TWO CASES OF FOLLICULAR LYMPHOBLASTOMA

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I

IT was after the leukemic diseases had been recognised by Virchow that Cohnheim first described the aleukemias. Pathologically the latter closely resembled the leukemias except for the large numbers of leucocytes in the peripheral circulation. Before long, yet other diseases were differentiated from the aleukemic leukemias. Clinically, these—the pseudo-leukemias—resemble the leukemias in showing enlarged lymph glands and an enlarged spleen, but from a pathological point of view they had to be classified differently, as for example lymphogranuloma malignum (Hodgkin) or lymphosarcoma (Kundrat).

The disease of this group which has been most recently differentiated is lymphoblastoma folliculare, first described by Brill, Baehr and Rosenthal [1] in 1925. They had observed three patients, two of whom showed a generalised enlargement of the lymph glands and all three a greatly enlarged spleen, while the blood-picture remained in every case unchanged. One of the patients had also an enlarged liver, whereas another was dyspnœic and later developed a hydrothorax. It was, however, in the latter that the application of X-rays was tried for the first time, with very favourable results.

Histologically, the enlargement of the spleen and lymph glands was found to be due to the presence of numerous very large follicles, visible even to the naked eye, and consisted principally of enormous germinal centres surrounded by a small margin of lymphocytes.

Shortly afterwards, Baker [2] described a further case, which also showed enlarged peripheral glands, enlarged spleen and liver, while the blood-picture again appeared normal. Biopsy demonstrated hyperplasia and hypertrophy of the lymphoid follicles, due to enormously large germinal centres. Although, according to a personal communication, this patient later developed a typical chronic lymphatic leukemia, yet

autopsy disclosed the characteristic microscopical features of lymphoblastoma folliculare, which in the region of the pancreas had even penetrated the capsule of that organ and had infiltrated the surrounding tissues. So far, this finding is uncommon and cannot be regarded as exemplifying the typical course of the disease.

According to Symmers [3] enlarged lymph glands around the bile ducts may result in jaundice. Other signs which have been described include hydrothorax, ascites, hæmosiderosis of the peritoneum, extension of the red bone-marrow in all the long bones, enlarged para-aortal, mesenterial, peripancreatic and tracheo-bronchial lymph glands as well as in the gastro-splenic ligament, and typical areas of hyperplastic formation in liver and bone-marrow (Terplan),[4] dry pleurisy and anæmia (Ferrata and Introzzi),[5] dyspnœa, attacks of diarrhœa, anæmia, pathological lymphocytes in the peripheral circulation, swollen lymph glands around the external and internal iliac vessels, in the mesentery and lymphatic nodules under the pleuræ, siderosis of the liver with slight periportal infiltration while the remnant of the thymic gland was replaced by several large glands (Ross, case I),[6] secondary anæmia with enlarged glands in the gastro-splenic ligament (Decker and Little),[7] dyspnœa, chylothorax and chyloperitoneum (Scott and Robb-Smith),[8] and secondary anæmia and chylothorax (Ewing, Montclair and Fein).[9] It may also be added that the case described by Scott and Robb-Smith responded very well at first to neoarsphenamine. Here also, at autopsy, typical changes were again observed in the peripheral and retroperitoneal lymph glands, the spleen, liver, and bone-marrow.

The observations of Kellert [10] and Fieschi [11] do not give any material contribution to our knowledge of follicular lymphoblastoma.

Baehr's [12] account, supported by a number of unpublished cases, enables us to elucidate the characteristic features of the disease. His cases show, for example, that the histological changes described above can occur wherever lymphatic tissue is present ; for example, in the adnexa, mammæ, subcutaneous tissues, lacrimal glands, and orbits. In the last two sites a unilateral exophthalmos may result ; in the mediastinum the disease often results in dyspnœa and chylothorax ; in the deep abdominal lymph glands it may cause chylous ascites, jaundice, or pyloric obstruction. In one case a pathological fracture of

the femur occurred which united after X-ray treatment. This form of therapy is at present the only known remedy for the disease.[13] The usual dose is said to be 170-200 r ($\frac{1}{5}$-$\frac{1}{3}$ erythema dose), at intervals of three to four days, although when treating a case with exophthalmos it is advisable to commence with a preliminary dose of 125 r. Of all the cases so far identified only two did not respond well to X-ray treatment, and these two died after a short time, in six months and two years respectively.

The course of the disease is usually intermittent. After X-ray treatment the local tumours decrease in size and symptoms of compression, if present, tend to disappear. The patients then enjoy comparatively good health except for a tendency to become rapidly exhausted on physical exertion. This remission may last for months or years, but after this interval the symptoms recur, with perhaps new complications. The tumours will again respond well to irradiation. This sequence of events may be repeated several times, until eventually, in a final relapse, the disease suddenly becomes malignant, and the new growth no longer respects anatomical boundaries. Histologically, it shows an aggregation and fusion of the germinal centres, which consist of polymorphic lymphoblasts with large, irregular nuclei and many mitoses. The capsule and surrounding tissues of both lymph glands and spleen are infiltrated. Occasionally small groups of lymphocytes and the remains of the layer which formerly encircled the giant germinal centres are to be seen. At this stage, in view of these appearances, the only possible diagnosis is that of lymphosarcoma.

As regards the prognosis, in 1932 eight patients had died, and in these the average duration of the disease was five years and nine months. Those patients who were then still alive had been under observation for periods of one to fourteen years, with an average of five years, but the very chronic course of some made it probable that this figure would be greatly exceeded in the future. As opposed to this, the average duration of lymphosarcoma is not more than a year to a year and a half (Baehr, Naegeli, Schittenhelm). Finally, it is important to note that radium is sometimes effective when the neoplastic growth will no longer respond to X-rays.

Sarcomatous degeneration of follicular lymphoblastoma seems to have been recorded by Foix and Roemmele[14] thirty

years ago. Recently Symmers [15] has again drawn attention to the disease. He gives an account of twenty-five cases. Except for leukopenia in one patient and a hyperplastic focus in the clavicle of another, he records no new signs. It may be mentioned, however, that one of his patients showed a marked pigmentation of the skin and a second an exfoliative dermatitis.

Yet Symmers points to two important facts. Apart from the ordinary cases of follicular lymphoblastoma and those which showed sarcomatous degeneration he gives definite proof of the association of follicular lymphoblastoma with Hodgkin's disease in seven cases and adds three more cases to the one described by Baker, which turned finally into lymphatic leukemia.

II

Of the two patients observed in the Netherlands the first was a man of 41 years. He first was seen on 15.10.1932 by Dr Enneking. In the out-patient department dullness on percussion was detected at the base of both lungs and enlarged glands were found under the jaw, in both axillæ and both groins. There was nothing abnormal in the urine. The Wassermann and the Sachs-Georgi reactions were both negative.

On 18.10.32 the patient was admitted to hospital. He complained of slight abdominal pain over a period of six months. Three months previously, glands on the right side of the neck had become enlarged, as well as those in the right axilla and in both groins ; they were not painful. The swelling beneath the right mandible had since decreased in size. During the few months previous to admission he had felt very tired, particularly in the last fortnight. Since then his abdomen had become enlarged and tense. Shortly after meals he suffered from a feeling of distension and sometimes even of pain, but he had never vomited nor had heartburn or flatulence. Some important changes were observed on physical examination. There was dullness to percussion at the bases of both lungs, especially on the right where also the respiratory sounds were weaker ; ascites was present and was so extensive that palpation of the abdominal organs was virtually impossible. The liver and spleen were not enlarged to percussion. There were no distended veins in the abdominal wall. Below the right mandible, in the right axilla, and in both groins there were large lymph glands the size of a hazel-nut, not tender, not soft

on palpation and not adherent to the skin. The von Pirquet reaction was strongly positive both to the human and the bovine types. Apart from a secondary anæmia the blood-picture remained normal throughout, as did the temperature. The platelet count was normal and the sedimentation rate of the erythrocytes was 22-49 and 39-66 after one and two hours respectively. Digestion of food was satisfactory.

On 25.10.32 the patient was X-rayed. There was seen to be a fairly extensive exudate on the right side and a smaller one on the left. The heart shadow was not enlarged.

The abdomen gradually increased in size, and on 18.11.32 the right pleural cavity was explored, and 30 c.c. of a reddish, opalescent fluid was withdrawn. After the erythrocytes had been allowed to settle the supernatant fluid appeared white and opalescent. The sediment consisted principally of red cells, some leucocytes, and a few lymphocytes. After shaking with ether the fluid became light yellow and transparent. Fat was proved to be present in the ether. Broth and glucose-agar cultures remained sterile, as also did a culture on Hohn's medium.

On 21.11.32 and 21.12.32 pleural punctures were repeated on both sides of the chest. In each case the fluid was of the same appearance. The blood cholesterol was 144 mg. per cent. Although injection of salyrgan resulted in a good diuresis it did not reduce the abdominal distension, so on 28.12.32 the abdomen was tapped and three litres of a chylous fluid were withdrawn, resembling that previously removed from the pleural cavities. Its specific gravity was 1022, Esbach 24 per mille, urea-content 800 mg. per cent., sodium chloride 5·5 per mille, and there was some fat present. The sediment resembled that of the pleural exudate.

The sputum was tested twice for tubercle bacilli, but was negative on both occasions. On 4.2.33 a small median supra-pubic incision was made and 12 litres of a chylous fluid were withdrawn. The peritoneum had a normal glistening appearance. The intestinal lymphatics were dilated to the size of an ordinary strand of wool and were distended with chyle. No tumour could be felt from the site of incision. After the puncture, however, it was possible to feel on the left side of the abdomen a tumour which was firm, irregular and not tender. After two days, the ascites began to reappear, and on 11.2.33 a left pleural puncture was carried out. The exudate had the

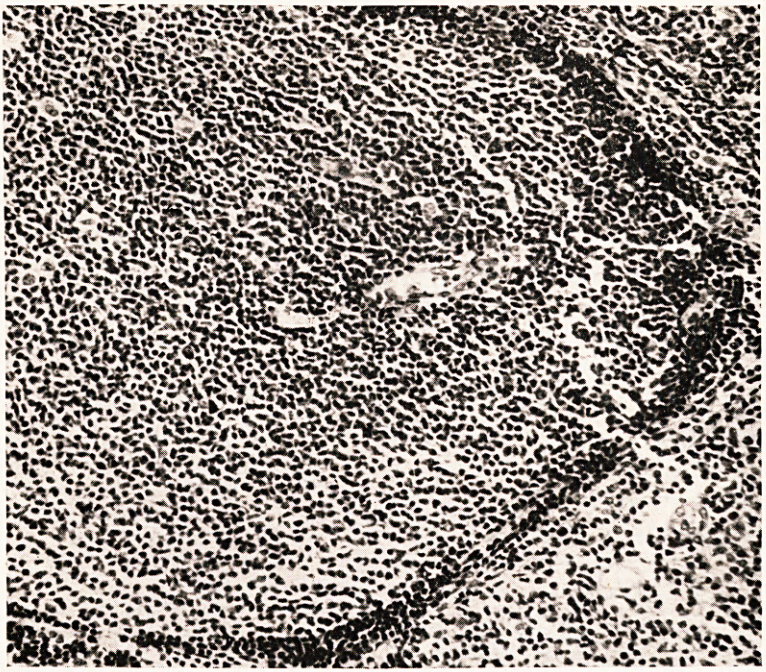

FIG. 1.

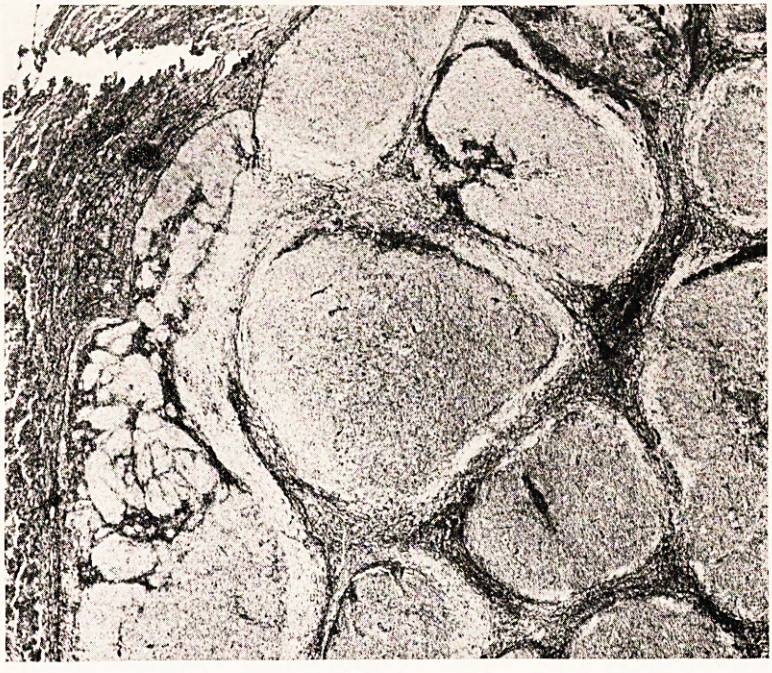

FIG. 2.

same composition as that withdrawn from the abdomen. Gastric analysis was negative. Radiological examination suggested elevation of the stomach as if caused by a tumour lying behind it. No blood could be detected in the fæces. On 23.2.33 a further paracentesis was necessary. Although 11 litres were withdrawn, the ascites had reappeared within a fortnight, accompanied this time by œdema of the legs. In April, after yet another puncture (13 litres), the sharp lower border of the liver could be felt below the costal margin. A tumour, as big as a fist, irregular in shape, somewhat tender and with ill-defined edges, could be palpated above the umbilicus. The patient was discharged from hospital, but had to be punctured regularly by his family doctor. In June 1933 he died quite suddenly at home. A post-mortem was not carried out.

Biopsy of a cervical lymph gland showed the typical features of follicular blastoma. The capsule surrounding the gland was intact, but a lamellation of its fibres by lymphatic tissue was clearly evident. Moreover, lymphocytes, and at one place even a germinal centre, were actually present outside the capsule. There was little evidence of normal lymphatic tissue, for the entire gland consisted of large germinal centres, 250-1500 μ in size, with an average diameter of 600 μ. Normally germinal centres are between 100 and 600 μ in size. In two other cases of follicular blastoma, slides of which Fein and J. Ewing kindly sent to me, the diameters of the centres were 125-2000 μ in one and 100-1500 μ in the other, the average diameters being 750 μ and 500 μ respectively. Connective tissue and ordinary lymphocytes formed a thin ring around the partly fused, giant germinal centres (Fig. 1). The latter were composed of cells with somewhat polygonal and polymorphic nuclei, staining comparatively dark and surrounded by a thin rim of cytoplasm, generally basophilic. There were also large, pale eosinophilic cells whose nuclei were poor in chromatin. Here and there, these formed giant-cells containing two or three nuclei. Mitoses were infrequent. There were no swollen reticular cells and all the cells were closely aggregated. In the germinal centres a central artery could usually be seen. In slides stained with Mallory or Hortega-Volterra it was noticed that the thick reticular fibres are apparently pushed aside by the growing centres and thus come to surround them in a concentric fashion (Fig. 2), while within the germinal centres

some rests of argentophil fibres were seen; these were completely absent at some places, but at others they were more numerous than usual. The histological picture therefore is quite consistent with that of follicular blastoma.

The second patient, a married woman aged 48, noticed a swelling in her left axilla about the end of 1935. A blood film was taken, but was normal. Then her neck swelled, and a few months later she noticed enlarged glands in both groins. The family doctor prescribed arsenic, which resulted in a decrease in the size of the glands, but they did not disappear. As soon as the administration of arsenic was stopped, the glands again increased in size. They were not painful. Over a few months the patient had lost 10 kg. She complained only of some slight flatulence and borborrhygmi. The family history showed that a brother had died at the age of 2½ years from some "glandular trouble."

On 2.1.37 the patient was examined again (Dr Groen). She had no pyrexia. Her tonsils were of normal size. There were a number of enlarged glands along both sternomastoid muscles, in both supraclavicular fossæ, and in both axillæ and both groins. They varied in size from a hazel-nut to a chestnut, and were soft and elastic, and slightly adherent to each other, but not to the underlying tissues. The colour of the overlying skin was unchanged and its temperature not increased. The swellings were not tender to palpation. A slight dullness to percussion was present above the manubrium sterni. Nothing was found in the lungs. The spleen, which was elastic and had a blunt margin, could be felt two to three fingers' breadth below the costal margin. The liver was normal in size. The diazo-reaction of the urine was negative, and the blood-picture showed nothing abnormal. The sedimentation rate of the erythrocytes was 3 mm. after one hour. Radiological examination of the thorax demonstrated hilus glands which were just within normal limits of size.

In September the patient complained of a tendency to diarrhœa. The glands had enlarged still further and the parotid glands had swollen too. The circumference of her abdomen had increased. Arsenic (optarson injections) now had no effect. There was an exudate in the left pleural cavity, and the spleen and liver were easily palpable below the costal margin. A biopsy was carried out on glands removed from the

left axilla. She then had X-ray treatment (±200 r), but in spite of this she developed ascites, and large masses appeared in front of the vertebral column. These were irregular in shape and tuberculated. Blood films showed pathological lymphocytes, occasionally as high as 11 per cent., but, apart from this, only a secondary anæmia, which was improved by administration of iron and two series of liver injections. The patient also became a little dyspnœic. However, by the end of one month's irradiation her condition had begun to improve. The ascites and the pleural effusion had disappeared, but the spleen and the lymph glands were still enlarged. No tubercle bacilli could be found in her sputum.

In November 1937 she developed a severe diarrhœa. The benzidine test of the fæces was negative, and no leucocytes were seen. On radiological examination the barium meal was observed to pass rapidly through the gastro-intestinal tract. The patient received pepsin-hydrochloric acid while the X-ray treatment was being continued. Her symptoms then gradually disappeared and the lymph glands and parotid glands also decreased in size.

In December the administration of pepsin-hydrochloric acid was suspended for a while, but as the diarrhœa reappeared it was given again. Gradually the lymph glands, liver, and spleen became smaller, the patient gained weight, and her adiposity then prevented any further palpation of the prevertebral masses. Irradiation was then stopped.

In May 1938 the patient had two attacks of pain in the chest with difficulty in breathing, and pain on swallowing. These attacks were accompanied by frequent palpitation and a completely irregular pulse. An electrocardiogram demonstrated the presence of auricular flutter, with negative T-waves in all leads. X-rays showed again free fluid in the left pleural cavity, which had pushed the heart to the right. The cardiac shadow was large and was suggestive of pericarditis. Four days later the palpitation had disappeared and the pulse had returned to normal.

In September 1938 severe diarrhœa began to recur. The glands increased again, and the liver and spleen were also enlarged. X-ray treatment was started at once, but had no obvious effect on the abdominal masses. In October a sharp systolic souffle was noticed at the base of the heart and this persisted. Her general condition became gradually worse.

Although her temperature remained normal, she became emaciated. The ascites reappeared and œdema developed in the legs. The glands did not respond to treatment. Towards the end, free fluid again formed in both pleural cavities and on 3rd January 1939 the patient died in a state of cachexia. Permission for autopsy was refused.

On reviewing the symptoms we cannot readily find any satisfactory explanation for one of them—the diarrhœa. It is obvious that it was not a simple infection. Our attention is drawn to the rapid passage of food through the stomach and intestine as shown radiologically. Therefore it is possible that the gastric secretion was ineffective, and when pepsin-hydrochloric acid was administered it did in fact suppress the diarrhœa. Since for special reasons a gastric analysis could not be carried out, definite confirmation could not be obtained. It may be that " specific " changes had occurred in the stomach wall, or, in other words, that in this case, just as with leukemic or lymphosarcomatous infiltrations, a hypertrophy and hyperplasia of the lymph follicles of the gastric mucosa might have been a factor.

All the other signs are characteristic of the clinical features of follicular blastoma, symmetrical enlargement of the peripheral lymph glands, bilateral swelling of the parotid glands, enlargement of the deep abdominal glands, of the spleen and of the liver. During her illness the patient developed ascites and free fluid in the left pleural cavity, both of which disappeared temporarily on irradiation of the mediastinum and of the deep abdominal lymph glands. Although to a lesser extent and more slowly than usual, the enlarged organs did respond to X-ray treatment at the onset. Subsequently, however, the irradiation had very little effect. Pyrexia was never present. The blood-picture was almost normal, except for a slight anæmia and the presence of pathological lymphocytes.

Thus the course of the disease was typical. Although the diagnosis was not confirmed by post-mortem, it could definitely be established as a result of the biopsy. The lymph gland from the left axilla was received fixed in formol. It was an oval mass weighing 32 gm. On its cut surface the tissue had a somewhat glassy appearance, which suggested malignancy.

On slight magnification the slides (stained by hæmatoxylin-eosin, Mallory) show a large number of pale, round or oval areas, which lie close to one another and are distributed over

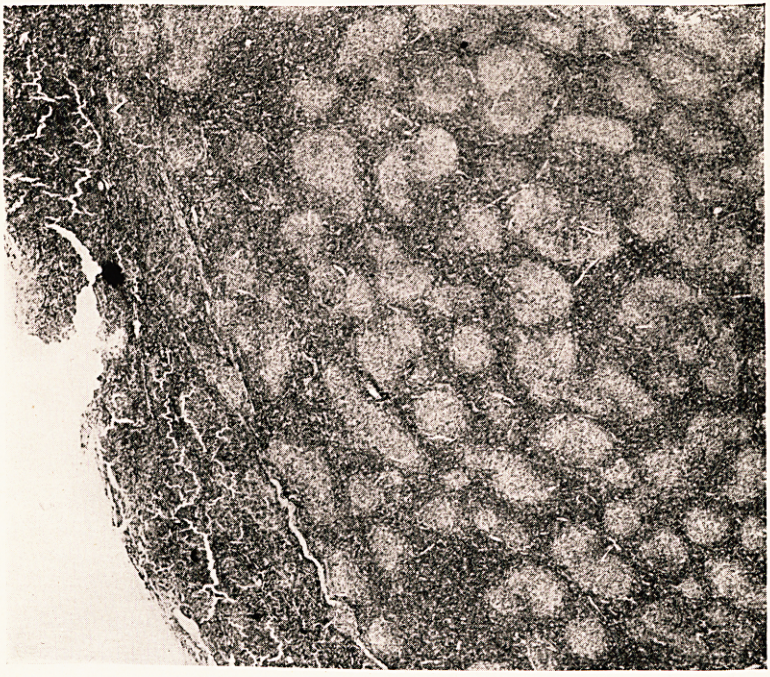

FIG. 3.

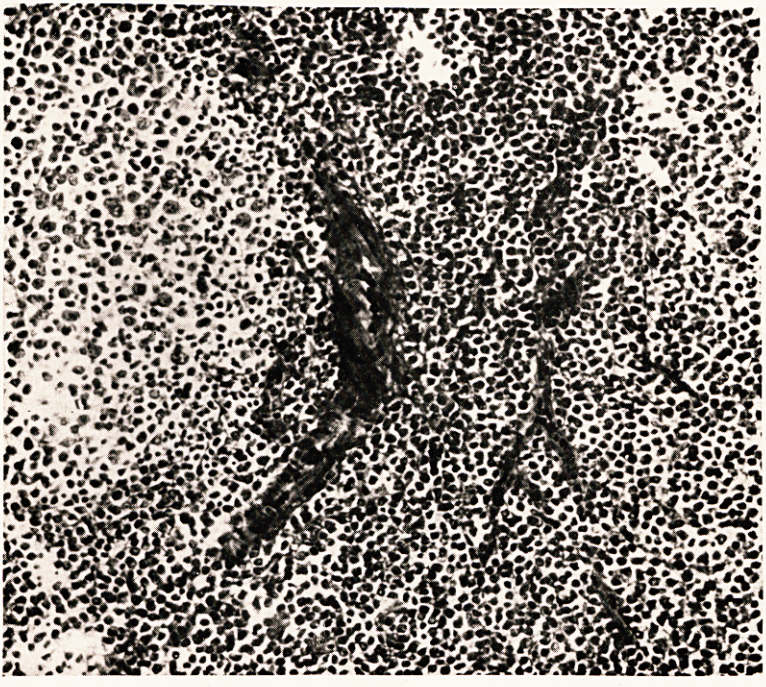

FIG. 4.

the whole gland. Under the low-power these can be identified at once as germinal centres (Fig. 3). There are lacking only the dark peripheral layer of lymphocytes, usually encountered in germinal centres, and the pale, unstained reticular cells among the darker lymphoblasts. The boundary between the germinal centres and the surrounding lymphatic tissue is quite sharp. The centres have not penetrated through the capsule of the lymph gland, but, especially in the Mallory slides, it appears that the connective tissue of the capsule is lamellated by newly formed germinal centres and lymphatic tissue. The centres vary in size between 100 and 1150 μ, with an average diameter of about 400 μ. With high-power magnification one is struck by the great variation of the cells. Some are very large, vesicular, pale cells with a hazy cytoplasm, eosinophil in some cases, and basophil in others, and have nuclei with few chromatin granules and a distinct nuclear membrane ; others are extremely polymorphic, usually round, but at times somewhat polygonal, staining either pale or dark although never as dark as the lymphocytes, while some are larger and others smaller than lymphocytes. Their nuclei which are surrounded by a small rim of cytoplasm are usually spherical, but may be kidney-shaped or irregular ; they stain comparatively dark. If we adopt the terminology used in describing erythrocytes we could then speak of a strong polychromasia, poikilocytosis and anisocytosis. Isolated giant-cells are also found, seldom with more than two or three nuclei, which may have been derived from any of the cells, but most likely from the reticular cells. Few stainable bodies (" tingibele Körperchen ") are, however, to be seen, and few pyknotic cells, while there is little evidence of phagocytosis. The arteries in the germinal centres are small and can only be identified with difficulty. At some places the centres are so large that they have fused, and in Mallory sections these aggregations are at once identifiable because the blue-stained reticular fibres encircle the centres (Fig. 4) and produce figures of a trefoil shape. Within the centres we find only a few thin blue fibres. The same appearance is seen in sections stained by Perdrau's silver method in which fibres are stained black ; here again the reticulum encircles the centres. Within the germinal centres more rests of argentophile fibres are found than is the case in normal centres.

The denser basophilia of the cells of the germinal centres and the delayed response to X-ray treatment gave rise to the

supposition that here we were confronted with a more active form of follicular blastoma. The total duration of the illness was, indeed, not much more than three years.

III

Finally, some mention must be made of the characteristic histological feature—the hyperplasia and hypertrophy of the germinal centres. The question arises as to whether the normal germinal centres as first described by Flemming are different from those met with in the follicular lymphoblastoma. We believe they are. In the first place, the investment of peripheral lymphocytes in follicular lymphoblastoma is not very obvious, and is sometimes even totally absent. In the slides stained with hæmatoxylin-eosin the lymphoblasts appear to be more basophilic, darker stained, and give the impression also that the " physiological " polymorphism of the cells of the centres is greater than normal. Again the very pale, swollen reticular cells of ordinary centres are not found at all in follicular lymphoblastoma.

In recent years many investigators have examined the function of the so-called germinal centres.[16] Various lines of evidence, which cannot be discussed here, have led the majority of them to regard the " germinal " centres not as sites of production of lymphocytes, but as " reaction " centres (according to the conception first put forward by Hellmann), in which the lymphatic tissue reacts to external irritants. We are still ignorant of the source of the lymphocytes, although it is quite probable that they are derived from the reticular cells or possibly even from cells still more undifferentiated.

Are we then to regard the follicular lymphoblastoma as a disease in which the lymphatic tissue reacts to noxious irritants by producing " germinal " centres ? Since at least the condition is not one of simple inflammation, we do not think that this is the case, and we believe that, as the germinal centres in follicular lymphoblastoma lack the properties, which always characterise the normal centres, they are related much more closely to the tumours ; but, on the other hand, we cannot classify them as genuine tumours. Their limited tendency towards growth, the absence of all signs of inflammation, the rôle of the reticular cells, the occurrence of pathological lymphocytes in the peripheral circulation, the association with leukemia in four cases and with Hodgkin's disease in seven,

the more or less simultaneous appearance of multiple foci in the body, all point, in our opinion, to the probability that we are dealing here with a disease of the reticulo-endothelial system, and that follicular lymphoblastoma should be grouped as one of the reticulo-endothelioses. Since, however, in the later stages it has often been reported to change into lymphosarcoma, it can be regarded also as a link between the reticulo-endothelioses and the tumours.

Summary

Following a brief review of the literature a detailed account is given of the clinical and microscopical features of two cases of follicular lymphoblastoma observed in the Netherlands.

The differences between ordinary germinal centres and those met with in this disease are emphasised. Nosologically the view is put forward that it represents one of the reticulo-endothelioses, and in view of the fact that in the later stages it often changes into lymphosarcoma, it links up the reticulo-endothelioses with the tumours.

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