroid gland during pregnancy, and when there is a diseased thyroid, as in Graves' disease, the administration of thyroid substance, by supplying the

deficiency of the normal thyroid secretion and by diuretic action, may materially improve a faulty metabolism and thus have a favorable influence upon the manifestations of the toxæmia of pregnancy.

7. The use of a saline extract of thyroid proteids made from fresh normal human glands is much more efficient in rapidity and reliability of action than the sheep thyroids as ordinarily prepared; therefore much more satisfactory results may be expected from its use.

8. The hypodermic administration of thyroid proteids is greatly superior to oral administration, especially when used in cases of toxic vomiting of pregnancy or in eclampsia.

9. As the whole subject is yet so very obscure, much further research work along the same lines and many clinical observations are essential to a more definite understanding of the relationship of the thyroid gland to toxæmia, but in view of some results already obtained the field is at least a promising one.

10. It is not improbable that further research may show that the parathyroids have an important relation to the manifestations of the toxæmia of pregnancy.

Since the above was written, investigations and clinical observations made by different observers along the same line have tended to confirm many of the above conclusions. Several studies adding to our knowledge of the problem have been contributed to the medical journals by both laboratory workers and clinicians. Among the former, the work of Carlson and Jacobson (2), and of MacCallum and Voegtlin (3) is of interest, while clinical observations have been reported by Leitz (4), Stowe (5), Bonnaire (6), Goodall and Conn (7), Porter (8), Davis (9), Rogers (10), and others.

The value of the nitrogen partition of the

¹ Read before the American Gynecological Society, Baltimore, May, 1912.

urine as a guide to the state of the metabolism in the toxæmias of pregnancy cannot be overestimated. In no other way can we judge the degree of the disturbance present, and the limits of safety. Blood pressure is too variable to be relied upon in these cases, as has been emphasized by Davis in a recent paper.

An excess of ammonia nitrogen and rest nitrogen is indicative of marked failure in metabolism.

The work of Williams (11) on the relation of an excess of ammonia to toxic vomiting of pregnancy is familiar to all. He has stated that normally in the first half of pregnancy the ammonia coefficient varies from four to five per cent, while in toxic vomiting it may rise to 10, 20, 30, or even 40 per cent; and in one case (death) it reached 48 per cent. He places 10 per cent of ammonia nitrogen as suspicious if not pathognomonic of toxæmia.

Folin (12), and also Ewing and Wolf (13), however, believe from their investigations that 10 per cent of ammonia nitrogen may be normal when there is a pronounced reduction in the total nitrogen, as under such circumstances they have always found a relative increase in the ammonia.

In 1907, Coronedi and Luzzatto (14), finding the tendency to alkaline reaction in the urine of dogs after complete thyroidectomy, attributed this to the increased ammonia content. In 1909, Berkeley and Beebe (15) found both a relative and an absolute increase in the ammonia in urine after thyroid-parathyroidectomy in dogs.

Recently, MacCallum and Voegtlin have established the further important fact that under similar thyroid removal there is a greatly increased ammonia content in the blood, and Carlson and Jacobson have contributed an important paper on the depression of the ammonia destroying power of the liver after complete thyroidectomy.

Beebe has recently told the writer that some of his unpublished experiments prove beyond a doubt the marked influence the thyroid has on the excretion of ammonia. He has found that under thyroid administration the ammonia excretion was reduced where it had previously been increased after

thyroidectomy. These experiments still further add to the accumulating proofs of the importance of the thyroid and parathyroid glands to some of the physiological processes in the liver.

The liver, then, undoubtedly has an ammonia destroying or converting power, and when this power is inhibited and the liver fails in this function ammonia appears in the urine and also in the blood. Thyroidectomy produces a marked depression in this ammonia destroying power of the liver. An excess of ammonia output in the blood and urine means a depressed functional activity of the liver or a failure in the metabolic processes, and produces ammonia intoxication.

In the light of these observations it would appear logical that when there is a high ammonia output shown by the nitrogen partition, as in a disturbed metabolism of the toxæmia of pregnancy, thyroid administration is indicated.

Among recent clinical contributions that of Goodall and Conn is especially interesting, as showing the intimate relationship between the thyroid gland and the generative organs. They are of the opinion that the ovaries stand in very close relation with the thyroid, and that the uterus is devoid of any influence upon thyroid activity, except indirectly through the ovarian function; also that ovarian hyperactivity is a frequent cause of the development of exophthalmic goitre and that diminished or absent ovarian activity usually coincides with myxœdema. They cite cases where hypothyroidism has been associated with disturbance in the functions of the generative organs, especially menstruation, which were greatly benefited by thyroid administration.

Porter reports a case of pregnancy associated with thyroidism and has advocated the treatment of the diseased gland by the injection of boiling water. E. P. Davis has very recently written on thyroid disease complicating pregnancy and parturition, and states that in his experience it is no unusual thing to observe disturbance of the functions of the genital organs in women, associated with various degrees of thyroid disease. He reports four cases occurring in his practice in

the last few years, in which a diseased thyroid proved an important factor in the outcome. His first case, a 2-para, presented herself with no observable thyroid enlargement but was in an unusually neurotic state. Spontaneous labor developed rapidly with great excitement, the patient becoming unmanageable. The labor terminated normally. There was an excessive secretion of milk and she nursed the child, but remained in a highly hysterical condition. Five months later the patient developed exophthalmic goitre and eighteen months after her labor she was operated upon for cystocele by another surgeon and promptly died in delirium. The second case, a 2-para, had a narrowed and flattened pelvis, which caused a most difficult labor in her first pregnancy. He advised her to have a Cæsarean section on account of her previous history and the pelvic deformity. After the early months the patient began to suffer with nausea, exhaustion, and headaches, and there was an enlargement of the thyroid. The urine showed a deficient nitrogenous metabolism. Thyroid extract was administered, with occasional intermissions, throughout the pregnancy in very moderate doses with some benefit. The patient went to term, when labor began with attacks of great nervousness. An immediate Cæsarean section was done, with happy outcome for both mother and child. A partial thyroidectomy was done six months later, and eighteen months after the delivery, she was in excellent health. The third case reported was in her seventh pregnancy, with a history of having lost all of her children by abortion, or by their dying a few days postpartum. There was a very much enlarged thyroid and marked nervous disturbances. Patient was suffering with considerable nausea and other symptoms of disturbed metabolism, which was confirmed by the nitrogen partition, the ammonia nitrogen being nearly 24 per cent, and the rest nitrogen nearly 20 per cent in one specimen. Patient was advised to have a Cæsarean section, as a living child was greatly desired. Thyroid extract was persistently used throughout the pregnancy with decided success, the urine analysis showing a continuous improvement in the metabolism,

and the patient feeling greatly benefited physically. Cæsarean section was done just before term, and mother and child left the hospital in excellent condition. Three months later her Graves' disease again developed and she had a partial thyroidectomy done by Dr. Charles Mayo and has been well since. The child is exceptionally vigorous.

The fourth case reported was a 2-para who was four months pregnant when first seen and evidently toxæmic, with insufficient metabolism. Thyroid extract was given, one grain three times daily, with benefit. The labor was spontaneous and a healthy child was delivered. During the puerperium, the mother was able to nurse the child. The child had several attacks of intermittent toxæmia which were relieved by the administration of thyroid extract to the mother. There was an immediate improvement in the nitrogenous metabolism following the use of the thyroid extract in this case.

Davis has had the greatest success in giving small doses of the thyroid extract, one grain three times daily, continued for from four to seven months. He advocates elective Cæsarean section as the method of choice where the previous history shows fetal mortality; and thinks that the induction of labor in these cases is seldom indicated, as it is too slow and uncertain. The pressure of elastic bags increases the mother's nervous disturbance, and the delivery of the child through a partially dilated birth canal exposes it to additional risk.

Since 1909 I have had the opportunity to make two further clinical observations on the relation of thyroidism to toxæmia. Both were on the same patients whose cases I previously reported.

A summary of the history of Case 2 as reported in my former paper is as follows:

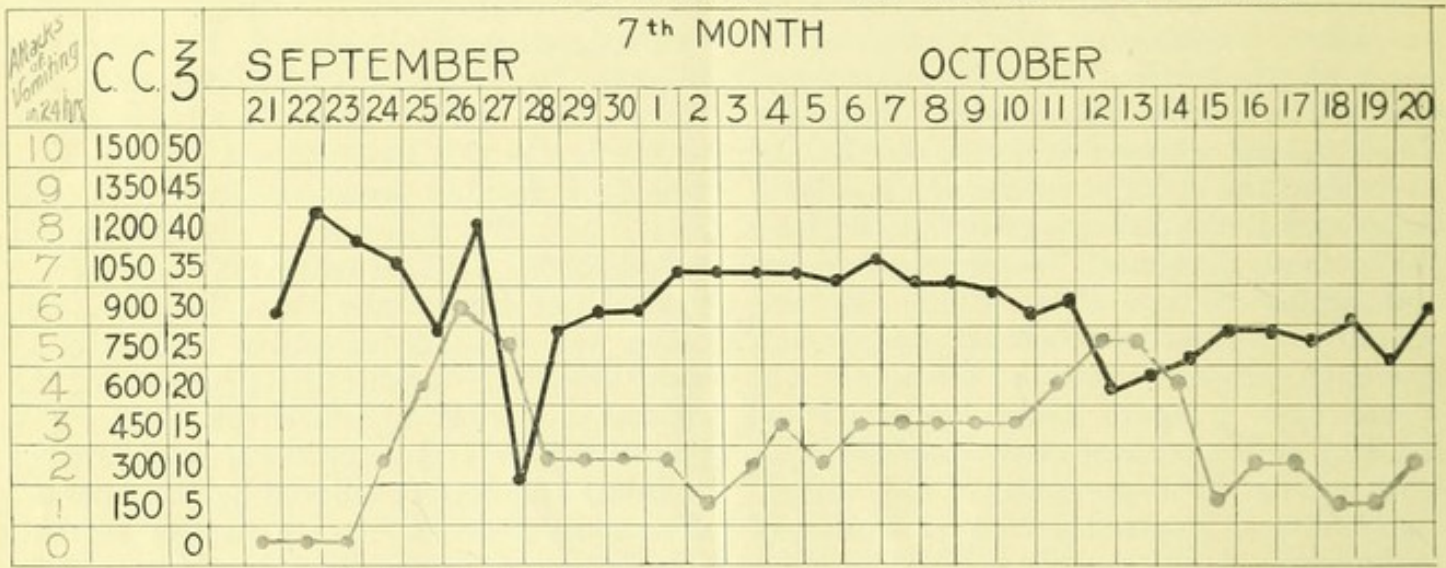
Mrs. A. T., aged 32, was delivered by me in November, 1908, by vaginal hysterotomy, her case being complicated by Graves' disease and a most severe toxæmia, manifested by a hyperemesis, that almost amounted to pernicious vomiting. She had been under the care of Dr. Rogers for her Graves' disease, and when her toxic vomiting began, hypodermic injections of the proteid thyreoglobulin were given, with unquestionable relief of symptoms. Her symptoms were most alarming when the urine

TOXAEMIA OF PREGNANCY. GRAVES DISEASE

CHART I

MRS A.T

DAILY TOTAL QUANTITY OF URINE——
ATTACKS OF VOMITING IN 24 HRS.——



URINE IN 24 HRS. { MAXIMUM 443
MINIMUM 103
AVERAGE 323

NO ALBUMEN
NO SUGAR

TOTAL ATTACKS
OF VOMITING 75

output was lowest. Several times the total quantity for twenty-four hours was below fourteen ounces, and the nitrogen partition at these times showed serious metabolic disturbance. The child lived but thirty-six hours. Five months after this labor the patient became pregnant again, her last menstruation being on March 15, 1909, and I delivered her on December 20, 1909, by a second vaginal Cæsarean section. The child was obtained by a version, and is alive to-day. The state of her Graves' disease was similar to what it was during the previous pregnancy. Dr. Rogers described the condition of her thyroid secretion as being an excess but of very poor quality, such as is observed in cases extending over several years. She had the same nervousness and restlessness, with a moderate hypertrophy of the thyroid and a pulse running from 90 to 100. Throughout this second pregnancy, the same toxic symptoms manifested themselves, but with a somewhat lessened severity than during the previous gestation. A nitrogen partition made during the third month showed a diminished total nitrogen, 6.43 grams; ammonia nitrogen, 7.55 per cent instead of 4.5 per cent; and rest nitrogen 8.6 per cent instead of 4 per cent. There was no albumin or sugar.

The same relation between the vomiting and the diminished output of urine was present as before. An accurate record was kept of the total daily quantity of urine excreted, and also of the number of times vomiting occurred each day. (See charts I, II, III.) The vomiting first appeared at the

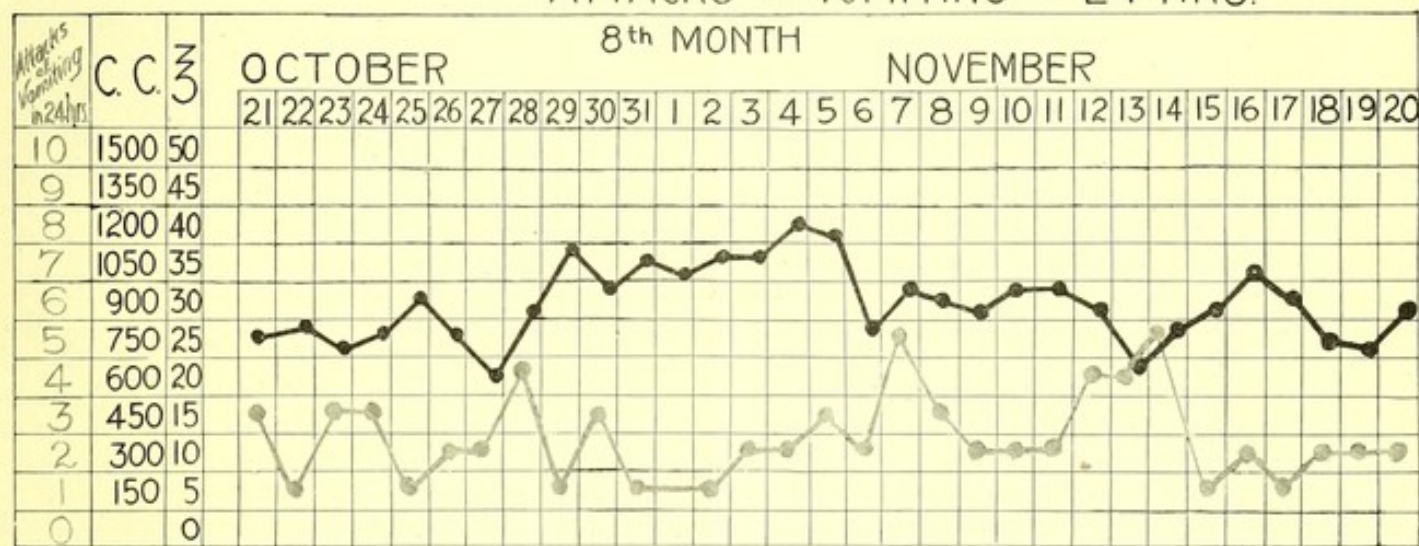
sixth week and was irregular and of moderate frequency until the end of the sixth month, when it began to be persistent and continued right up to the termination of labor at term. During the fifth month the daily average of urine was 34.3 ounces, the minimum being twenty-seven ounces and the maximum forty-five ounces. Vomiting occurred but seldom. During the sixth month the vomiting began to be more troublesome, occurring from one to three times daily except for two intervals of about ten days each, with a total of eighteen attacks for the month. The urine averaged 32.6 ounces, maximum forty-five ounces and minimum twenty-three ounces.

Throughout the seventh month the patient vomited daily, with a total of seventy-five attacks, the attacks varying from one to five each day, with an average of 2.5 per day. The urine averaged thirty-two ounces, with a minimum of ten ounces and a maximum of forty-four ounces.

During the eighth month, the condition of the patient remained about the same, so far as the urine output and vomiting were concerned, but her general state of health was going down hill. She was becoming more prostrated and her headaches were more troublesome. The urine average was thirty-one and four-tenths ounces, minimum twenty-one ounces and maximum forty-three ounces. The vomiting occurred one to five times daily, with a total of seventy-three times for the month, and a daily average of 2.3.

A nitrogen partition made at this time (November

TOXAEMIA OF PREGNANCY. GRAVES DISEASE.
 CHART II MRS A.T. DAILY TOTAL QUANTITY OF URINE ———
 ATTACKS OF VOMITING IN 24 HRS. ———



URINE IN 24 HRS. { MAXIMUM 433
 MINIMUM 213
 AVERAGE 314.3

NO ALBUMEN
 NO SUGAR

TOTAL ATTACKS
 OF VOMITING 73

17, 1909) showed a low total nitrogen, 3.918 grams; ammonia nitrogen, 6.63 per cent; and a very high rest nitrogen, 29.4 per cent. There was evidently a marked disturbance of metabolism.

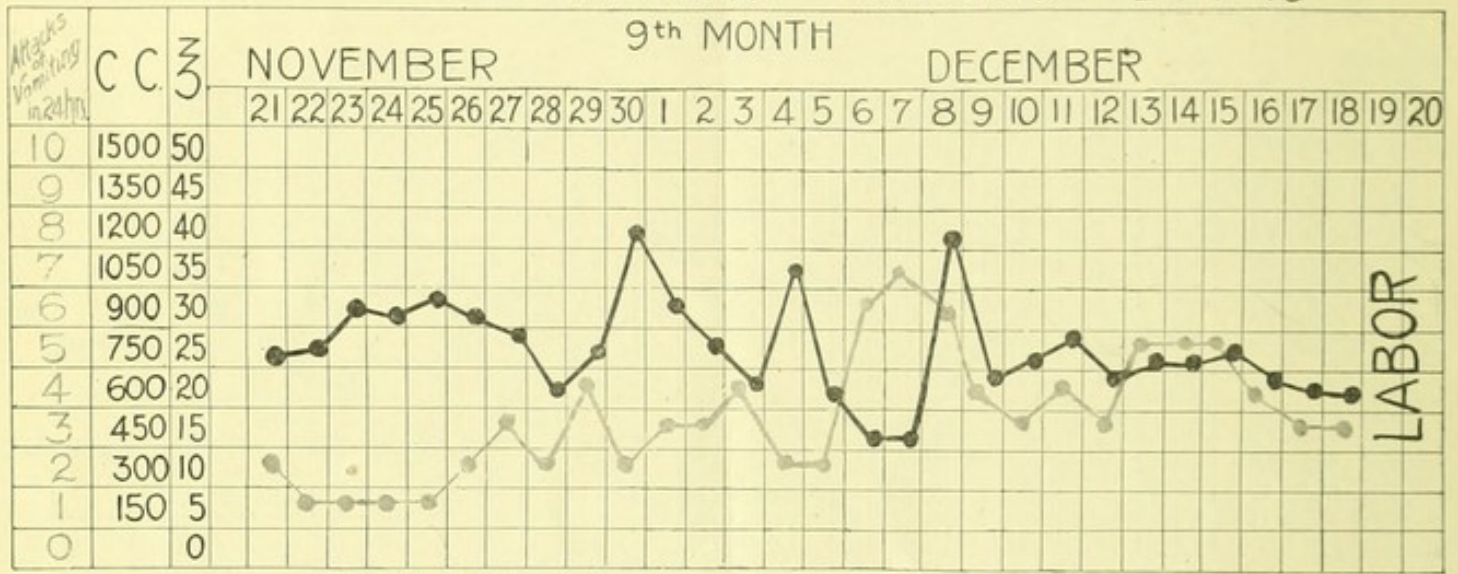
In the ninth month, all the symptoms increased in severity, and it was doubtful whether the pregnancy might not have to be terminated at any time. The vomiting occurred from one to seven times daily, with an average of 3.2 per day, and a total of ninety-one attacks for the month. The urine had diminished to twenty-seven ounces average, minimum fifteen ounces and maximum forty-one ounces. A nitrogen partition (December 7, 1909), showed total nitrogen 6.016 grams; ammonia nitrogen, 6.86 per cent; and rest nitrogen, 18.9 per cent. A study of the charts will show a direct relation between the output of urine and the number of attacks of vomiting. Whenever the total quantity of urine became diminished, the attacks of vomiting increased, and vice versa. Examples of this are markedly shown on chart III on November 30th and December 6th and 7th.

On December 17, 1909, the membranes ruptured spontaneously at nine P. M., the position of the child being L. O. A., no pains occurring for thirty-six hours. A No. 4 Voorhees bag was inserted. Only feeble pains resulted, and no real progress was made, so, after waiting twenty-four hours, the highly nervous condition of the mother made it seem best to operate. Traction was made on the bag for ten minutes, until it was delivered. As the cervix still presented a resisting ring, and bearing in mind the lesson of the previous labor, a vaginal

hysterotomy was done at once. The anterior uterine wall was very thin at the site of the cicatrix of the previous operation, and it began to tear when dissecting the bladder free from the uterus. A bi-manual version was performed without difficulty, but in passing the hand to reach for an extended posterior arm the uterine incision was evidently extended high up on the anterior wall of the uterus, close to, or into, the peritoneal cavity. The child was extracted in good condition, and with the exception of a too highly organized nervous system, is well to-day. The uterus was sutured with catgut and a gauze drain was inserted between it and the bladder. The patient had a stormy convalescence. For six days she ran a temperature up to 103°, with a pulse as high as 148 at times. There was marked tympanites, and evidently a moderate infection, as there was a leucocytosis of 22,000, with a polynuclear count of 91 per cent, and the lochia showed cultures of the colon bacillus. The case was still further complicated by a most severe sciatica, which developed on the second day. In spite of all this, the temperature was normal on the seventh day, and the recovery was otherwise uneventful. All nausea and vomiting ceased with the termination of the labor, as in the previous pregnancy.

Throughout the last four months of the gestation, the patient received daily hypodermic injections of thyroglobulin made from normal human thyroid glands, as in the previous pregnancy. The dosage and frequency of the injections varied according to the severity of the symptoms. The results ob-

TOXAEMIA OF PREGNANCY GRAVES DISEASE
 CHART III MRS A T DAILY TOTAL QUANTITY OF URINE
 ATTACKS OF VOMITING IN 24 HRS



URINE IN 24 HRS. { MAXIMUM 413
 MINIMUM 153
 AVERAGE 273

NO ALBUMEN
 NO SUGAR

TOTAL ATTACKS OF VOMITING 91

tained paralleled those obtained before. The nausea and vomiting were relieved and controlled to some extent, and the urine output was increased. The pulse rate and tension were so erratic in this case that no reliance could be placed on blood pressure. The nitrogen partition proved a more valuable index as to the degree of the toxæmia. Certainly I do not believe the patient could have been carried to term without the use of thyroid extract.

In view of my two experiences with this patient, I am in accord with the views of Davis, that elective Cæsarean section gives the best chance for the child, with the least danger to the mother, in this class of cases; and as this patient is very anxious for further offspring, I should adopt that procedure another time.

The patient reported as Case 1 in the previous paper, also became pregnant about nine months later, and I again delivered her at term after a normal labor.

This patient had a typical Graves' disease of an early type, or a condition of *hyperthyroidism*. She received marked benefit from the anti-serum of Beebe and Rogers, but was difficult to keep under control, and therefore had occasional relapses. She felt much better and her symptoms were in abeyance

while pregnant, and her nervousness and pulse rate promptly increased as soon as the labor was terminated.

In this second pregnancy her condition was similar to that of the previous one, she having about the same degree of hyperthyroidism. Her thyroid showed considerable enlargement and her pulse varied from 95 to 120, and she was troubled with considerable itching of the skin, according to my notes. Her urine showed a trace of albumin, and 4.4 grains per ounce of sugar at one time. However, she stated emphatically that she felt much better than when she was not pregnant, as she always did. There was not so marked a change in the pulse rate during her puerperium as before, but still it averaged an increase. It was 84 to 92 at the time of the labor, and after the second day it averaged from 104 to 108.

The history of this case would seem to support the opinion of Charcot and others, that certain Graves' cases are relieved of some of their symptoms during pregnancy. The increased metabolism made necessary by the growing foetus utilizing the excess of thyroid secretion common to cases of hyperthyroidism, as seen in the earlier stages of Graves' disease.

Beebe personally communicated to me the following two cases which he has recently ob-

served, and has kindly permitted me to report them.

Case 1. Mrs. S., aged 26, primipara. No Graves' disease or excessive enlargement of the thyroid. She began to have excessive vomiting at the end of the fourth month, which continued throughout the gestation. The urine contained no albumin or sugar, but the nitrogen partitions showed faulty metabolism. Hypodermic injections of normal human thyreoglobulin were given, according to the severity of the symptoms, and they were sufficient to control the vomiting so that it was possible to carry the patient to term, when she was successfully delivered of a healthy child. The blood pressure in this case was high.

Case 2. Mrs. F., aged 30; primipara. Three years previously she had developed exophthalmic goitre, and was treated with Rogers' and Beebe's serum and recovered. When six and a half months pregnant, she developed a marked toxæmia, which was accompanied by myxœdematous manifestations, as dry skin, dull mentality, vomiting, tender liver, and constipation. Her condition was that of *hypothyroidism*. Hypodermic injections of normal human thyreoglobulin were administered, with the result that all myxœdematous symptoms were relieved and the toxic vomiting was controlled. She went to term and was delivered of a healthy child. Two months later she developed a state of *hyperthyroidism*, which was corrected by the use of thyroid cytotoxic, or anti-serum. The urine showed some albumin, and the nitrogen partitions showed marked disturbance of metabolism. The blood pressure in this case was not high, ranging from 110 to 120.

SUMMARY

In the light of many experiences, the present status of the toxæmias of pregnancy of this type may be stated as follows:

1. That these cases may be classified into two groups: (a) Cases having no Graves' disease, but without sufficient thyroid secretion to promote the increased metabolism in the liver made necessary by the pregnancy, and probably due to the failure of the thyroid to hypertrophy. (b) Cases associated with Graves' disease, which condition usually causes serious disturbance in the metabolism.

2. Toxæmias of the first group are frequently much benefited by the administra-

tion of thyroid substance, in the form of either dry extract or a serum.

3. In toxæmia of the second group, it is essential to determine whether the Graves' disease is in a condition of *hyperthyroidism* or *hypothyroidism*. If the former, rest, applications of ice, milk diet, and sedatives should be employed, and if these measures fail, an anti-serum such as the cytotoxic serum of Beebe and Rogers should be administered. If the latter (*hypothyroidism*), thyroid substance should be given in the form of the dry extract, or, what is more efficient if possible to obtain, a saline extract prepared from normal human glands for hypodermic administration.

4. Reliance should be placed upon the nitrogen partition of the urine as a guide to the severity of the toxæmia, rather than on the blood pressure.

5. Induction of labor is very slow and uncertain in these cases, and where the history of former labors is that of dystocia, elective Cæsarean section is probably the safest method of delivery for both mother and child.

REFERENCES

1. WARD. Surgery, Gynecology and Obstetrics, December, 1909.
2. CARLSON AND JACOBSON. Am. Jour. Physiology, xxv, p. 403, March, 1910.
3. MACCALLUM AND VOEGTLIN. Jour. of Experimental Medicine, 1909, xi, p. 118.
4. LEITZ. Arch. f. Gynaek., 1909, lxxxix, h. 1.
5. STOWE. Am. Jour. Obst., May, 1909.
6. BONNAIRE. Presse méd., 1910, No. 28.
7. GOODALL AND CONN. Surgery, Gynecology and Obstetrics, May, 1911.
8. PORTER. Am. Jour. Obst., 1911, No. 5; Jour. of Am. Med. Assn., September 30, 1911.
9. DAVIS, E. P. Am. Journal of Medical Sciences, May, 1912.
10. ROGERS. Jour. Am. Med. Assn., Sept. 2, 1911.
11. WILLIAMS. Am. Jour. Medical Sciences, 1906, cxxxii, 343.
12. FOLIN. Am. Jour. of Physiology, iii, 1905, pp. 45 and 66.
13. EWING AND WOLF. Am. Jour. of Medical Sciences, May, 1906.
14. CORONEDI AND LUZZATTO. Archives Italiennes de Biologie, 1907, xlvii, p. 286.
15. BERKELEY AND BEEBE. Jour. Med. Research, xx, No. 2; New Series, xv., No. 21, Feb., 1909, p. 149.

