Leukæmia in Pregnancy, and Congenital Leukæmia.

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An Abstract Translated and Arranged by Dr. J. Chalmers Cameron, Montreal

This paper being also a contribution to the question of the transmission of formed elements from the mother to the fœtus.[1]

I.

ACCORDING to the observations of Ehrlich, Birch-Hirschfeld and others, leukæmia occurs in females only half as often as in males. This is remarkable since the blood-forming system of the female is more active than that of the male, and still more so since it is generally assumed (though not proved), that a causal relation exists between leukæmia and diseases of the sexual organs. Virchow, the discoverer of leukæmia, in one of his early communications says of its ætiology, "the only thing which can be laid down with any certainty is its dependence upon the sexual functions in women." It so happened that the first few cases observed were women; but neither they, nor any since published, have established its closer relationship to sexual disorders than to malaria or other ætiological conditions. Mosler says that disturbances of the sexual functions in women have an undeniable influence upon the production of leukæmia, that a certain relation exists between the female organs of generation and the spleen, that an acute splenic tumor with slight increase of white blood corpuscles often begins after menstrual anomalies, and that in women sexually mature leukæmia almost always begins with anomalies of the sexual functions.

It is evident that these views of Mosler's are not in accord with those of modern gynæcologists; moreover, the observations upon which they are based lack definiteness and precision. In fact, the whole question respecting the relationship existing between leukæmia and splenic enlargement which has been hitherto entirely relegated to general medicine, must be examined anew by gynæcologists who till now have paid little attention to it except for diagnostic purposes in cases of laparotomy. Mosler's warning to gynæcologists to pay attention to splenic changes in diseases of the female sexual organs, holds good for obstetricians as well. Hitherto we have known very little respecting the influence of leukæmia upon pregnancy, labor and the puerperium, and even that little is not securely established. To the cases of leukæmia in the puerperium reported by Virchow, Leudet and Bennett, two more must be added, (Quain's and Vidal's). But among them all, how very little bears precisely upon the relationship between leukæmia and the generative processes!—not one single observation

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during pregnancy, labor or the puerperium proper. Furthermore, the older reports are silent as to the conditions of the children of leukæmic mothers, proving how insufficiently these cases must have been observed, for one could hardly pass over such interesting and important questions so slightly. In Leudet's case the diagnosis was first made *post-mortem*. Bennett's first case was an emaciated woman, 33 years old, who had aborted several times with great loss of blood and suffered from menorrhagia, leucorrhœa, hæmorrhoids and ascites. Physical examination showed enlargement of liver and spleen. In his second case, a swelling appeared in the left side three months after a labor, with much hæmorrhage; she emaciated rapidly and died in three months; spleen and liver were found much hypertrophied, and the blood contained twice as many white as red corpuscles. The supposition that this woman might have been already leukæmic at the time of labor was not mentioned. Vidal's case was that of a woman, aged 44, who died of leukæmia nineteen months after confinement. Although Vidal himself calculated the average duration of leukæmia to be thirteen months, yet without farther evidence he concludes that splenic enlargement had developed after labor and had been caused by it. Only ten cases of leukæmia in women were known to him, including those of Leudet and Bennett. The fact that four of these developed the disease after their last pregnancy sufficed for him to draw the general conclusion that in four cases out of ten leukæmia was caused by confinement. How little support this view derives from late observations will be shown presently. In Quain's case, leukæmia developed after several abortions. This concludes the list of reported cases. On account of the paucity, unreliability and incompleteness of the material hitherto at command, it is not surprising that obstetrical text-books and journals do not mention leukæmia in pregnant or lying-in women. Their mutual relations, so important to the physiology of pregnancy, have not yet been studied closely by obstetricians. It is not likely that leukæmia would occur so seldom if there really existed such a close physiological and pathological connection between the blood-forming and reproductive organs as has been assumed. One would think that Virchow's doctrine of a *physiological leucocytosis of pregnancy* (an increase of white blood corpuscles and fibrin, would arouse the attention of obstetricians and direct it to true leukæmia. To my great surprise I found on looking through the literature that even the most recent examination of the blood of pregnant women, made after the most approved methods by Ingerslev, Fehling, and Paul I. Meyer, did not even mention such a leucocytosis. H. Nasse, who first gave a precise description of the white blood corpuscles, was the first to state that their number is increased in pregnancy. Virchow says that there is a remarkable increase of leucocytes in puerperal fever. Isambert thinks a connection exists between the leucocytosis of pregnancy and puerperal fever. Thus we see that the earlier theories of puerperal fever are involved, the physiological and pathological being confounded, just as in many text-books on general pathological anatomy we find the leucocy-

tosis of pregnancy considered along with cholera, acute yellow atrophy, pyæmia, etc.

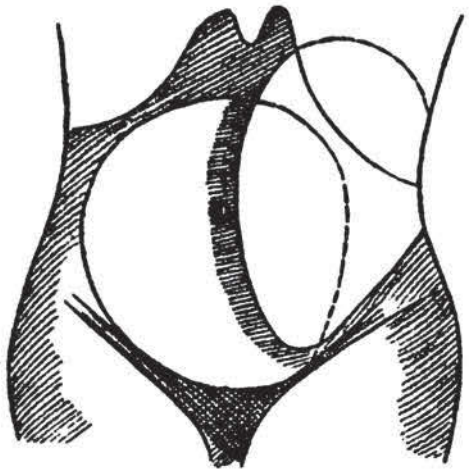
Progressive pernicious anæmia in pregnant and puerperal women must be carefully distinguished from leukæmia, which it closely resembles, clinically. We are chiefly indebted to Gusserow for our knowledge respecting this disease. For the earliest account of pernicious anæmia in a puerpera we must go back to Andral (1845). The same and similar conditions were described (1850) by Stoltz and his pupils Thierry, Lauth and Chalot as *cachexie séreuse*, and by Lebert (1854) as *chlorose puerpéral aigue*. But none of these observers made any sharp distinction between the *milder* forms of anæmia and hydræmia (Kiwisch's serous plethora), and the *malignant* form described by Gusserow, and further elucidated by Bischoff, Eichhorst, Graefe, and in France by Ferrand, Lépine, Dujardin-Beaumetz, and Batut. In several of the cases described by Gusserow and others slight splenic enlargement and softening and swelling of the lymph glands occurred, but never any other than anæmic changes in the bone marrow, and never any increase of white corpuscles. Lauche has suggested the possibility of pernicious anæmia developing into leukæmia or pseudo-leukæmia; it is quite certain, however, that no case has yet been reported where pseudo-leukæmia developed into leukæmia. Acute blood diseases in pregnancy manifest themselves sometimes by developing a hæmorrhagic diathesis, or hæmorrhages into different organs. Wiener has shown how difficult it is to differentiate these hæmorrhagic diseases, and urges that in all such cases an examination should be made of the spleen, lymph glands and blood.

About a year ago, when I had my own case of leukæmia in pregnancy under observation, and searched the literature of this subject, I found no similar case on record. Prof. Mosler, whom I consulted, informed me that he was not aware of any similar observations where both maternal and fœtal blood had been examined. In veterinary literature I found one case, a cow which died three months after calving. I had given up looking for farther cases when I happened upon an excellent article on this very subject by J. C. Cameron, of Montreal, which most admirably supplemented my own observations. Shortly afterward, a communication appeared from J. L. Green, of Morgantown, Ind., which added two more cases to our list.

I will first describe my own case, seen in consultation with Dr. Gelbke, of Rochlitz, on July 6th, 1887. Patient, aged 32; unmarried; complains since the beginning of May of gradual abdominal distention with darting pains in left hypochondrium, and an increasing sense of fatigue. Menstruation had been regular, recurring every four weeks, lasting two days, scanty and pale, preceded and accompanied by cramp-like pain; it ceased about the end of April. Patient was over middle size, with strong frame, thin and of pale complexion. The abdomen was much distended. On the left side could be felt an immovable insensible tumor, sharply circumscribed, extending from the left hypochondrium down to within two finger-breadths of Poupart's ligament, laterally not extending beyond the middle line. Percussion

showed encroachment of the tumor upward and backward upon the thorax. The tumor was an enlarged spleen; liver normal; glands not swelled; marked increase of leucocytes in the blood, W. : R. = 1 : 15. No albumen in the urine. The family history was good; she herself had never had malaria, nor lived in a malarial district.

There was sufficient evidence to warrant a diagnosis of pregnancy in the second or third month, complicated with leukæmia. A course of iron and arsenic was prescribed. On December 6th, Dr. Gelbke wrote me that the abdominal enlargement had



Leukæmia.
Enlarged Spleen in a Pregnant Woman.

become unbearably great though the splenic tumor which lay in front of the uterus did not seem much larger. We determined to induce labor, the child being viable. Accordingly on the 11th, daily hot baths and hourly hot vaginal injections were administered. Labor pains began on the 14th, and in a few hours a living child was safely delivered. The blood lost during labor was pale, slightly coagulable and small in amount. The placenta was pale. The patient was much relieved, though the abdomen remained nearly as large as before

The child was well developed, neither liver nor spleen being enlarged. An examination was made of the placenta and some blood taken from the umbilical cord. All the blood preparations from the placenta were leukæmic, while those from the cord were normal. The convalescence was normal and involution satisfactory. In March, 1888, Dr. Gelbke reported that the splenic tumor had gone on increasing steadily till the abdomen seemed as large as at the seventh month of pregnancy. The appetite and digestion were good. She was able to attend to household duties but complained of fatigue and showed signs of leukæmic marasmus. W. : R. = 1 : 10. The child was fed on cow's milk from the onset and thrived well; the blood was normal and no signs of leukæmia were evident. At last accounts the patient's condition remains unchanged and the child continues to thrive. The following points may be noted:

1. Leukæmia already existed at the time of conception.

2. No disturbance of the menstrual functions existed before the onset of leukæmia.

3. An ætiological starting point can not be made out.

4. In the second half of gestation, the leukæmic symptoms became aggravated. The splenic tumor enlarged, and the patient's condition became unbearable chiefly from lack of room in the abdomen, circulatory disturbances and nervous excitement.

5. An unusual increase in the leukæmia was not observed.

6. Her suffering necessitated the induction of premature labor, which was easily accomplished with but little loss of blood.

7. The puerperium was normal throughout.

8. The patient experienced great relief after the conclusion of labor, but her leukæmia progressed slowly, pregnancy not seeming to have had any effect in hastening its progress.

9. The child was viable, was born healthy and remained so. The case was seen only once, so that no opportunity was afforded for more exact observations. Cameron has described his case better, since he had the opportunity of having it under observation in a well-regulated hospital. [Here follows a full report of the case, which is published in the *International Journal of the Medical Sciences*, January 1888. The following is a condensed abstract :]

Mrs. S., aged 36, vii-para, was under treatment for leukæmia in the Montreal General Hospital from September 15th to November 2d, 1885. She first noticed a splenic tumor about the beginning of her sixth pregnancy (September, 1884). When admitted to hospital, the tumor extended from the sixth left rib obliquely downward toward the umbilicus, and backward to the post-axillary line, showing an oblique measurement of 23 cm. Liver dulness extended 5 cm. below the costal border. Lymphatic glands not enlarged. Red corpuscles were 2,400,000 per cmm. and W. : R. varied from 1 : 40 to 1 : 12.5. She entered the Montreal Maternity in the seventh month of her seventh pregnancy (October, 1886). The splenic dulness then was 28 cm., oblique measurement; hepatic dulness 15 cm. Red corpuscles 1,070,000 per cmm., W. : R. = 1 : 10. Her chief symptoms were thirst, anorexia, vomiting, dyspnœa, general œdema, epistaxis and diarrhœa. As gestation advanced the attacks of epistaxis became more frequent and uncontrollable, and the dyspnœa and weakness alarming. Labor lasted three hours; not a drop of blood was lost during the delivery of child or placenta. The lochial discharge was scanty, slimy, and ceased in a couple of days. She recovered rapidly and left hospital on the twelfth day. The child, born on the 214th day after the cessation of last menses, was apparently strong and healthy, and nursed vigorously from a healthy breast. The next day the patient surreptitiously put the child to her own breast; it sickened at once, in a few hours a purpuric rash appeared on its face and spread slowly over the back and chest. It vomited and purged, and died on the fourth day.

The following table shows the blood counts of mother and child :

Mother.	(Two hours after birth.)	R.	990,000.	W. : R. = 1 : 4.
Child.		R.	5,210,000.	W. : R. = 1 : 175.
Mother.	(On third day).	R.	1,000,000.	W. : R. = 1 : 20.
Child.		R.	5,000,000.	W. : R. = 1 : 156.
Mother.	(On twelfth day.)	R.	1,900.000.	W. : R. = 1 : 35.
Unbilical Vein.	*Trunk.*	R. 4,610,000. :	W. 26,000.	W. : R. = 1 : 173.
	Branch.	R. 4,600,000. :	W. 36,000.	W. : R. = 1 : 128.
Umbilical Artery.		R. 5,410,000. :	W. 20,000.	W. : R. = 1 : 270.
Placental Sinus.		R. 950,000. :	W. 263,000.	W. : R. = 1 : 3.6.

The autopsy upon the child showed nothing leukæmic.

The chief points of interest in the case are:

1. The family history. The grandmother, mother and brother have suffered from symptoms pointing to leukæmia. Two of her own children have had well-marked leukæmia, another is in ill health with diminished red cells and enlarged spleen. None of her children reach R. 5,000,000 per cmm. All have had attacks of jaundice.

2. Splenic enlargement was first noticed by herself at the beginning of her sixth pregnancy.

3. During her pregnancies there is always increased enlargement of liver and spleen, with tenderness.

4. During pregnancy the white cells increase and red decrease.

5. Absence of uterine hæmorrhage during labor and puerperium.

6. Rapid recovery and ability to attend to household duties.

7. Recurrence of pregnancy several times since the onset of leukæmia.

8. Remarkable difference between the blood of mother and child and the blood in the placental vessels and sinuses.

9. The disastrous effect upon the child of nursing from its mother's breast.

I agree with Cameron in rejecting the cases reported by Ingle and Paterson. Ingle's case is one of leucocytosis; Paterson's first case was probably one of diphtheria or angina Ludovici; his second was some infective disease, such as puerperal sepsis, diphtheria, abscess or acute yellow atrophy of the liver, and his third was certainly not one of leukæmia.

Of Greene's two cases (reported in the *New York Medical Journal*, February 11th, 1888) only one can be admitted, so that in all medical literature only three cases of leukæmia in the pregnant or puerperal state are on record, one each reported by Cameron, Greene and myself. In Cameron's case and my own conception occurred in a woman already leukæmic; in Greene's case the disease first made its appearance during pregnancy. From a consideration of all three cases it is evident that leukæmia, as such, does not destroy the power to conceive. With regard to the relationship between menstrual disturbances and leukæmia, it is more probable that oligomenorrhœa and amenorrhœa are secondary results of the leukæmic blood dyscrasia than that they cause leukæmia. Neither can I accept as a cause of leukæmia the sudden suppression of menstruation, so much insisted upon by Mosler, but think it more reasonable to suppose that the same trouble which suppressed the menses sowed the seeds of leukæmia also. How can one suppose that a brief disturbance of a periodical sexual function can be the cause of a disease which affects the whole blood and lymphatic system? That ovulation may occur even in advanced leukæmia is proven by Cameron's case and my own, but the general infrequency of conception shows that it is probably affected in some way. At any rate, I think it has been satisfactorily proved, contrary to the general teachings, that, as far as leukæmia is concerned, disturbances in menstruation, ovulation and conception are either secondary or have no connection whatever. This view finds confirmation in the behavior of pregnancy in a leukæmic female; the dis-

ease pursues its own course. Even if premature labor does occur, it is not necessary to invoke leukæmia as the cause; sufficient natural conditions are present to account for it, such as increased abdominal pressure from the presence of a large splenic tumor, ascites, intestinal flatus, etc. My case was the first in which premature labor had to be induced on account of the unusual abdominal distention and the consequent distress.

Leukæmia seems to have no special effect upon labor itself or the puerperal period; the placenta separated easily and very little blood was lost. In this respect leukæmia differs markedly from pernicious anæmia. In the former both subjective and objective symptoms seem to improve after the conclusion of labor; in the latter the patient rapidly grows worse.

The condition of the children born of leukæmic mothers is especially interesting; all were born without a trace of the disease. Only Cameron and myself examined the blood of the placenta and child. In his case the child died four days after birth; in mine the child was not only born healthy, but remained healthy, although reared artificially. With regard to the question of hereditary influence raised in Cameron's paper, I cannot accept heredity as the cause of leukæmia in the children. Several of the children were undoubtedly born healthy, and the cause for a subsequently developing leukæmia must be sought in some extra-uterine cause, probably residence. Cameron's observations and my own have proved beyond any possibility of doubt that intra-uterine transmission of leukæmia from mother to child does not exist, but it still remains an open question whether or not an hereditary predisposition may be transmitted which may lead to the subsequent development of the disease, and, beside, as I shall show in the second part of this paper, we may have an autocthonous congenital leukæmia without the mother being leukæmic. The indisputable fact that the child born of a leukæmic mother is not itself leukæmic has a most important bearing upon the question of fœtal nutrition. Nature here provides in the human species an experiment capable of absolute proof, whereby it is evident that *leucocytes cannot pass through the placenta from mother to child.* Whatever may occur in animals, we must, by reason of these observations, deny that microcytes, cocci, bacteria, spores, etc., can pass from the blood of the mother to that of the child, unless a rupture exists in the placental wall. This is well shown in our cases. After the birth of a healthy child the blood in the umbilical vessels contained healthy blood, while that of the placental vessels was as leukæmic as that of the mother.

II.

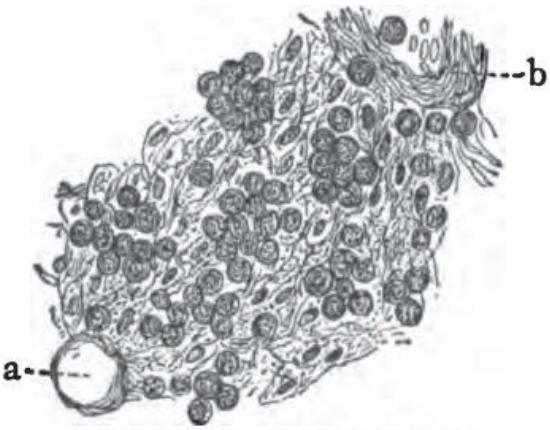
CONGENITAL LEUKÆMIA.

Not only is it a fact that leukæmic disease in the mother does not necessarily exert an unfavorable influence upon labor itself or the health of the child, but conversely it is also a fact that a congenital form of leukæmia may exist which is strictly confined to the fœtus. My own case, observed

in April, 1881, was briefly communicated to the Leipzig Obstetrical Society in May of the same year, but has not been fully reported till now. The patient, aged 24, was spontaneously delivered of a still-born child. The child was only recently dead and presented a peculiar appearance, the result of general dropsy. During the usual manipulations after the birth of the head, the fleshy part of the neck was torn down to the spine, the arm was almost torn off, and the skin was partly separated from the abdomen, although the child had been alive within a short time. The result of the autopsy was as follows: Fœtus about thirty-second week; length, 41 cm.; weight, 4.85 pounds; right arm and leg larger than left; right forearm as large as a boxing-glove; skin of head purple-red; scalp raised 4 cm. from the cranium and elastic, like a large caput succedaneum; eyes closed; eyelids resembling sacs of water; right half of face more swollen than the left; belly distended; limbs much swollen, the skin being pushed up as much as 3 cm. into irregular furrows. When the abdominal cavity was opened a quantity of thick brownish flocculent fluid came away. Spleen about double the normal size; lymph glands not enlarged; double hydrothorax, hydropericardium; heart valves normal; brain pale; meninges not œdematous; ecchymoses scattered through the brain substance. The placenta pale red, very soft and watery and weighed

Congenital Leukæmia.

about two and three-quarter pounds; cord also dropsical. Under the microscope the ascitic fluid was found to contain numerous large leucocytes besides red corpuscles and peritoneal endothelium. The blood showed a ratio W : R = 1 : 3. Cover-glass preparations of the splenic pulp showed little else than leucocytes, mostly with large nuclei and nucleoli. Scrapings of the liver swarmed with white blood corpuscles, singly or in masses. Sections of the liver showed in every acinus very small lymphomes arranged in a radiating manner from the central vein to the portal vessels. At



Leukæmia. Lymphomata of the Liver.
a. Branch of the Central Vein. b. Portal Vessel.

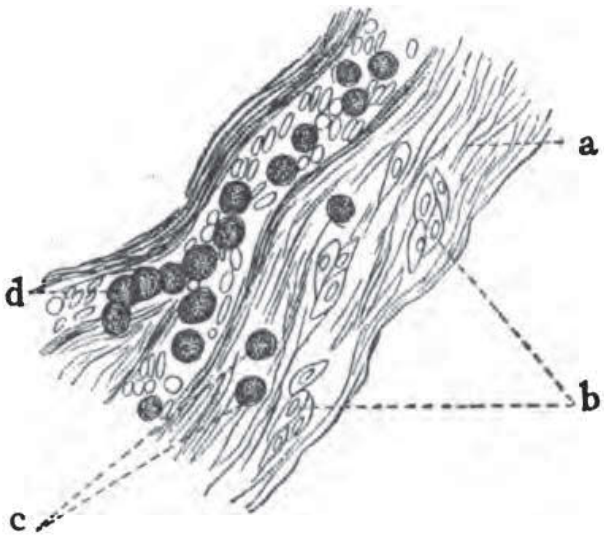
some places these lymphomes were so numerous and dense that they were as large as the parenchyma cells of the acini themselves. The bone marrow showed almost only leucocytes, with but a few red cells. In the placental villi the connective tissue was found greatly swollen and the epithelium in most part gone. The villous capillaries carried as large a proportion of leucocytes as the rest of the fœtal blood. The mother showed likewise evidences of general dropsy, which, taken along with a highly albuminous urine, systolic heart murmurs and impairment of vision, led to a diagnosis of chronic nephritis, with albuminuric retinitis. Unfortunately, there was no chance of examining the blood; nevertheless, the absence of splenic enlargement and of swelling of the lymph glands warrant exclusion of the leukæmia. Three weeks after confinement the mother died of nephritis.

The parallel Prague case, described clinically by Jakesch, anatomically and microscopically by Klebs and Eppinger, may be briefly summarized as follows:

Patient, aged 30, vi-para, miscarried in the thirty-second week of pregnancy. The abdomen was much distended, as in hydramnios; there was œdema over the mons veneris and in the lower extremities. The child was alive and presented in the second position of the breech. The labor was difficult on account of the great size and elasticity of the breech, and notwithstanding every precaution many injuries were inflicted during extraction, among others fracture of the cervical vertebræ. The child was generally œdematous; the placenta was also œdematous and three times the usual size. The patient made a good recovery, afterward bore a healthy child, and is now in good health. In this child the œdema of the skin was less than in my case; ascites, double hydrothorax and hydropericardium existed. The umbilical vessels were normal, the heart flabby and pale, the ductus Botalli as large as the pulmonary artery and aorta; liver and spleen were both enlarged. The microscopical examination confirmed the diagnosis of leukæmia. Like my own case, this was undoubtedly one of congenital leukæmia of the splenic or spleno-myelogenic variety. The rapid course of the disease in the fœ-

tus is remarkable; an eight months' fœtus was found to be in a condition corresponding to the advanced stage in adults. In this rapidity of development we see a striking resemblance to the higher degrees of congenital syphilis, where the child is born with the gravest tertiary lesions. No other relation exists between the two diseases; congenital syphilis is very common; congenital leukæmia and general dropsy very rare.

Gravidarum is by far the most complete which has yet appeared, and will repay careful perusal. In condensing it for the ANNALS OF GYNÆCOLOGY AND PÆDIATRY, I have been obliged to pass over many interesting points, in order to keep within the prescribed space limits. In a letter, dated April 20th, 1890, Dr. Saenger informs me that his leukæmic patient has since died, but that the child is still alive and well. With regard to



Leukæmia. Large Villus of the Placenta with Capillary.
a. Œdematous Connective Tissue. b. Epithelia of the Villus.
c. Infiltrated Leucocytes. d. Leucocytes Collected at the Bifurcation of the Capillary.

From the consideration of these cases, we may come to the conclusion that no transudation of serum occurs from the fœtal to the maternal blood, and that no formed elements or leucocytes pass from child to mother. It may, therefore, be accepted as proven that leukæmia of the mother is not transmitted to the child, and conversely that leukæmia of the child is not transmitted to the mother.

[Dr. Saenger's article on Leukæmia

my own case, Mrs. S. has since been confined *twice*. Neither child was leukæmic, but both died shortly after birth. The patient herself was in such a critical condition during her last pregnancy that premature labor had to be induced at the seventh month. The further notes of this case I intend to embody in a paper for the International Congress at Berlin this Summer.]

J. C. C.