Optochin has very limited powers of penetration as was demonstrated by superimposing a 1 in 1,000 solution on an infected column of clotted centrifuged blood in an emigration tube. After ten hours the solution had only succeeded in penetrating to a depth of $\frac{1}{5}$ millimetre. Below this depth the microbes had grown with undiminished vigour. This fact would seriously limit its efficacy in the treatment of bacterial infections for it would be unable to diffuse into and exert its influence in abscess cavities, infiltrated tissues (such as would be found in croupous pneumonia and wound infections) and other dead spaces. It would appear that it might find its useful sphere of application in cases of streptococcal bacteriæmia. But opportunity of putting this to the test has not yet been offered.

In conclusion it is a pleasant duty to acknowledge my indebtedness to Colonel Sir A. E. Wright and to the Medical Research Committee under whose auspices this work was carried out.

ACUTE HODGKIN'S DISEASE WITH INVOLVEMENT OF INTERNAL GLANDS AND RELAPSING PYREXIA.

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The following case is worthy of publication for three reasons. In the first place the general course, amongst other peculiarities, presented a combination of an acute onset in an "internal" form of the disease with a relapsing pyrexia and signs and symptoms chiefly abdominal. Secondly, it formed an interesting problem in diagnosis, and the endeavours to solve this gave rise to much speculation, for the case deceived the very elect. Finally, at the post-mortem many interesting pathological features were discovered, and only then was the diagnosis settled.

In McNalty's study of "Lymphadenoma with Relapsing Pyrexia" (*Quarterly Journal of Medicine*, October, 1911), of thirty-two cases there were eight without enlargement of the superficial glands. Only two of these had a shorter duration than the case here reported. One, a male, aged 23, with involvement of mediastinal glands, spleen, liver and kidney, died in five weeks; the other, also recorded by Dreschfeld, had enlargement of the mesenteric and bronchial glands, the liver and spleen, and lived seven weeks. The others lived periods varying from four to fifteen months.

Description of Case.

Onset.—Private L., aged 19, reported sick on November 21, for "Frost Bite," occurring in the trenches in Flanders. He was admitted to a Base Hospital for this complaint on November 23.

On admission, the patient looked pale and complained of pains in toes and soles of feet, but nothing abnormal was seen in these parts. The temperature and pulse-rate were normal. He was badly constipated and therefore was given a strong aperient pill. Two hours later he complained of severe abdominal pain mostly in the right side. The abdomen was then tender, held rigid, but not absolutely so, and moved slightly with respiration. The patient's temperature and pulse-rate were raised, and during the next few hours he vomited two or three times.

The appearance of the case was suggestive of peritonitis, but no localized tender or dull spot could be made out, and the patient's general condition being good the case was carefully watched without resort to operation.

Previous History.—The patient was a recently enlisted soldier and was not inoculated against typhoid. He had been quite well until the onset of pains in the legs. There was no history of previous illness except two attacks (at 14 and 16 years of age) suggestive of recurrent appendicitis. He had never been abroad. No family history of tubercle, syphilis, or blood disease could be obtained.

Subsequent Course.—The following day, November 24, the temperature remained up at 103° to 104°, the patient was lethargic and pale, with a soft and relatively slow pulse.

His abdomen was now distended, slightly tender all over, and still rather rigid. The tongue was dry with brown fur. A leucocyte count showed a leucopenia of 3,500. During the next two days he remained about the same except that his abdomen became tumid and less tender.

On November 27, owing to the above symptoms and signs, he was sent to the Infectious Diseases Hospital as probably "Enteric Fever" and came under my charge. His condition was as described, but the following additional facts were noted. The patient was very pale, with a rather "renal" appearance and complained of much headache. There was occasional muttering delirium with picking at the bed-clothes. The pulse was very soft and occasionally dicrotic. There was marked tenderness in the left hypochondrium and left lumbar regions of abdomen, and this tender area was dull on percussion. The spleen was not felt, but this dullness appeared splenic and reached down towards the umbilicus four fingers' breadth below the costal margin. The heart sounds were good and normal. There was diminished resonance over the lower lobe of left lung behind coming round to blend with the aforementioned dullness. No spots were seen. No enlarged glands were felt anywhere. The stools were fluid and yellow, with no slime, blood or curds. The urine was quite clear, no pus cells or casts were found and there was no bacilluria, but a trace of albumin was present. The serum gave no agglutination with the *Bacillus typhosus* or with either of the paratyphoid bacilli.

The diagnoses which so far had been suggested at various times were

acute peritonitis, recurrent appendicitis, and typhoid fever, the last being especially favoured. Acute lymphatic leucæmia was also suggested.

During the next six days the patient remained about the same, but the abdominal distension got much less, enabling the firm and slightly tender spleen to be felt easily.

On December 2 a leucopenia was still present—2,200 white cells per cubic millimetre—and the hæmoglobin was only fifty-two per cent of the normal. A blood culture made into a bile salt medium proved sterile and the agglutination reactions were again negative.

From December 2 to 5 the temperature came down in a "step ladder" manner and at the same time the patient rapidly improved; there was no distension of the abdomen and the spleen grew much smaller. Treatment had consisted in tepid sponging and the administration of a fluid diet, and constipation had been treated by enemata. The case was considered for the time being as one of typhoid fever. However, on two occasions both stools and urine failed to grow the typhoid bacillus or either of the paratyphoid organisms. The patient continued apyrexial for nine days, being quite bright and cheerful, and on December 31 commenced to take a little solid food. The temperature then quickly went up by steps, and this rise was associated with listlessness, headache, a dry furred tongue, a tumid abdomen, enlargement of the spleen, and some loose motions, and the pulse was soft and compressible. In other words, the whole condition was much like a relapse in typhoid fever, and it was feared that this had been caused by injudicious dieting. The patient, however, showed a marked pallor unlike a typhoid case, no spots were seen during the "relapse" and a second blood culture proved negative, and for the third time the serum failed to show agglutination with bacilli of the enteric group.

By December 30 the patient had steadily improved after seven days' normal temperature. He was not nearly so pale, was bright and cheerful, and with his thin skin and blue eyes had a look of the "sanguine" tuberculous type.

During this time the spleen had rapidly contracted until at this date it was no longer palpable.

On the evening of December 31 he again became listless and pale; the next day these features were very noticeable, and he again complained of pain in the toes and soles of the feet. Coincidently with this the temperature went up and the spleen again rapidly enlarged. The temperature soon came down only to rise again quickly on January 4. There was then a rapid increase in pallor and a still greater enlargement of the spleen. The abdomen was full and the liver was now made out to be slightly enlarged. The pulse was very soft but not dicrotic. There was diarrhœa and the stools were almost "typhoid" in character. Patient later complained of sore throat, bnt nothing was found and there were no enlarged glands in the neck. A blood examination at this time

showed 3,000 white cells and 3,600,000 red cells per cubic millimetre. A differential white count showed the following percentages: polymorphonuclears 80 per cent, lymphocytes 15 per cent, large mononuclears 5 per cent. No eosinophiles or nucleated red cells were seen and no parasites were found.

He was seen by several consultants and the diagnoses suggested were: A typhoid relapse, a splenic anæmia, and tuberculous peritonitis. The difficulties of the case at this time are shown by the possibilities also discussed, viz., Hodgkin's disease, Malta fever, kala-azar, congenital syphilis, and septicæmia. A blood culture made into broth was sterile and the agglutinations were again negative. The blood count was repeated a few days later, and again showed a leucopenia, and stool and urine cultures were again negative as regards bacilli of the typhoid group.

The temperature came down satisfactorily, and by the 20th the patient was better, although rather emaciated, with a weak pulse, and hæmic murmurs were heard at the base of the heart. The spleen also was smaller but still palpable and firm. Other than the spleen there were no glands to be felt anywhere. On January 21 he was given a mixture with arsenic and iron, and he had this for a little over a fortnight. On January 29 the temperature again began to go up, and the abdomen got markedly distended. This time there was free fluid in the flanks and lower part of the abdomen. The splenic dullness again increased and the pallor again became marked. There appeared to be a very indefinite mass felt on firm palpation above the umbilicus. Operation for tuberculous peritonitis was strongly advised by one of the consultant surgeons who saw him at this time and who thought that the above mass was matting of the omentum. Operation was, however, not performed, as the patient was getting rapidly very weak.

A blood count again showed marked leucopenia, the relative numbers of the white cells being normal except that only two eosinophiles were seen. The red corpuscles were down to 3,000,000 and the hæmoglobin down to thirty-five per cent, giving a colour index of about 0·5.

By February 8 the patient was very emaciated, with a gradually increasing jaundice of an obstructive kind, and there was some cutaneous mottling of a purpuric nature. Diagnoses which now suggested themselves were a splenic anæmia (especially Banti's disease), tuberculous peritonitis, or obscure malignant disease.

By February 13 the patient appeared to be dying. He was markedly jaundiced, very emaciated and weak, and the abdomen was distended. The general appearance was that of malignant disease in the abdomen with obstructive jaundice. The white-cell count had risen to 15,000, this probably being a rise associated with a dying condition, as death supervened thirty-six hours later, just twelve weeks from the apparent onset.

DIAGNOSIS AND DISCUSSION.

The most noticeable features (considering the ultimate diagnosis) and the ones which led observers astray were as follows:—

(1) The acute onset with symptoms and signs suggestive of peritonitis.

(2) The subsequent remarkable resemblance of the case to typhoid fever. This was evidenced by the lethargy and quiet delirium, the soft, compressible and rather slow pulse, the "typhoid" tongue, the tumid abdomen and the enlarged spleen, the leucopenia, the supposed "relapses," and the diarrhœa with suggestive stools.

(3) The general resemblance to an acute infective fever.

(4) The relapsing course in which there were not only relapses in pyrexia but also a curious periodicity of symptoms and signs. At the onset of and during each pyrexial period there was rapid wasting and increasing pallor and a regular marked increase in the size of the spleen. This rapid alternate enlargement and contraction of the spleen seemed a noticeable feature of the case.

(5) The signs suggesting portal obstruction.

(6) And lastly and very important) the entire absence of enlarged external glands.

The above facts are some excuse for the failure to make an accurate diagnosis during life.

Hodgkin's disease was discussed in connexion with the enlargement of the spleen, but the above facts led us off the track. The patient was of the usual age for the disease, and it is more common in males than females.

The onset was remarkable. Cases have been described in which enlarged external glands were present for a long time or in which the process appeared "latent," and which then became suddenly acute in association with a bursting out into activity of the pathological processes in the glands. But when the deep glands only are involved the onset is usually insidious and the acute onset in such a case as this one seems very exceptional. Jaundice and ascites are commonly associated with the abdominal type of Hodgkin's disease. In at least seventy per cent of the cases enlargement of the superficial glands is the first thing noticed, and in the great majority the cervical glands are most affected. The entire absence of enlarged superficial glands in a case showing the relapsing fever of Pel and Ebstein is therefore most unusual. It has been suggested that these pyrexial periods may be due to the presence of some secondary infection, and it should be noted, therefore, that besides the two blood cultures made into a bile salt medium, a blood culture was made into broth at the commencement of one of the periods and that all the cultures were found sterile.

As regards the blood cells, the leucopenia and the scarcity of eosinophiles are possibly unusual features. On the other hand, the very marked chlorotic anæmia is often seen, but the rapidity with which the

hæmoglobin (as estimated by Sahli's apparatus) reached as low as thirty-five per cent is unusual, and with other facts seems to be a sign of the very severe form taken by the disease in this case.

The resemblance to typhoid fever has already been mentioned. The onset, the absence of spots, the rapid general recovery as soon as the temperature was normal, and the completely negative findings in the laboratory were the chief points against this diagnosis in the early stages, while the later stages were quite unlike enteric fever.

In Banti's disease the probable source of the trouble is in the spleen itself, and the alterations in the size of the spleen suggested an affection in which the spleen displayed a leading part. Also the blood examination revealed a condition quite typical of this malady, namely, the secondary anæmia with a very low colour index and a leucopenia with no special change in the differential leucocyte count. Finally, the enlargement of the liver with the development of ascites and jaundice added decidedly to the resemblance of the case to this disease. In such a diagnosis, however, there were many obvious difficulties, namely, the onset, the rapid course and the general appearance, and the fever.

Tuberculous peritonitis was suggested by the tumid feel of the abdomen, there being present some generalized distension, and a soft elasticity on palpitation. Also, later there was ascites, and it was thought that rolled up omentum could be felt. An acute onset is not infrequent in this disease, and a high temperature is then common. The patient, too, appeared a tuberculous type.

Against this diagnosis were the general course, with relapses, the enlargement of the spleen and the absence of signs of tubercle elsewhere.

The leucopenia and the subsequent course were against the following earlier suggestions, viz., acute peritonitis, appendicitis, septico-pyæmia and lymphatic leucæmia.

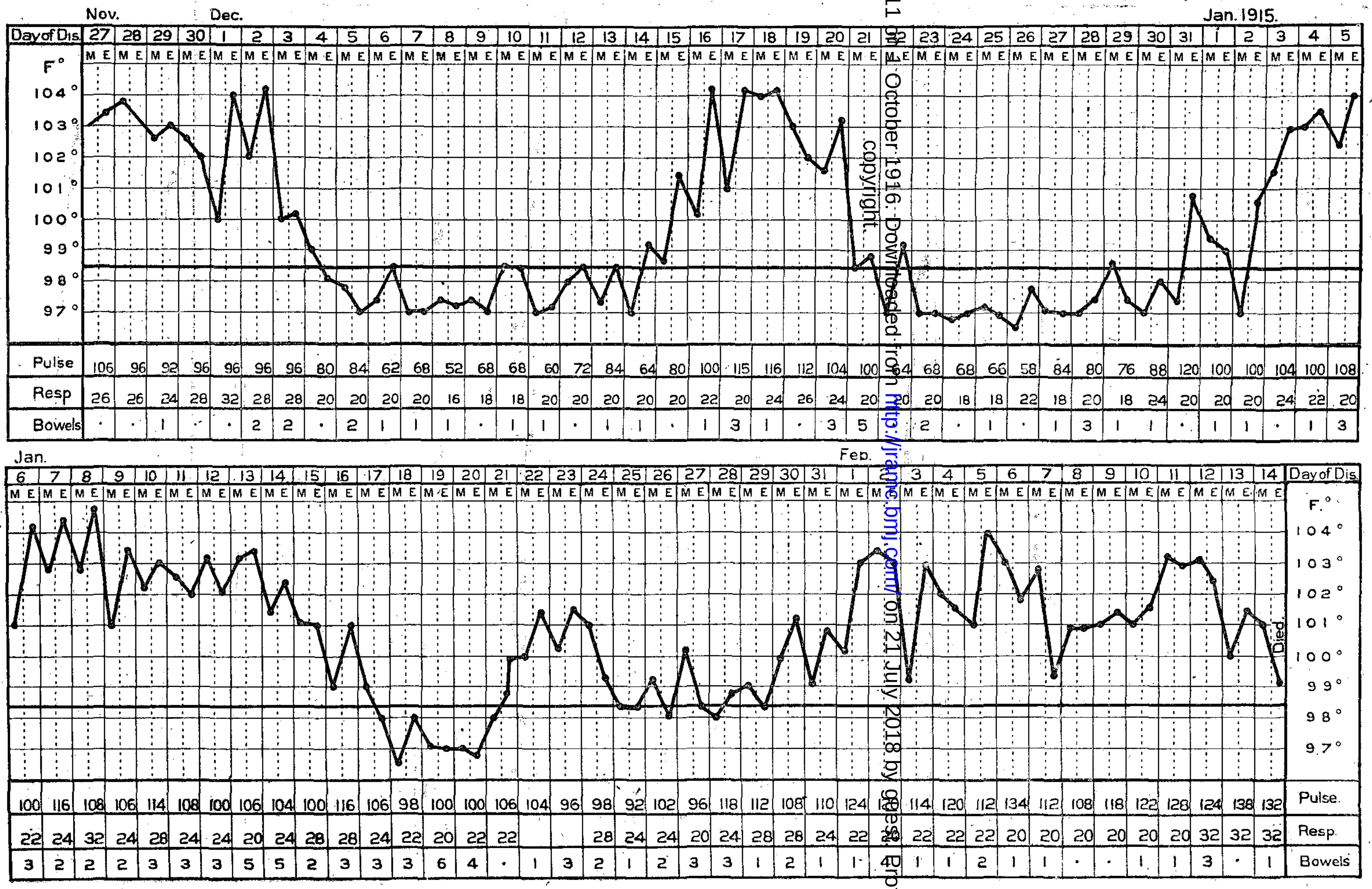
The predominant part apparently taken by the spleen, the resemblance to some infective fever, and the fact that the patient was a soldier suggested at one time, in the search for a diagnosis, such diseases as Malta fever, kala-azar, and relapsing fever, affections not usually thought of in dealing with Hodgkin's disease. Against these possibilities were the locality and previous history, besides the clinical and laboratory findings.

Post-mortem.

The body was very emaciated and deeply jaundiced.

Abdomen.—A large amount of free clear yellowish fluid was found. The omentum was normal except for a very diminished quantity of fat, and it showed no matting together. The rest of the peritoneum appeared normal, no tubercule or carcinomatosis being present.

The intestines and mesenteric glands appeared normal. The spleen was at least three times the normal size, of a dark slaty-blue colour and



decidedly firm and hard and not friable. On its surface were seen scattered yellowish-white spots about the size of a pin's head and slightly raised. There was no perisplenitis. On cutting the spleen open similar areas, in some cases larger, were seen scattered all about, and being yellow stained seemed like points of pus. They were found, however, to be fairly firm like little pieces of firm yellow fat. The structure in the hilum of the spleen appeared normal. The liver was a little enlarged but otherwise appeared normal. A gland in the portal fissure was enlarged and cut firm and hard, but it was quite discrete. It seemed to be pressing on the hepatic duct before this joined the cystic duct and the hepatic duct appeared dilated. The gall bladder was full, but the dilatation was not definitely more than might normally occur. It contained viscid mahogany-coloured fluid. The bile duct seemed a little dilated and appeared to have been pressed on by some enlarged glands behind the pancreas. It could, however, be easily separated from them and these glands were quite discrete. The kidneys were apparently normal and did not show any nodules, and both suprarenal capsules were normal to the naked eye. On attempting to remove the left kidney some very interesting abnormalities were found. On tracking down the left ureter it was found to enter a large irregularly lobulated hard mass—discovered to be retroperitoneal glands—extending from the level of the left renal artery down to the bifurcation of the aorta. This mass had prolongations downwards along the common iliac and iliac arteries of the left side and for a short distance along the common iliac on the right. The aorta and left ureter were enclosed in this mass, but did not appear to have been pressed on unduly. On dissection the glands were found to be regularly oval or rounded, smooth and discrete and apparently not obstructing ureter, arteries, or veins, or encroaching into surrounding structures. They were creamy-white in colour and cut firm, and some showed on the cut surface bulging areas between restraining connective tissue.

Nearly all showed a mottled appearance due to hæmorrhagic areas near the capsule. There was no growth at all through or outside the capsule and the glands appeared typically lymphadenomatous. The testes were normal. Some enlarged glands, one about the size of a walnut, were also found behind and above the neck of the pancreas, and were like those above described. The lungs, heart, and pleuræ showed no obvious abnormalities. The tracheal and bifurcation glands were decidedly enlarged, hard and discrete, cut firm and showed mottling, with areas of congestion, and were of a similar nature to those already described. They did not appear to have pressed on surrounding structures. Some old calcareous and caseous glands with sooty deposits were found adherent to bronchi at the root of the right lung and appeared to be old tuberculous glands. Some enlarged glands were found just behind and below the inner end of the clavicle on each side, one on the left being the size of a walnut. They also appeared lymphadenomatous like the

others. Otherwise the cervical glands were not enlarged. Portions of the retroperitoneal, portal, thoracic and subclavicular glands and spleen were kept for histological examination. They were found to show the typical appearance of Hodgkin's disease. These glands showed proliferation of the endothelial cells and of the reticular tissue, in the meshes of which numbers of moderately large lymphoid cells and the characteristic giant cells or "lymphadenoma cells" were evident. These were nearly all of the mononuclear type, the big nuclei showing pale blue indefinite staining with deeply stained dots scattered about (nucleoli and chromatin granules). No giant cells with the "horse-shoe" arrangement of nuclei were seen. The proliferation of the connective tissue did not seem far advanced in any of the glands examined, and this fact, in conjunction with the presence of hæmorrhagic areas, suggested (apart from the clinical evidence) that the disease was rapid and acute in this case, and not as is usual, slow with progressive and finally marked increase in the connective tissue.

One can say that the mass in the abdomen did not appear old, and that the case was probably not one of the "latent" variety with a subsequent bursting out into activity.

The indefinite mass felt during life and supposed at one time to be matted omentum was probably this mass of retroperitoneal glands, and this mass by pressure on nerves possibly accounted for the pains down the limbs and in the feet and toes, for which the patient went sick and which he again had while in hospital. Such symptoms do not appear uncommon in cases of the abdominal variety. That a case of Hodgkin's disease should first come under observation for this complaint and be diagnosed "frost bite" must certainly be uncommon. The associated circumstances and the prevalence of "trench foot" amongst the soldiers at the time accounted for his being sent down to hospital with this diagnosis.

It was interesting to find that the supposition of an enlarged gland in the portal fissure was confirmed, but more interesting to find that this enlargement was due to lymphadenoma. Almost all the symptoms and signs were now explained except the acute onset, the toxic symptoms, and the fever.

The whole aspect of the case seems to support the view that Hodgkin's disease is due to some infective organism, which in this case was particularly virulent, and which had its chief habitat in the retroperitoneal glands and spleen.

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