REPORT OF A CASE OF TOXEMIA OF PREGNANCY, WITH ACUTE YELLOW ATROPHY OF THE LIVER*

By Frank R. Oastler, M.D., and Harry G. Jacobi, M.D.,
New York City

(*From the Gynecological Service and Pathological Laboratory, Lenox Hill Hospital.*)

Mrs. C. B., age twenty-nine, admitted to Lenox Hill Hospital December 12, 1921. No history of jaundice or liver disturbance. One child born nine years ago, without incident. Miscarriages: the first occurred 10 years ago following the lifting of a heavy weight. Fetus of about seven weeks expelled. No curettage. No complications. The second occurred about six years ago, same cause. About four months' gestation. Expelled everything but placenta and was curetted. No complications. The third in February, 1921, same cause, four months pregnant, curetted in this hospital. Urine negative. Wassermann negative. No complications. Following curettage for second miscarriage, patient never menstruated regularly, only a drop or two of blood at intervals.

Menstruation began at thirteen years, regular, every twenty-eight days. Duration two to four days. Moderate flow. Menstrual cramps before and after menstruation. For the past six years periods irregular, very scanty and associated with severe cramps in both lower quadrants.

On admission patient complained of persistent vomiting, severe headaches, and dizziness of two weeks' duration and pain in lower abdomen, (left side), of one day's duration. For the past six weeks she had noticed that her feet were swollen and she felt generally miserable. The pain in the lower abdomen came on acutely while the patient was at rest and radiated to the back and left iliac region. At the onset the patient felt dizzy and fainted. She was carried to bed, became extremely thirsty and restless and had very little sleep that night. The next morning, ten hours prior to admission, she began to bleed from the vagina, had air hunger and extreme thirst. She had not menstruated for seven months.

On admission to the hospital patient's general condition was very bad. She was cyanotic, gasping for breath, dry furred tongue and violent headache. Temperature 105° F., pulse 120, of poor quality, respirations 28. There was no jaundice. General physical examination of heart and lungs was negative. Abdominal examination revealed considerable general soft distention with marked tenderness in left lower quadrant. Pelvic examination revealed purplish hue to external genitals; moderate bleeding from the vagina; the uterus was enlarged somewhat and soft; cervix, bilateral laceration and soft; cervical tug illicited sharp pain in region of left broad ligament. No masses were felt in the regions of the adnexa but the left side was extremely tender. Blood count showed white cells 28,000, polys 80 per cent, hemoglobin 70 per cent. Blood pressure 105/70. There was a large subcutaneous hemorrhage on the right thigh.

In view of the history of sudden onset of pain in the lower abdomen with distention and rigidity, air hunger, cyanosis and extreme thirst and the presence of marked tenderness in the L. L. Q. the tentative diagnosis of ruptured ectopic gestation was made and a laparotomy was immediately performed by my associate. The uterus was found to be enlarged and the tubes and ovaries perfectly normal.

*Read at a meeting of the New York Obstetrical Society, December 12, 1922.

toxemia. The extreme rarity with which recovery takes place in this condition and the fact that our patient eventually recovered and is still alive makes it still more difficult for us to establish definitely the underlying pathology in this case.

The further progress of the case is very interesting.

On October 21 the blood chemistry showed that both the urea nitrogen and the uric acid retention were greater than upon the previous examination. The creatinin value, however, had dropped from 8.25 mg. per 100 c.c. of blood to 2.5 mg., which may be considered as an almost normal value. The icterus index on this examination was 62. The interpretation of this marked decrease in the creatinin content of the blood without a corresponding decrease in the other constituents is of extreme interest and importance. It was at this point in the course of the disease that the laboratory findings gave evidence of a hopeful prognosis while clinically the outlook, though improvement was apparent, nevertheless was very much in doubt.

The general treatment consisted in the administration of large doses of alkalies by mouth and by rectum, rectal irrigations, glucose solution by Murphy drip and general sustaining medication and sedatives. When the patient was able to swallow, water was pushed to the limit. By November 7, 25 days following the operation for the removal of the fetus the patient was up, though the jaundice had not entirely disappeared. Temperature and pulse were normal and the urine still contained albumin 2 plus, but no casts, with total amount of urine 1950 c.c. for 24 hours. The blood chemistry was normal.

The case presented brings out rather forcibly the value of correlating clinical findings with those of the laboratory. It demonstrates clearly how modern laboratory methods, if used wisely, in such conditions as these, will aid both in diagnosis and prognosis.

We were indeed fortunate here to be able to follow the various changes in the chemistry of the blood during the course of so marked a toxemia, and while we fully realize that our analyses are perhaps not as extensive or as complete as might be wished for, it must be remembered that at the time this work was done we had but one aim and that was to obtain as much data as possible to aid us in the management of the condition without subjecting the patient (who was very sick) to any unnecessary manipulations.

METHODS USED

In the blood the urea nitrogen, uric acid creatinin, sugar content, icterus index, and CO_2 combining power of the blood plasma, were determined at each examination. For the urea nitrogen, the method described by Van Slyke and Cullen was employed. For the creatinin and blood sugar, we used the Meyers modification of the Folin method. The CO_2 combining power of the blood plasma was determined by the Van Slyke method, and the uric acid by the old Benedict method. To determine the amount of icterus present, we were rather fortunate in being able to make use of a method that was recently devised by our laboratory. The urine was examined from time to time to determine the presence of bile, albumin, casts, leucin and tyrosin.

TABLE I

BLOOD CHEMISTRY AND URINE CHART

DATE	UREA N.	URIC AC. MG. PER 100 C.C.	CREAT. MG. PER 100 C.C.	SUGAR	ICT. IND.	CO_2 COMBINING POWER	URINE	CLINICAL CONDITION
10/13	50	3.3	2.05	.144	187	40 vol %	bile - blood - alb. casts W. B. C.	Very grave
10/15	100	6.2	5.6	.120	100	50	same	Condition improved
10/18	83	7.1	8.25	.144	–	49	same also leuc. and tyr.	Condition improved
10/21	96	8.3	2.5	.126	62	59	same	Condition improved though still serious
10/25	43.5	6.0	1.35	.110	31	63	leucin and tyrosin	Marked improvement
10/31	12	1.5	1.00	.100	23	69	alb. casts, etc.	Condition improved
Normal	12-15	1-2.5	.5-2	.08-.12	3-6	53-77		

The laboratory findings here presented show strikingly that at the onset there was a retention of all the nitrogenous products. The most marked was that of the urea, then the uric acid, and finally the creatinin. In other words the urea which is the least soluble of all three began to show its increase in the blood first, while the creatinin which is the most soluble was the last to increase. It is really upon the creatinin that great stress should be laid as far as prognosis is concerned in any given case. In chronic nephritis for instance the occurrence of a high creatinin content almost invariably means a fatal outcome. In acute conditions of the type we are dealing with here, and also those encountered in the intoxications with bichloride of mercury, phosphorus, chloroform or uranium salts, a high creatinin content, while pointing to a dubious outcome, is not always fatal. In our case the sudden drop in the blood creatinin, in spite of the persistence of a high urea nitrogen and uric acid, was the important finding which pointed to a favorable outcome. One must remember also that urea, uric acid and creatinin in themselves are nontoxic. Their presence in the blood in increased amounts, indicates the presence of their more toxic antecedents.

The careful studies of Abderhalden have revealed that the blood of every pregnant female animal contains enzymes which have a specific proteolytic action and so the possibility exists that abnormal or excessive products of such proteolysis or a lack of adequate defensive digestive action may be responsible for the toxemia of pregnancy. The toxins that are usually liberated in such conditions act in a harmful way upon the liver and kidney, impairing their functions of detoxication and elimination and in this way lead to the production of a vicious cycle. When their poisons effect the liver more and the other tissues less we approach the condition of acute

yellow atrophy, e.g., if the amount of toxin is not so great as to kill the patient through injury to the vital organs, after a few days, the necrosed liver cells undergo autolysis and if enough have been destroyed hepatic insufficiency may cause death. Hence it is possible for any poisons to produce this condition under certain circumstances, whether they are the poisons of the toxemias of pregnancy, the metallic poisons, acute syphilis or any of the others. Losee and Van Slyke,[1] in their study of ten cases of eclampsia arrive at the conclusion that "toxemias of pregnancy can neither be attributed to failure of deaminization of the amino acids nor to the moderate degree of acidosis present." They also state that they have been unable to determine the nature of the toxins in such cases. In their series the highest urea nitrogen figures approximated about 26 mg. and their lowest about 10 mg. Sherwin and Killian[2] attempt to differentiate between normal pregnancy, chronic nephritis, nephritic toxemias and hepatic toxemias by the blood chemistry reporting in hepatic toxemia a high nonprotein nitrogen with low urea nitrogen and high uric acid values. C. A. Herter[3] reports his findings in six cases of eclampsia and states that he failed to find any increase in the percentage of the urea. In a subsequent paper,[4] he concluded that in cases of eclampsia without chronic nephritis the percentage of urea in the blood was almost normal or slightly increased in amount. When chronic nephritis existed, the urea was apt to be high, and when this was the case a fatal outcome was to be expected.

Farr and Williams[5] report a series of cases which are divided into two groups, A and B. The former consists of seven cases of normal pregnancy where the urea nitrogen figure ranged approximately between 7 to 15 mg. per 100 c.c. The second group consisted of three cases with renal insufficiency where the urea nitrogen ranged somewhat higher between 11 to 30 mg. per 100 c.c. They also state that Dienst now accepts the view that eclampsia and acute yellow atrophy are due to the same general causes, the chief of which is the failure of the metabolic functions of the liver. Ewing and Wolfe,[6] noting the anatomical changes in the liver and the fact that leucin and tyrosin have been reported in eclamptic urines, suggested that the amino-acids were incompletely catabolized in the degenerated liver and were the cause of the toxemia and abnormal nitrogen distribution.

As a measure of the acidosis present in our case we have determined the percentage volume of CO_2 bound in the form of the bicarbonate by the blood plasma.[7] This pointed definitely to a marked

[1]Am. Jour. Med. Sc., 1917, cliii, 94.
[2]Am. Journal Gynec. and Obst., ii, No. 1, July, 1921.
[3]Montreal Med. Jour., 1898, xxvii, 321.
[4]Johns Hopkins Hospital Report, 1900, ix, 69.
[5]Am. Jour. Med. Sc., 1914, cxlvii, 556.
[6]Am. Jour. Obst., 1906, lv, 289.
[7]Van Slyke, D. D.: Proc. Soc. Exper. Biol. and Med., April 21, 1915.

acidosis from the beginning and was the earliest to show a definite improvement in our case. In this connection it must also be remembered that Hasselbach and Gammeltoft[8] state that even in normal pregnancy a slight degree of acidosis is present as indicated by the carbon dioxide content of the alveolar air.

Another important finding in our case which requires mention is the presence of leucin and tyrosin in the urine. The finding of these constituents in the urine in a case with marked jaundice, vomiting and pain in the right hypochondriac region, have long been regarded as pathognomonic of acute yellow atrophy. The condition was first fully described by Frerichs. An interesting exception, however, has been reported by W. G. Smith[9] who found great quantities of leucin in the urine of a young woman who was apparently not at all ill. Rosenbloom[10] found tyrosin crystals in the urine of a healthy pregnant woman and cites cases of tyrosinuria without hepatic atrophy. Reiss[11] states that they are nearly constantly present in acute yellow atrophy (in thirteen out of fourteen studied), tyrosin usually being the more abundant. The earliest conception of the source of the leucin and tyrosin found in the urine was that it came from the products of tryptic digestion absorbed from the intestinal tract, which the liver could not convert into urea because of its damaged condition. On the demonstration by Jacoby[12] that these same bodies were present in the livers of phosphorus poisoned animals because of autolysis, it became probable that the leucin and tyrosin found in the urine were formed from the degenerated liver cells rather than in the intestines, which view has become generally accepted. It seems most probable, however, that the urinary amino-acids are derived partly and perhaps chiefly from the autolysis of the liver and partly from the amino-acids produced both in the intestines and within the body during tissue metabolism. The liver in its damaged condition is unable to transform these into urea, as it normally does, for several observers have reported that even relatively slight disturbances of hepatic function are accompanied by a considerable rise in the amino-acids in the urine.

In concluding we wish to state that this case is one of extreme interest: (1) Because we were fortunate in being able to study the chemical changes in the blood and urine throughout the course of so marked a toxemia. (2) Because the case presented many of the clinical and laboratory findings of acute yellow atrophy, with recovery. (3) To show the benefit of laboratory work as an aid to diagnosis and prognosis.

170 WEST FIFTY-NINTH STREET.

[8]Biochem. Ztschr., 1915, lxviii, 207.
[9]Practitioner, 1903, lxx, 155.
[10]New York Med. Jour., Sept. 19, 1914.
[11]Berl. klin. Wchnschr., 1905, xlii, 54.
[12]Ztschr., physiol. Chem., 1900, xxx, 174.

THE NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 12, 1922

DR. RALPH H. POMEROY IN THE CHAIR

DR. FRANK R. OASTLER presented a paper entitled **Toxemia of Pregnancy. Acute Yellow Atrophy of Liver.** (For original article see page 271.)

DR. ELIOT BISHOP reported a case of **Prolonged Ante- and Postpartum Toxemia of Pregnancy, with Recovery.**

This twenty-nine year old primipara, a physician's wife, was seen October 19, 1921, four and one half months pregnant, with no outward symptoms except occasional vomiting. Her general condition, blood pressure and urine were normal until January 10, 1922, when she developed edema of the legs, and albumin and casts appeared in the urine. On January 12, the blood pressure was 150-90, but she had no subjective symptoms of any kind.

She was put on a carbohydrate diet, allowed out of bed only an hour or two a day and, with that regime, the blood pressure rarely reached 150, the urinary output was ample, though the albumin heavily persisted; subjectively she considered herself to be not at all sick. As this child was considered, from several social aspects, extremely desired, interruption was postponed.

On February 14, near the end of the eighth month, however, the edema, which had been slight, suddenly increased, as did the blood pressure, which rose to 190, with a pulse of 120, the vision was markedly reduced, and the patient entered the Brooklyn Hospital; there the urine of sp. gr. 1.018 showed only a heavy cloud of albumin, and no acetone, but many hyaline and granular casts. The blood chemistry was: C.02-45; urea, 37-89; creatine, 1.78; sugar, 128 mg.; red blood cells, 47 per cent. There was marked edema of the back, genitals and lower extremities, and the phthalein output was 35 per cent in the first two hours, with an additional 10 per cent in the third.

The next morning, after consultation, it was decided to terminate the pregnancy, and the membranes were ruptured.

The onset of labor was slow, and the blood pressure ranged between 190-200 systolic. As active labor began, she was given a quarter of a grain of morphine. During labor, the systolic pressure reached 218. When the vertex got to the vulva, forceps were gently applied, and a four pound, six ounce baby was easily lifted out. The baby did not look at all well, but thrived, and at ten months weighs 21 pounds.

Aside from vomiting, the day after delivery was comfortable to the patient. She was catheterized at the end of twenty-four hours, and 49 ounces of urine was obtained, which contained a trace of albumin, but no acetone or casts. The blood

pressure dropped to 154-110, and we were misled into believing that the danger was rapidly disappearing.

However, the systolic blood pressure returned to 190, and averaged that for the next week. The urine output kept up, even developing a polyuria of 176 ounces on February 20; but, on Febuary 26 it became scanty, though hard to measure on account of lack of control. During the period of the arterial hypertension, the patient's greatest complaint was pain in the back of the head, neck and arms, particularly the latter. On February 23 temporary deafness occurred and the patient became restless and "nervous," and quite weak; the pulse was running from 120-136, and the rectal temperature between 100-101°, in fact, her pulse continued at that rate until a few days before her discharge from the hospital, thirty-six days postpartum, when it averaged 110.

The urine again contained a moderate number of casts. On February 24, however, she developed irrational periods and also stupor; and, on February 27 a left-sided hemiplegia. A diagnosis of cerebral thrombosis was made. From the ophthalmologist's report, which I shall summarize later, and his own findings, the internist did not concur in the neurologist's diagnosis, but felt that there were miliary cerebral hemorrhages, with edema. On March second, after a bad night, irrational and with Cheyne-Stokes' respiration, the general condition showed improvement, and the hemiplegia began to disappear, but a left saphenous phlebitis occurred, with a leucocytosis of 19,400, with 85 per cent of polynuclears.

General condition continued to improve, the mentality slowly clearing until it seemed normal, though a little sluggish on March seventh, and on March ninth, the ophthalmologist noted a definite improvement.

On March eleventh, a right saphenous phlebitis occurred, accompanied by temperature of to 101°. Examination of the chest that day, by the internist, showed the following. "Heart-apex in the fourth interspace, three and one half inches to left of middle line; the right border slightly to the right of sternum; sounds at apex suggest fetal rhythm; no gallop rhythm; lungs clear. Diagnosis, probable myocarditis." The urine at this time showed a faint trace of albumin, and no casts, and the systolic blood pressure, which, for a week, had been running between 130-140, now reached 120.

The second phlebitis subsided in eight or nine days, and on March twenty-first, in spite of the continued rapidity of the pulse, the patient was allowed up in a chair, and went home on March twenty-fifth. Her pelvic condition was negative; her appetite was good; her sleep was fair, and strength returning; her malaise was gone and her mental condition normal. A few days before discharge her blood showed 61 per cent hmgl.; 2,880,000 red blood cells; 11,600 white blood cells of which 82 per cent were polynuclears; her urine showed a heavy trace of albumin, but no casts or acetone.

On December 9, 1922, the ophthalmologist reported that with the beginning of her toxemia, the patient suffered an absolute scotoma (central) of the left eye, due to a retrobulbar neuritis, which cleared up completely in about three weeks, solely under the toxemia regime. This ocular pathology was another evidence of, and due to the toxemia. Retrobulbar neuritis is uncommon in the toxemias, in this case especially noteworthy in being monocular, also in the production of an absolute central scotoma which completely cleared up in so short a time. Prior to her entrance into the hospital, her vision was normal in all respects. Before induction, the vision in each eye was reduced to mere form perception due to papilledema, retinal edema, retinal exudate and hemorrhage, the exudative stage of albuminuric neuritis. This eye pathology was due to the increased intracranial pressure of cerebral edema and therefore dependent upon the intracranial complication. The fundus condition did not begin to improve until after she

had her cerebral accident. Yesterday the vision of the right eye was 20/20; of the left 20/70. The right fundus showed normal nerve; vessels apparently normal; several scattered areas of punctate pigment deposit in the retina; the macula which contained the radiant figure of albuminuric neuroretinitis, was clear. The left fundus was similar to the right, and in addition, the macula showed in its upper portion slight remains of the scar.

On December 9, 1922, her urine totalled 40 ounces, 1.019 sp. gr., with no sugar, a trace of albumin, 9 grains of urea to the ounce, no casts or kidney epithelium, and on December eleventh her blood pressure was 110-70.

This case is of interest for the following reasons:

1. To interrupt a pregnancy is an extremely difficult decision to make in toxic cases of this sort, as much, if not more so, than in eclampsia. Any woman who is toxic is better off without the child, but, what about the child? Moreover, the mother may be too toxic to stand interference that is too late. Each case must be sharply differentiated, particularly with the help of the internist; it is as much a medical as a surgical problem.

2. Termination of pregnancy may not terminate our troubles, as this woman developed a subacute nephritis, cerebral and retinal hemorrhages, with a resultant hemiplegia, with the strong possibility of permanent eye and brain damage, evidence of myocarditis, and a double saphenous phlebitis.

3. This train of pathology shows us that the toxins of pregnancy attack parenchymatous tissues, retina, brain, kidney, heart muscle, usually the liver; particularly the retinal and brain vessels, and the saphenous veins. Here the disturbance was not like an ordinary phlebitis, the redness and swelling and the tenderness in Scarpa's triangle were all missing, and there was only a slight temperature with the onset of one side.

4. A most suggestive clinical observation is that, during the period of greatest excretion of urine, this patient was not improving, but developing her gravest state. As the kidneys drew the water from the patient, toxemia increased; may not the toxins be in the edema? At this time, blood chemistry might have been of diagnostic value. Practically, this is the time, for purposes of dilution, to saturate a patient with fluids in one method or another, and mayhap, the common use of morphine may be beneficial, as it retards tissue depletion.

The obvious conclusion from the above is that these problems are primarily medical, and the major conduct of such a case, with the assistance of the ophthalmologist's diagnostic precision, belongs to the internist, where this was placed.

DISCUSSION

DR. HARRY G. JACOBI: (speaking on Dr. Oastler's case).—When one considers the blood chemistry as charted, without the clinical history of the case, it is rather difficult to say whether it is the blood picture of an acute yellow atrophy, a bichloride poisoning, a phosphorus poisoning, or of any other toxins which may produce tissue degeneration. In other words, in this case there was a definite toxemia, and once the toxic substance was removed by emptying the uterus, improvement was noted.

The important determination is the creatinine figure. The creatinine determination is particularly interesting in acute conditions because it is in these conditions that the creatinine content of the blood reaches enormous figures and really determines the outcome of the case. On the 18th of October the creatinine content was 8.25 and the next examination, performed on the 21st, showed a practically normal creatinine content of 2.5. If this were a chronic condition with a creatinine content of 8.25 the prognosis would be very grave. Such figures one frequently encounters in the terminal retentions of the chronic nephritides. In the acute

tation. The woman, pregnant 2½ months, was suddenly seized with violent abdominal pain and went into shock. There were several facts that made me feel that the case was not one of ruptured ectopic. First of all, she had a temperature of 105° F. She was comatose and her hemoglobin was 75 per cent, the leucocytosis was high and the urine contained a large amount of albumin with blood (catheterized specimen). The case showed very marked evidence of kidney disturbance and on that basis we emptied her uterus. The patient was entirely comatose. The next day she became jaundiced and then a diagnosis of acute yellow atrophy was made. She remained comatose for about a week. Two spinal punctures were done during that time and proved absolutely normal. The patient finally recovered. I was glad that I did not accept the diagnosis and operate on this case.

DR. FRANK R. OASTLER.—The CO_2 combining power in my case, considering the degree of acidosis, was comparatively high. I figure, from my experience, that if it gets up around 30, the case is almost certain to terminate fatally. The normal is 53 to 77, but 56 to 60 is, I think, a pretty good average. The uterus, was about the size of a two months' pregnancy. She had not menstruated for seven months. After one of her pregnancies she was curetted and following this she only had a drop of blood once in a while. In other words, she had pretty nearly ceased menstruating.

I would say she was taking her food regularly up to the time of admission. Following that, for a period of three days, she had practically no food. The only thing she got was 5 per cent glucose solution by rectum. She was vomiting and nauseated and in such a serious condition that she was practically moribund for two or three days.