every hour by the mouth with the addition of ten minims of brandy in each spoonful of water. At 9.30 P.M. the woman was comfortable and free from pain. There had been no more vomiting and the bowels had not acted again. The temperature was 100° and the pulse was 100.

At 3.30 A.M. on Saturday I was sent for again. The woman had become much worse, had vomited repeatedly, complained of intense abdominal pain, and become much collapsed. She was clearly *in extremis*; the temperature was 98°, the pulse was 140, but the abdomen was not rigid or distended. There was slight tenderness on the left side of the uterus. The tongue was clean and moist. There was no dulness in the flanks. Hot-water bottles were applied to the abdomen and a quarter of a grain of morphine tartrate and $\frac{1}{16}$ th of a grain of strychnine-hydrochloride were given hypodermically. The patient never rallied and death occurred at 5 A.M.

Post mortem there was about an ounce of blood-stained serum in the pericardium and in each pleural cavity. The lungs, heart, brain, spleen, liver, and kidneys were healthy. The small intestine was hyperæmic in places. Round the left ovary and in Douglas's pouch and in the lesser sac of the peritoneum was some flaky lymph. The stomach, pancreas and duodenum, and the appendix were healthy. There were several old adhesions round the left ovary and Fallopian tube, both of which were deeply congested. A drop of thick yellow pus was escaping from the left Fallopian tube, which contained about half a drachm more of the same material. The interior of the uterus was quite healthy. I could obtain no history of any symptoms of salpingo-oophoritis from any of the relatives.

The baby, having been taken out of the mother's room on Friday morning, was put to sleep on a cushion in an armchair in the kitchen. He was seen at 1 P.M. and was then all right, but at 2.30 P.M. he was found dead. A post-mortem examination showed that death was due to suffocation.

Weybridge.

HÆMATOLOGICAL AND CHEMICAL OBSERVATIONS IN A CASE OF SPLENO-MEDULLARY LEUKÆMIA UNDER X RAY TREATMENT,

WITH AN ACCOUNT OF THE HISTOLOGY OF THE HÆMOPOIETIC ORGANS AFTER DEATH.

By J. C. G. LEDINGHAM, M.B., B.Sc., M.A. ABERD.,
LISTER INSTITUTE OF PREVENTIVE MEDICINE ELSTREE.

(From the Bacteriological Departments of the University of Aberdeen and London Hospital.)

At a laboratory meeting of the Pathological Society of London held at Claybury in July last a paper under the above title was read by me and will appear in due course in the published Transactions of the society. In view of the fact, however, that a preliminary communication on the same case was made to THE LANCET in January, 1905,¹ I propose here to record briefly the main results obtained during the latter history of the case.

The first series of x ray séances lasted from May 17th to August 8th, 1904, and at the end of that time the patient's general condition had enormously improved while the changes in the blood picture were most striking. The white cells fell from an average of 200,000 to an average of 20,000 per cubic millimetre in the course of six weeks and there was also a very appreciable rise of the red cells in the same time. The red cell maximum was not reached, however, till the middle of August when the white cells were already mounting slowly upwards after the suspension of the x rays. Arneth² in a recent paper has also noted this late response on the part of the red cells to x ray influence. During September, October, and November, 1904, the patient remained in a convalescent home where he enjoyed excellent health. Frequent blood examinations were made during this time and it was found that the white cells were rising very gradually and in a somewhat irregular fashion. At the end of November a level of 60,000 had been reached. It is

an exceedingly suggestive fact that the suspension of radiotherapy for three months did little more than raise the total count of the white cells to one-third only of their numbers at the commencement of the treatment. It certainly shows that the radio-therapy had exerted an inhibitory influence on the proliferative functions of the blood-forming organs.

After the patient's return to hospital a second series of x ray séances was commenced on Dec. 1st, 1904, and again there was a remarkable response on the part of the blood elements. The white cells fell progressively in the course of six weeks to the normal, or rather subnormal, level of 7000. When this low level had been reached the question of the advisability of continuing the x ray treatment was raised, the risk being that the circulating blood might be completely depleted of leucocytes, and in the light of the recent animal experiments of Halber and Linser³ to which I shall refer later, this fear would have been perfectly justified. However, no such effect took place. This low level proved again to be a position of unstable equilibrium and the white cells rose very slowly to a level of 12,000. It is impossible to say whether the white cells could have been retained for an indefinite period within normal limits, owing to the unfortunate intervention of an influenzal attack leading to the fatal conclusion. On Feb. 24th the temperature, which hitherto had run a consistently normal or subnormal course, rose to 101° F. This heralded an attack of bronchitis during which the temperature rose on one occasion to 102° 5°. The clinical symptoms were not, however, very pronounced and the end came rather unexpectedly on March 8th—i.e., 14 days after the commencement of the intercurrent affection. One count only was made during the fatal illness and the white cells were found to have mounted up to 43,000. The leukæmic leucocytes had in fact reacted to the intercurrent affection somewhat more vigorously than normal leucocytes would but in the same direction. Now it is a well-established fact that intercurrent affections in leukæmia produce a great fall in the number of leucocytes but here in the leucopenic stage of leukæmia the reaction was in the opposite direction.

A necropsy was fortunately obtained and I am indebted to Dr. G. M. Duncan of the Pathological Department, University of Aberdeen, for notes of the necropsy and for the tissues which were kindly forwarded to me for microscopical examination. The opportunity was thus afforded me of comparing the organic lesions with those described by Heineke⁴ Mosse and Milchner,⁵ Halber and Linser,⁶ and others in experiments on animals. Heineke found that the exposure of small animals such as mice to the x rays produced a destruction of the lymphoid follicles in the spleen and lymph glands. The nuclear detritus was taken up by phagocytes and the node was replaced by connective tissue and epithelioid cells. Prolonged exposure was followed by partial destruction of the granular cells of the marrow. Mosse and Milchner showed that in animals exposed to the x rays the bone marrow is profoundly influenced. The changes affect principally the cells of the neutrophile series which are greatly diminished in numbers, the surviving cells exhibiting great deficiency of granules. The experiments of Halber and Linser are even more remarkable. By prolonged exposure of small animals to the x rays they were able to deplete the circulating blood entirely of leucocytes (as measured by ordinary counting methods). The larger the animal the more difficult it was to free the blood of leucocytes and frequently in rabbits and dogs it was impossible to get lower counts than 1500 or 2000 by continued exposure. They maintained from examination of films that the destruction of leucocytes took place in the general circulation and not in the blood-forming organs. Further, fatal results sometimes ensued which they attributed to the evil effects of leucotoxins set free from the broken-down leucocytes. The serum of x-rayed animals had also the power of causing the destruction of leucocytes when injected into fresh animals. The question as to whether a destruction of leucocytes takes place in the general circulation is an important one. Most observers, with the exception of Grawitz,⁷ Aubertin and Beaujard,⁸ Weil and Aubertin,⁹ are inclined to doubt that

³ Halber and Linser: *Ibid.*, April 11th, 1905.

⁴ Heineke: *Mittheilungen aus den Grenzgebieten der Medicin und Chirurgie*, Heft 5, 1905.

⁵ Mosse and Milchner: *Berliner Klinische Wochenschrift*, No. 49, 1904.

⁶ *Loc. cit.*

⁷ Grawitz: *Deutsche Medicinische Wochenschrift*, No. 50, 1904.

⁸ Aubertin et Beaujard: *Comptes Rendus de la Société de Biologie*, 1904, No. 21, p. 982, and 1905, No. 4, p. 177.

⁹ Weil and Aubertin: *Ibid.*, 1905, No. 25, p. 85.

¹ Ledingham and McKerron: *THE LANCET*, Jan. 14th, 1905, p. 71.

² Arneth: *Münchener Medicinische Wochenschrift*, Nos. 32, 33, 34, 1905.

intravascular leucolysis takes place to any great extent in leukæmia. At least, cytolytic changes in dried films have not been specially noted in the recorded cases but it is quite conceivable that in the lymphatic form of leukæmia more particularly large numbers of lymphoid cells are destroyed in the circulating blood. From Halber and Linser's experiments these latter cells appear to be the most susceptible to x ray influence. Is the diminution of the leucocytes in the circulating blood to be attributed to increased destruction of cells in the hæmopoietic organs or to inhibited production? If increased destruction is the cause one might expect to find evidence of this in the uric acid output. During the five months preceding the adoption of x ray treatment in our case frequent analyses of the uric acid output were made with a view to determine whether according to Horbaczewski's theory any relationship could be found between the purin output and the leucocyte count. At the same time estimations were made of the total nitrogen and total phosphoric acid. Before commencing these investigations it was anticipated that a stage in the progress of the disease might supervene in which the leucocytes might show a progressive tendency to diminish, so that one might definitely demonstrate whether a simultaneous rise in the uric acid took place as the result of leucocyte destruction. As already noted, however, no progressive diminution took place in the leucocyte count during these five months, although marked oscillations were frequent. As has been so frequently noted in leukæmia, the absolute amount of uric acid excreted was found to be much in excess of the normal but it was impossible to demonstrate constantly any rise in the uric acid as the immediate result of a temporary fall of the leucocytes lasting, perhaps, one or two days. Nor could any clue as to the occurrence of leucocyte destruction be obtained from the amount of phosphoric acid excreted. This was slightly higher than normal but it bore the usual proportion to the total nitrogen excreted.

When the leucocytes were progressively falling under x ray influence a further short series of urinary analyses was made. It was found that the total amount of urine passed per day had slightly increased. The total nitrogen and total uric acid were both relatively high but the percentage of uric acid nitrogen in the total nitrogen remained only slightly affected. The phosphoric acid output was also relatively high but its proportion to the total nitrogen remained as before. It may therefore be assumed that the fall of the leucocytes in our case was not the result of increased destruction but more probably of diminished production.

During the last few months brief reports of urinary analyses in the course of the x ray treatment of leukæmia have been recorded. Rosenberger¹⁰ found a diminution in the uric acid while the leucocytes were falling. Schleip and Hildebrandt¹¹ found that the variations in the amount of uric acid passed were so great that no conclusions could be drawn. Strümpell,¹² Joachim and Kurpjuweit,¹³ and Lossen and Morawitz¹⁴ (in one fatal case) demonstrated an increase in the uric acid while the leucocytes were falling. The bulk of the chemical evidence, however, is in favour of the view that the x rays exert an inhibitory action on the hæmopoietic organs. What effects do the rays produce on the leucocytes and uric acid output of healthy persons? In this connexion Bloch¹⁵ has recently reported a rise of the uric acid with a fall of the leucocytes in a case of chronic eczema exposed to the x rays. As this is merely an isolated observation it would not be desirable to draw any definite inferences at this stage. The subject demands further investigation. I shall now record briefly the post-mortem and histological findings in our case.

Both the lungs were much congested and in the right lung were several patches of catarrhal pneumonia. Both liver and spleen were enormously enlarged, the latter organ weighing 7½ pounds. The lymphatic glands on each side of the spine, both in the abdomen and thorax, were also enlarged and varied in size from that of a pea to that of a large bean. The bone marrow, as seen in the sternum, vertebrae, and ribs, had a pale pink colour. Without entering into

detail it will be sufficient here to note the more important changes in the blood-forming organs.

Spleen.—Malpighian follicles were practically absent. There was a marked development of coarse connective tissue pervading the spleen pulp but this fibrotic process had not advanced to the degree which one generally finds in chronic cases of spleno-medullary leukæmia. The predominant cellular constituents of the pulp were large, mononuclear cells with intensely basophile protoplasm. Their nuclei were round or oval and slightly vesicular. In their morphology they resembled the basophile myelocytes of Dominici. Numerous mitotic figures in all stages were seen in these cells. Fully developed cells of the neutrophile series were very scarce.

Lymph gland.—No nodes were visible. Large basophile cells were here also predominant but there were also enormous numbers of giant cells mostly of the megakaryocyte type. Here and there were noted small groups of cells with ill-defined contours containing in their interior two or three densely stained half-moon-shaped bodies. It is probable that these cells represent degenerated megakaryocytes but it is difficult to explain how the broken-down nuclei should assume such regular semicircular forms.

Marrow from the sternum and ribs.—So far as its cellular constituents were concerned the marrow might be said to be in a markedly hypoplastic condition. Bony lamellæ and strands of connective tissue traverse the section, leaving small isolated cellular areas. Small or large lymphocytes were most numerous. Large basophile cells were scarce and giant cells were not nearly so numerous as in the lymph glands. Nucleated red cells were also very scarce.

Liver.—The interacinar capillaries were quite choked with leucocytes, the great majority of which consisted of the large basophile cells met with in the spleen and glands.

Can we bring these changes into line with those met with in the hæmopoietic organs of experimental animals that have been exposed to the x rays? The absence of Malpighian follicles in the spleen is a common feature in chronic spleno-medullary leukæmia and hence cannot be regarded *per se* as the result of radio-therapy. The great scarcity of lymphoid elements in the spleen pulp is certainly a conspicuous feature but the most remarkable change is the substitution of proliferating undifferentiated basophile myelocytes for the fully formed neutrophile elements which one usually finds in the spleen of chronic spleno-medullary leukæmia. In cases of acute leukæmia these cells have been found in active proliferation in the bone marrow, spleen, and lymph glands (*vide* Aubertin¹⁶) and one might presume that the real cause of death was an attack of acute leukæmia superposed on the chronic form during the leucopenic stage. The condition, however, permits of another, and to me more probable, explanation. During the first series of x ray séances the percentage of cells of the neutrophile series rose (the increase affecting the polynuclear elements), while the lymphocyte percentage fell. After the suspension of the rays in August the lymphocyte percentage began again to mount upwards. On the resumption of the x ray treatment in December the neutrophile percentage rose markedly while the lymphocyte percentage fell, but the change was only transitory. When the total leucocyte count was approaching normal limits the polynuclear percentage fell markedly while the lymphocyte percentage rose. So long as a relatively high leucocyte count obtained, the main effect of the x rays would be on the lymphocyte series, as Heineke noted. Now, from the histological appearances it would seem that the spleen and lymph glands were the hæmopoietic organs most actively functioning. Thus, in spite of the inhibitory action of the rays on the myeloid function of the spleen there would result, owing to the destruction of the more susceptible lymphocytes, a relative increase of fully formed polynuclear cells in the circulating blood. When, however, the leucopenic stage intervened during the second series of séances, the ever-increasing tendency to diminished production must have considerably curtailed the myeloid function of the spleen or its power of sending forth into the circulation more or less fully formed neutrophile cells. Moreover, what one might call the Mosse and Milchner effect already referred to would come into play. Hence the presence in such numbers of these basophile indifferent cells in the spleen and glands, accompanied by a diminution in the fully formed neutrophile cells of the circulating blood, might not be so unexpected a

¹⁰ Rosenberger: Centralblatt für Innere Medizin, No. 40, Oct. 7th, 1905.

¹¹ Schleip and Hildebrandt: Münchener Medizinische Wochenschrift, No. 9, 1905.

¹² Strümpell: Fortschritte aus dem Gebiete der Röntgenstrahlen, Band viii., Heft 3, 1905.

¹³ Joachim and Kurpjuweit: Deutsche Medizinische Wochenschrift, No. 49, 1904.

¹⁴ Lossen and Morawitz: Deutsches Archiv für Klinische Medizin, Band lxxxiii., Hefte 3 and 4.

¹⁵ Bloch: Ibid., Band lxxxiii., Hefte 5 and 6.

¹⁶ Aubertin: La Semaine Médicale, No. 24, 1905.

phenomenon. Whether such a spleen would serve the organism more beneficially than a more fully developed myeloid organ is difficult to decide. Most probably it would not, as undoubtedly the needs of the body would be better served by an organ whose power of manufacturing and sending into the blood stream an excess of fully developed neutrophile cells was well maintained.

The above considerations lead me to think that in the interests of the patient it would be advisable to exercise the greatest caution in continuing x ray treatment once the total leucocytes have attained normal limits. This is all the more necessary when one remembers the startling results of Halber and Linser's experiments which, though still lacking confirmation, suggest to us the greatest circumspection in the employment of radio-therapy under the conditions indicated; indeed, in the very few recorded cases of leukaemia which have ended fatally during or after x ray treatment the effects of leucotoxic products or liberated ferments have been assigned as exciting causes. As yet the only fatal case in which an accurate histological examination of the organs has been made is that recorded by Lossen and Morawitz. Krause¹⁷ reported shortly in one case that it was impossible to demonstrate in the hæmopoietic organs changes which are not usually associated with leukaemia, and Lommel¹⁸ who examined the spleen in a case of pseudo-leukaemia which had been exposed to the rays, noted that the organ was very poor in lymphocytes.

Lossen and Morawitz's case did not respond satisfactorily to the x rays. The leucocytes were profoundly influenced but the general condition did not improve. The histological changes they reported were briefly as follows. The spleen pulp showed a great scarcity of leucocytes, especially of myelocytes and lymphocytes. Fibroblasts were numerous. The lymph glands were also greatly deficient in lymphatic elements. The marrow especially showed great hypoplasia with regard to its myeloid and lymphatic elements. The interstitial tissue of the marrow was also increased. As a result of their findings the authors believe that in certain cases the x rays may give rise to a recognisable hypoplasia of the blood-forming organs. No satisfactory explanation has yet been given of the enormous improvement which almost invariably occurs in the general condition of the patient under the x rays. It is at least difficult to bring it into relationship with the blood changes. Of course, on the assumption of Senn and Ahrens that the x rays inhibit the development of, or actually destroy, the hypothetical parasite of leukaemia (Löwit), this improvement in the general condition would find ready explanation.

Certain investigations (to be recorded elsewhere) which I have made on the rôle played by the leucocytes of spleno-medullary leukaemia in the process of phagocytosis of bacteria have shown that in the leukaemic serum the substance preparing the bacteria for ingestion by the phagocyte ("opsonin" of Wright and Douglas) is generally in normal amount as measured by normal leucocytes, while a very much lower index is obtained when measured by the patient's own phagocytes. The myelocytes have exceedingly feeble phagocytic power and hence any factor that increases the number of ripe polynuclears in the circulating blood must also render the normal supply of opsonin more available for purposes of efficient phagocytosis and removal of effete matter from the tissues. It may be noted that in chronic lymphatic leukaemia the conditions appear to be reversed. At least in the two cases which I had the opportunity of examining frequently the polynuclear leucocytes, though constituting only 2 or 3 per cent. of the total, had almost double the phagocytic power of leucocytes of healthy people. In these cases the true opsonic indices as measured with the patient's own serum and phagocytes were relatively high. In performing these tests staphylococci and tubercle bacilli were employed.

Elstree.

¹⁷ Krause: Fortschritte aus dem Gebiete der Röntgenstrahlen, Band viii., Heft 3, 1905.

¹⁸ Lommel: Münchener Medizinische Wochenschrift, 1905, p. 904.

SEAMEN'S HOSPITAL, GREENWICH.—On Thursday, Feb. 15th, the members of the local branch of the British Medical Association are to visit the Seamen's Hospital, Greenwich, in connexion with the new post-graduate school which has just been established at that institution. The staff of the hospital wish it to be known that any medical man, whether belonging to the local branch or not, will be welcomed. There will be an exhibition of cases and it is intended to hold the meeting at about 4 P.M.

A CASE OF BILHARZIA INFECTION OF THE VERMIFORM APPENDIX.

By J. BURFIELD, M.B., B.S. LOND., F.R.C.S. ENG.,

RESIDENT ANÆSTHETIST, LATE HOUSE SURGEON, ST. BARTHOLOMEW'S HOSPITAL.

With a Pathological Report by ERNEST H. SHAW,
M.R.C.S. Eng., L.R.C.P. Lond.,

HOUSE SURGEON, ST. BARTHOLOMEW'S HOSPITAL.

THE patient, a well-developed but rather anæmic man, aged 36 years, was a goods clerk in a railway station in South Africa. He was admitted to St. Bartholomew's Hospital on June 24th, 1905, on account of a sinus in the right gluteal region. The sinus had persisted since January, 1904, when an abscess was opened there by Dr. J. B. S. Greathead at the Albany General Hospital, South Africa. He had come from South Africa to have the sinus cured. His history was as follows. In January, 1899, he had a slight attack of appendicitis which cleared up after rest in bed for ten days. In April, 1902, a large tender swelling developed in the right iliac region; he had fever and was constipated. He was sent to the Albany Central Hospital by Dr. E. G. D. Drury. At this time the swelling could be felt per rectum; it was painful and fluctuated. The pelvic swelling became smaller and the patient was discharged in six weeks without any operation being performed. But the swelling never entirely disappeared and the patient was very weak and unable to do any work till October, 1902, when the abscess pointed on the right lumbar region. Two incisions were made into this between the last rib and the iliac bone and some foul-smelling, dark brown pus was let out. In December, 1902, he was able to work again, wearing a drainage-tube in the sinus.

In January, 1904, another abscess developed in the upper part of the right gluteal region outside the posterior superior spine of the ilium and the patient was readmitted into the Albany Hospital. The appendix region was then explored by the usual oblique incision in the anterior abdominal wall. Dense adhesions were found and a fluctuating swelling was discovered behind the pelvic peritoneum in the region of the sciatic notch. The anterior incision was therefore closed. The abscess in the right buttock was opened up and its cavity was found to lead into the pelvis through the sciatic notch into an abscess in front of the sacrum, whence several ounces of dark fæcal smelling pus were let out. This sinus was still discharging on the patient's admission to St. Bartholomew's Hospital under Mr. C. B. Lockwood in June, 1905. His condition was as follows. There was a scar about four inches long in the anterior abdominal wall, which was the seat of a ventral hernia. Behind there were four scars in the right lumbar and gluteal regions, in the lowest of which there was a sinus leading forwards and inwards for about four inches. The sciatic notch could be felt with a probe but the bone was not bare. There were resistance and tenderness in the right iliac fossa. The urine was natural and did not contain blood or pus cells although systematically examined.

On July 14th, as the sinus showed no signs of closing, Mr. Lockwood explored the appendix region through the scar in the anterior abdominal wall. After a long and tedious search, lasting over an hour on account of the dense adhesions, the proximal end of the appendix was found very firmly adherent to the posterior pelvic wall near the sciatic notch; this part of the appendix was removed. The distal end had apparently sloughed away. A small drainage-tube was left in and the abdominal wall was sutured in layers. The patient left the hospital five weeks after the operation; the abdominal wall had soundly healed. The posterior sinus was healing quickly and was only about one inch in length.

On cutting sections of the appendix ova of bilharzia hæmatobia were seen; they are shown in the accompanying micro-photographs (Figs. 1 and 2). There was nothing to suggest bilharzia infection of the genito-urinary tract or of the rectum; the patient never had diarrhoea and no blood or mucus was ever seen in his stools. Apart from the extreme rarity of bilharzia infection of the appendix, this case is instructive because it throws some light on the way by which the parasite may enter its host.