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DR. ARCHIBALD CHURCH,
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Original Articles.

LEUKÆMIA AND PREGNANCY.

With Report of a Case.

BY W. W. JAGGARD, M.D.,
Professor of Obstetrics in the Chicago Medical College, and Obstetrician to Mercy Hospital, Chicago.

Read before the Chicago Medical Society, June 16, 1890.

The purpose of this communication is to place on record an example of fatal lienal leukæmia, that seems to have sustained some necessary relation to pregnancy, or to prolonged lactation during pregnancy, or to both these factors.

The notion of some necessary relation between the female generative organs and leukæmia has long been accepted. Thus Virchow,[1] the discoverer of leukæmia, writes on the etiology of the disease: "The only thing that can be asserted with any degree of certainty is the connection with the sexual functions in woman."

And Mosler[2] says: "Disturbances of the sexual functions in woman have an influence in the origin of leukæmia that is

[1] Gesammelte Abhandlungen, Frankfurt, 1856, p. 209.

[2] Die Pathologie und Therapie der Leukämie, Berlin, 1872, p. 113.

unmistakable. There exists a certain connection between the female genital organs and spleen. An acute splenic tumor with slight increase of the white blood-corpuscles often arises in consequence of anomalies of menstruation."

Within a recent period, however, the nature of the evidence upon which this notion rests has been called in question by Sänger,[3] in an excellent critical review of the literature of the subject. This testimony, he writes, is not the language of modern gynecology.[4] "The question, up to the present surrendered entirely to internal medicine, must be investigated anew by gynecologists, who hitherto have interested themselves in leukæmia and splenic tumors only in their relation to differential diagnosis for the purpose of laparotomy."

It is a fact that leukæmia occurs twice in men to once in women. Among 91 cases Ehrlich found 60 males and 31 females, while among 201 cases Birch-Hirschfeld found 135 males and 66 females. This unequal occurrence exists in spite of, or perhaps on account of, the greater demands on the blood-glandular system of women. Now, if menstrual disturbance, so commonly observed, were always of primary, causal moment, the world would swarm with leukæmics. On the other hand, does it not seem probable that the more active blood-metabolism is the factor that tends to shield the female sex from leukæmia?

On the reciprocal relations of leukæmia and menstruation it can be said that in most cases the menstrual blood-flow is lessened in the course of the disease even to the degree of complete amenorrhœa. Oligomenorrhœa and amenorrhœa, however, are secondary. They arise in consequence of the leukæmic blood-dyscrasia, just as they occur in chloro-anæmia, in the anæmia of obesity, in pulmonary tuberculosis and after severe hæmorrhages. With reference to sudden suppression of the menses, whose causal importance is insisted upon by Mosler, it is more probable that the same pernicious influence that effected the suppression at the same time produced the leukæmia.

It is alleged that among women the climacteric period has the greatest number of cases, and Mosler goes so far as to attach causal significance to the senile retrograde changes in the

[3] Ueber Leukämie bei Schwangeren, etc.

[4] Archiv für Gyn., Bd. xxxiii. H. 2.

genitalia. But it is irrational to suppose, as he does, in a single case that the numerous severe labors and abortions with considerable loss of blood should first avenge themselves at the menopause instead of immediately upon the reception of the injury. And, in general, it may be remarked that the recorded cases furnish no evidence that can incriminate the change of life.

No evidence whatever has been presented to prove a connection between primary affections of the ovaries and secondary leukæmia. It has been shown, however, that in the course of leukæmia these organs, or their analogues, are sometimes involved. Hérard demonstrated the formation of lymphomata in the ovaries in one case; Robin, in the testicles; Gillot, in the mammary glands.

The coincidence of pregnancy and leukæmia is rare. Still, in the cases of Cameron, Greene and Sänger conception occurred. Accordingly, the conclusion is justified that leukæmia, as such, does not inhibit capability to conceive, but, at the most, limits the function, though even limitation is not probable, since repeated conceptions have been observed in leukæmia.

From these considerations the opinion seems justified that disturbances of menstruation, of ovulation and of conception in leukæmia have either a secondary significance or are entirely independent of the disease.

Turning now to the connection between pregnancy and leukæmia, it seems to me that the evidence in hand does not warrant Sänger's absolute denial of all causal relation.

The history of my case is briefly as follows :

Mrs. F. G., thirty-four years old; born in Boston of German parents; wife of a mechanic; VI.-para. When in health a large, fine-looking woman, five feet four inches in height, one hundred and fifty pounds in weight. Menstruation established in sixteenth year, was regular every four weeks, painless and of three days' duration.

No serious illness during girlhood with the exception of an attack of "inflammation of the bowels" that lasted six weeks during her fourteenth year. No history of syphilis, alcoholism, injury, nor of rheumatism. Patient has lived in Boston, Mass., Milwaukee and Menasha, Wis., and in Chicago, and never suffered from malarial infection.

Married January 12, 1875, while in her twentieth year.

First child, male, born February 1, 1876, died of cholera infantum when eight months old (Dr. Root's certificate).

Second child, male, born September 7, 1877, nursed sixteen months; living and in health.

Third child, female, born November 12, 1879, nursed sixteen months; living and in health.

Fourth child, male, born May 4, 1882, nursed eighteen months; living and in health.

Fifth child, female, born December 12, 1886, nursed during her sixth pregnancy up to and on the morning of her confinement, July 8, 1888; child is now living and in health.

Sixth child, female, born July 8, 1888, small (premature). This child she was not able to suckle. At the end of the first week the child was artificially fed and died in convulsions at the end of the third week.

All her labors were easy and rapid. She was attended exclusively by a midwife. No miscarriages. With the exception of the sixth all the children large and vigorous. The four survivors, seen and examined June 1, 1890, present every appearance of health.

The course of the sixth pregnancy was normal. Three weeks before the sixth labor patient was a large and apparently healthy woman, with well-developed bust, and weighed one hundred and fifty-eight pounds. At this time she had a photograph taken, because, to use her own words, "she never looked so well."

Sixth puerperium, with the exception of the failure of lactation, was apparently normal. At the end of ten days she was up and at work as usual. At this time she first noticed stinging paroxysmal pains in the region of the left hypochondrium, although no tumor was perceptible. About six weeks after labor, August 22, 1888, menstruation was reëstablished, but was very scanty.

Menstruation for the second and last time, January 2, 1889; scanty.

Pains of a lancinating character in the region of the spleen became more severe, the loss of weight was progressive, and weariness and general malaise became marked. About eight weeks after this labor she first noticed, and called to her husband's attention, a painful lump in the region of the left hypochondrium,

which seemed to grow in size from week to week. Finally she consulted her physician, Dr. Glenn M. Hammon, of Chicago, who made an examination, January 21, 1889. He writes: "I found a large, densely hard, nodular mass extending downward from the spleen and filling nearly the whole of the left half of the abdominal cavity. It was easily outlined because of the emaciation. There were no other glandular enlargements. There was considerable pain of a lancinating character." The case came under my observation January 31, 1889, and remained under my control for four weeks. Patient greatly emaciated, pulse 116, temperature 100.3° F. Heart, lungs, and liver negative. Urine free from sugar and albumin. Palpation of the abdominal tumor, rendered easy by the disappearance of the panniculus adiposus and by the marked diastasis of the recti, revealed an enormously enlarged spleen that filled out the left half of the abdominal cavity and below the navel extended obliquely to a point near the right iliac fossa. The hilum and the free notched anterior margin were easily outlined. The organ, symmetrically enlarged and immobile, was painful spontaneously and on pressure. There were some ascites and slight œdema of the legs and feet.

Pelvic genitalia absolutely normal.

Lymphatic glands and long bones negative.

A drop of blood, notably viscid, showed an enormous increase of the white corpuscles. The white corpuscles apparently equalled in number the red disks.

Diagnosis.—Leukæmia lienalis.

February 4, 1889, Dr. Frank Billings saw the case with me, and together we made a careful examination of the blood

Blood-count (Hayem's hématimèter).—Red disks, per c.mm., 3,255,000; white corpuscles, per c.mm., 1,178,000; ratio of white to red as 1 : 2.7+.

On account of the viscidity of the fluid, due to the increase of white corpuscles, we encountered difficulty in the estimation of the hæmaglobin by Gowers' instrument. After many trials, however, we were successful, and fixed the quantity at fifty per centum. At this time we went over the history of the case and made a thorough physical examination, but discovered nothing

new. We detected no enlargement of lymphatic glands, no change in the bones.

Retina not examined.

Family history good. Both parents aged, but in health. Blood of father and only sister (II.-para) upon examination, normal.

Prognosis.—Absolutely unfavorable.

Treatment.—Nutritious food, arsenic, iron, anodynes.

Subsequent course of disease.—February 11. Paroxysms of terrible pain; vomiting large quantities of blood. Diarrhœa; dejecta streaked with blood. Rapid progressive emaciation. Pain always referred to the splenic tumor. Dr. J. M. Hutchinson, of Chicago, who saw the case later, kindly informs me that the paroxysms of terrible pain, always accompanied with violent vomiting, continued, the tumor increased in size, considerable ascites and œdema of the feet and legs developed; and that cachexia and emaciation progressed.

A few days before death patient weighed less than one hundred pounds.

She remained conscious to within three hours of death, which occurred June 27, 1889. Autopsy could not be obtained.

This case presents several points of interest:

1. The certificate returned to the City Board of Health, I am informed, assigns cancer of the spleen as the cause of the death of this woman. Now, as an ingenious figure of speech, it may be permissible to speak of leukæmia as carcinoma of the blood (Bard), or as sarcoma of the blood (Sänger), but it is a gross error to call a leukæmic spleen a cancer. Under adequate microscopical examination of the blood is it not possible that some of the examples of splenic cancer and of ague-cake reported here and elsewhere might be resolved into instances of leukæmia?

2. Exploratory laparotomy was actually proposed and very seriously considered in this case. But in view of the professional insanity that has attended the evolution of the "abdominal instinct," this proposal cannot be regarded as phenomenal. Splenotomy, according to Collier, has been performed in twenty-nine cases. Out of these, eighteen were in cases of leukæmia—all patients died immediately after the operation. Of the rest,

sixty-one per cent. recovered. The operation of extirpation of the leukæmic spleen is justly looked upon as an art error.

3. The family history of the patient is good. As before remarked, the father and mother, though aged, are in excellent health. The only sister is the healthy mother of a robust child. The patient's four living children are sound and active.

4. The history of the case seems to point to some necessary relation between pregnancy, or between prolonged lactation during pregnancy, or both these factors, and the leukæmia. The evidence, indeed, is only probable, but it is sufficient to create a presumption. As pertinent to the discussion, I beg to submit the following sentence, taken from the Introduction of Butler's *Analogy:* "In questions of difficulty, or such as are thought so, where more satisfactory evidence cannot be had or is not seen, if the result of examination be that there appears upon the whole the lowest presumption on any one side and none on the other, or a greater presumption on one side, though in the lowest degree greater, this determines the question even in matters of speculation, and in matters of practice will lay us under an absolute and formal obligation, in point of prudence and of interest, to act upon that presumption or low probability, though it be so low as to leave the mind in very great doubt which is the truth."

This view of the nature of the case receives some support from its antecedent probability. During gestation the organs of the blood-glandular system, notably the spleen, the thyroid and lymphatic glands, increase in size and their functional activity is augmented. According to Birch-Hirschfeld,[5] the normal average weight of the spleen in the non-gravid woman is one hundred and forty grammes, while at term it is one hundred and eighty grammes. Virchow says that the number of white corpuscles is normally increased during pregnancy. Sänger, indeed, questions the evidence upon which this assertion rests, but he does not prove that the physiological leucocytosis does not occur. Clinical experience teaches that physiological processes are liable to undergo pathological exaggeration during pregnancy. Restricting attention to the blood we have examples of the truth of this statement in the chlorosis, hydræmia, and pernicious anæmia of the gravid woman. It is conceivable that under certain conditions

[5] Berliner klin. Wochenschrift, 1878, p. 324.

the physiological leucocytosis of pregnancy and the normal splenic hypertrophy may undergo pathological exaggeration and terminate in leukæmia. This notion is not forced nor strange, but is altogether in harmony with what we know of the constitution and the course of nature.

As to the exact effects of lactation during the usual period, upon the blood-glandular system, but little is known, and our ignorance is still greater when we come to lactation during pregnancy. From carefully conducted examinations of the mammary glands of guinea-pigs, during and after pregnancy, Rauber concludes that "Milk owes its origin to the entrance of countless leucocytes into the lumen of the gland-vesicles. The emigrated lymphoid elements penetrate the alveolar walls, passing through the single layer of epithelial cells which lines them. Arrived in the interior of an ultimate acinus, the leucocytes undergo fatty metamorphosis and thus furnish the most essential and characteristic ingredient of milk, viz., the milk-globule."

Satterthwaite says:[6] "Thus the primitive opinion advanced by Empedocles, describing milk as white pus, is in a measure revived, and milk is held to be directly derived from the white corpuscles of the blood."

But, as at present informed, Rauber's ingenious hypothesis has never been definitely corroborated, and it is not positively asserted that in this case the excessive demand by the lacteal secretion upon the white corpuscles was the cause of the splenic tumor.

The probable time of the commencement of the leukæmia in this case coincides with the latter days of the sixth pregnancy. This is the period when the blood-glandular organs are most severely taxed by pregnancy itself. Add to this the additional strain of suckling a vigorous babe, and it seems that there is presented a cause adequate to the phenomenon.

This proposition rests chiefly upon the history of the case, obviously a precarious basis. Still, three weeks before labor the woman was the picture of health, as shown by her photograph, and by her weight, one hundred and fifty-eight pounds. Soon after labor and after the failure of the milk the pains were felt in the side, and the splenic tumor, small then, appeared. All

[6] Manual of Histology, 1881.

these facts fix with tolerable accuracy this time as the date of the commencement of the disease. This impression is confirmed by the duration and by the character of the course of the disease. The patient died eleven months and nineteen days after her sixth confinement, and the course of the disease was steadily progressive.

Out of the sixty-three cases tabulated by Gowers, the duration of the disease was under a year in the thirteen examples whose symptoms more or less closely resemble the clinical picture of this case, and in general the average duration of the malady may be reckoned as between one and two years (Eichhorst).

The history of the case offers no other explanation of the leukæmia. Trauma, syphilis, alcoholism, can be absolutely excluded. The patient never resided in a malarial region, and to the best of her knowledge never suffered from malarial infection.

A few cases have been published that seem to point to a causal relation between some phase of the puerperal state and leukæmia. Sänger, indeed, insists that this connection has never been established. On the one hand, he thinks that pregnancy does not affect the origin or course of leukæmia; on the other hand, he seeks to prove that leukæmia affects pregnancy in the determination of premature labor only indirectly by the greatly increased intra-abdominal tension, on account of the presence of the splenic tumor, ascites, meteorism of the intestines and the like. "The leukæmic quality of the blood, as such," he writes, "does not need to be invoked in explanation." But, as before remarked, the weight of evidence, as it seems to me, is in favor of the older view, of some necessary reciprocal relation between pregnancy and leukæmia. For my purpose, it is sufficient to mention merely one old and three new cases.

Leube[7] and Fleischer describe a case of a myelogenic leukæmia. A woman, strong and healthy up to the time of examination, developed four months after a normal labor, signs of a somewhat rapidly increasing leukæmia, without demonstrable cause. There were impairment of nutrition and strength, syncope, headache, anorexia, and also painfulness and swelling, which

[7] Ein Beitrag zur Lehre von der Leukæmie, Virchow's Archiv, lxxxiii., p. 1124.

finally in part disappeared, of the left lower extremity. Five weeks later, there were signs of a high degree of anæmia, blowing murmur over the heart and a small compressible pulse. No enlargement of spleen, liver, or lymphatics. The number of red corpuscles was significantly decreased and there were both relative and absolute increase of the white corpuscles. The left tibia and left tarsus were painful on pressure. On account of rapidly increasing gangrene of the skin, amputation of the left foot was performed and was followed by death, six days later. Section revealed extreme anæmia of all internal organs, advanced degeneration of the cardiac muscle and chronic ulcer of the stomach, but no change in the liver, spleen or lymphatics. The bone-marrow was red and hyperplastic, with numerous nucleated red blood-corpuscles (transition forms, and numerous marrrow cells).

According to Osler's[8] interpretation "This was no doubt a case of post-partum anæmia aggravated by the presence of ulcer of the stomach, and the great interest of the case lies in the transition of the anæmia into leukæmia."

In Cameron's[9] case, there were presented among others, the following points of interests: "1. Splenic tumor was first noticed by her at the beginning of her sixth pregnancy." "2. Spleen and liver always enlarge during pregnancy and become tender." "3. The progressively enormous increase of white cells and decrease of red cells, as pregnancy advances." "4. The rapid subsidence of œdema and dyspnœa after the termination of labor, together with the rapid increase of red and decrease of white cells."

Of the later course of this case, Dr. Cameron, under date of June 3, 1890, writes me: "My patient is still living and has been confined twice since the Washington meeting. The first time she made an excellent recovery and regained her health so much that she was able to do all her own housework. The child was premature and died very shortly after birth, but was quite free from all trace of leukæmia. During her last pregnancy her health was poor. She became very anæmic and suffered so much

[8] Pepper's System of Medicine, vol. iii. p. 920.

[9] Transactions of the International Medical Congress, Ninth Session, Washington, 1887. Vol. ii. p. 330.

from dyspnœa, palpitation, and threatenings of heart failure that I was obliged to induce labor about the seventh month. The fœtus had perished some days previously. She barely escaped with her life, and is slowly going down-hill. The splenic tumor and her blood-count remain about the same."

James L. Greene's[10] report of two cases of leukæmia, so sharply criticised by Sänger, while defective, is still of a certain value. His first case, during a first pregnancy, was an example of acute lienal leukæmia that was fatal within six months of the apparent outset. Although malarial infection cannot be absolutely excluded in this case, the course of the disease creates the presumption that malaria, if present, must have played a minor *rôle*. It is to be hoped that the history of Greene's second case will be filled out in the near future, since, as at present described, the diagnosis of leukæmia, to say nothing of the variety, is not established. The case is that of a young primipara, the sister of the patient of the first example, who suffered from symptoms pointing to leukæmia. Upon the artificial induction of abortion, the patient promptly recovered. Of this case Dr. Greene, under the date of May 30, 1890, writes me: "The second case mentioned by me, Mrs. C., has conceived since the report was published, and with this condition returned all of the symptoms of leukæmia. An abortion was produced and she regained her health as before."

On account of the antecedent probability of the view, on account of the coincidence of the apparent onset of the disease with the later days of pregnancy, on account of the absence of any other demonstrable adequate cause, and finally, on account of the evidence accumulated from the cases cited, it seems to me to be highly probable, that in this case, the leukæmia sustained some necessary relation to pregnancy, or to prolonged lactation during pregnancy, or to both these factors.

2330 Indiana Avenue.

Dr. Archibald Church.—Mr. President: At the courteous request of Dr. Jaggard I present here under the microscope a specimen of leukæmic blood taken from a case this afternoon, and will briefly outline the clinical history:

The subject of these few and hasty notes is a typical New

[10] New York Medical Journal, February 11, 1888, p. 144.

England housewife. She is tall, slender, delicate, fair, and has never had any severe illness during her lifetime, and has never been in robust health. There is no history or indication or suspicion of malarial infection. She is now fifty-four years of age and has been a widow for sixteen years. Her father is stated to have died of some obscure liver complaint, one sister of galloping consumption and one brother and another sister of acute diseases. She had an uneventful childhood, and was considered fairly vigorous, but did not menstruate until the age of eighteen. From that time on until the menopause, which occurred at forty-four, menstruation was never marked by peculiar symptoms or difficulty; it was usually scanty in quantity and unaccompanied by particular pain. She gave birth to two sons, both of whom are living and in good health. After the first confinement she presented a high degree of anæmia, lasting some months, and passing away during the second pregnancy. After her husband's death she supported herself and family by taking in boarders. She was subjected to a great deal of anxiety and worry, but her health was not considered impaired until a year ago. Menstruation suddenly ceased at the age of forty-four, and for seven years afterwards she was troubled with all the subjective symptoms which afflict some women at the menopause; during this entire time flashes of heat and suffocative attacks were a constant annoyance. Following that epoch which brings us to within three years of the present date, she was in comparatively good health and did a large amount of work and was subject to a great amount of responsibility. About a year and a half ago when I first made her acquaintance I noticed a peculiar pallor, but she insisted that she was in good health and no one of her acquaintances or her family considered her ill or even ailing. How long previous to this time the pallor had existed I cannot learn, but I am inclined to think it extended back possibly to the end of the subjective condition following the menopause. That is a mere supposition, however. About a year ago she commenced to run down very rapidly and during the past eight months has been confined to her bed. During this time she has been under the care of some eminent homeopathists of this city, who pronounced the malady "consumption of the bowels." She has had no elevation of temperature and no anorexia, but, on the

contrary, the appetite has been extremely good. She sometimes experienced an amount of thirst that was wonderful, requiring a large amount of water, milk or other fluids, every hour. During the past three years there has been a little looseness of the bowels, but the stools have never been peculiar nor have they shown signs of blood. She has been subject to attacks of syncope, which were considered as pointing to brain trouble by her family, and to frequent epistaxis. The case came under my care about a week ago. I found her general appearance that of extreme anæmia, with considerable emaciation; the lips were perfectly white, the tongue almost devoid of redness, as were the palate and fauces. Her pulse was fair as to volume and in the recumbent position eighty to the minute. Anæmic murmurs were heard over the cervical vessels. Her temperature was normal. Her appetite and digestion left nothing to be desired; she eats everything and takes care of it without distress. I found the urine normal to all tests and reactions, except that it was a little over-acid.

Upon examination of the abdomen I found the spleen much enlarged, extending downward to the iliac crest, anteriorly to within three inches of the median line and apparently encroaching on the lung space above, dullness being present as high as the sixth rib in the axillary line. Its surface to palpitation was smooth. The liver is also much enlarged, extending downward about four inches below the costal margin of the thorax and on the left is in apposition with the spleen. There is no enlargement of the lymphatic system as far as I can detect. There is slight œdema of the feet and puffiness of the face. Sometimes I am inclined to think that the integument about the abdomen feels boggy, but no ascites is present. There is nothing abnormal so far as the lungs and heart are concerned; the skin presents nothing unusual. Upon examining the blood I found a large increase in the white elements, there being about one white to six of the red; I have not had time to make an accurate estimate of the proportion, but in the ordinary microscopic field the ratio is nearly as stated. When she has nose-bleed the blood scarcely stains a handkerchief, and the drop obtained by pricking the finger tip is yellowish and sticky.

Upon examining the retina with the ophthalmoscope, I found

in the periphery of the retinal expanse a number of white patches, and the reflex is yellowish instead of pink. At present there is no interference with vision, which is tolerably acute. Her mind is bright and she talks as much and as interestingly as any woman could in her condition, and is extremely hopeful and ambitious for the future.

I have given an absolutely unfavorable prognosis, although during the past fifty days she has gained some in strength and is now able to sit up the greater part of the day, owing, perhaps, to removal from the worry of her business and to quieter surroundings. Upon the recommendation of a homeopathic physician she has been taking cod liver oil, with plenty of milk and some brandy, all of which I approve. I have ventured to put her on a compound of arsenic, quinine and iron, not expecting to do much good, but hoping it will do no harm, and as at present she is slightly on the mend, I am in hopes that for a time at least she may rally. But as to the final result, it is unquestionably fatal.

NOTE.—This patient died in July, 1890, and the homeopathic practitioners into whose hands the case had returned, made an autopsy, finding to their surprise an enlarged spleen.