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CLASSIFICATION OF NON-INFECTIVE ENLARGEMENT OF LYMPH NODES *

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In dealing with the "non-infective" enlargement of the lymph nodes it is necessary that uniformity of description and terminology should be arrived at by all pathologists on whom the onus of biopsy diagnosis rests. The reaction of various conditions to therapeutic measures cannot be pronounced with certainty until we are sure that similar conditions are being compared, nor can any prognosis be made until a considerable number of adequately diagnosed and classified conditions have been treated and the results assessed. In this paper a classification is put forward based on the cytology of the lymph gland, and the clinical conditions represented by the various groups are summarized so far as they are at present established.

Structure of Lymph Glands

According to the views of Maximow (1927), in the lymphatic glands and lymphadenoid tissue generally, and in the bone marrow, the same fundamental structure is present. This consists of a framework of argyrophil reticulin fibrils, closely associated with which is an undifferentiated syncytium. In the meshes are located the immature and maturing free cells of the blood. The undifferentiated syncytium is mesenchymal in its nature and is capable of differentiating along various lines (Table I).

TABLE I

The reticular syncytium does not perform any metabolic function, is not phagocytic in character, and does not store vital dyes. Under stimulation, reticulum cells are formed from the reticular syncytium. These are large oval or stellate cells, with an oval vesicular nucleus; a well-defined nucleolus is present. They still possess unrestricted potentialities for differentiation, and may be phagocytic and store vital dyes. Similar cells are found in connective tissues near the blood vessels.

The venous sinuses of the splenic pulp and bone marrow, and the lymphatic sinuses in the lymph glands,

are lined by specially differentiated reticulum cells (sinus reticulum, or littoral cells). The stellate cells of von Kupffer in the liver are of this nature. Littoral cells are phagocytic in character and, under stimulation, differentiate to the actively phagocytic free histiocytes.

In the bone marrow the undifferentiated tissue gives rise at first to a primitive free cell, which was called the haemocytoblast by Ferrata. This cell may differentiate along various lines—to the monocyte, the myelocyte, the erythroblast, or the megakaryocyte. Maximow regards the haemocytoblast as similar in every way to the large lymphocyte of the lymphatic tissue—that is, the lymphoblast. This large lymphocyte (lymphoblast) arises normally from the reticulum cells in the lymphatic tissue. It does not enter the blood. It gives rise to the medium-sized lymphocyte, and that in turn, by mitosis, gives rise to the small lymphocyte. The medium-sized lymphocyte of the lymphatic tissue is the large lymphocyte of the peripheral blood stream. The plasma cell arises by alteration of the lymphocyte.

Another line of differentiation which has its origin through the reticulum cell results in the formation of the fibrocyte, and collagen fibres are thus produced. Normally reticulin fibres are produced by the reticular syncytium and its derivatives. Under pathological conditions a somewhat specialized reticulin-forming cell, the dictyocyte, becomes recognizable. It is a polygonal cell with cytoplasmic projections, which may be in contact with projections from adjacent cells. It is specially important in the discussion of the neoplasms of the lymph nodes.

The point which I wish to emphasize is this: There is, in the haemopoietic tissue and elsewhere, a common ancestral or stem-cell type which, given appropriate stimulus, may differentiate along any of the lines of development shown in the table. The appropriate stimulus, in a normal human adult, for the development of the myelocyte is present in the bone marrow; the appropriate stimulus for the development of the small lymphocyte is present in the lymphadenoid tissue. Under abnormal conditions there may be action of such stimulus in abnormal situations; or an abnormal stimulus may cause overproduction of any of the cell types, or abnormal combinations of cell types. This means that the tissue changes, in myeloid and lymphatic leukaemia, for instance, are not due to a fundamental difference in two tissue elements, but to the action of a different stimulus on a common

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stem-cell. In the normal adult tissue of a human the development of this stem-cell into free blood cells rarely happens, except, possibly, in lymphatic tissue. This development does, however, become apparent in certain diseases.

Before going on to the classification of the diseases of the lymph glands, it remains to summarize the occurrence of these tissue elements in the lymph nodes. The reticulin fibrils in the medulla of the lymph node form a mesh-work which supports the undifferentiated syncytium. The derivatives of the syncytium—reticulum cells, lymphocytes of all sizes, and histiocytes—lie in the meshes. At the margin of sinuses there is some condensation of these reticulin fibrils, and some cross the lumen of the sinus and are continuous with the capsule. These fibres serve as a support for the littoral cells. The follicles contain few reticulin fibrils, if any, the reticular syncytium acting as a supporting stroma for the large, medium, and small lymphocytes.

Classification

The non-infective enlargements of the lymph nodes are essentially hyperplasias, or neoplasms, of the reticulum or its derivative cells. The term "reticulosis" should be used for those diseases in which there is systematized hyperplasia of differentiated or undifferentiated mesenchymal cells, leading to generalized enlargement of the lymph nodes, the spleen, and the liver, with alteration of the bone marrow. This idea of cytological classification is an old one. MacCallum in his textbook gives it as his opinion that "if we knew accurately all the cellular types existent in the bone marrow and in the lymphoid tissue, and assumed that each is capable of undergoing independent hyperplasia, we should be able to tabulate all the possible diseases arising in this way." The recently acquired knowledge of the existence of the undifferentiated mesenchymal cell and its capacity for differentiation enables us to go a long way further in classification.

We may now assume that the unknown factor stimulating hyperplasia of any cell elements does not necessarily inhibit differentiation of that cell, although it may be regarded as determining the line or lines of differentiation which the hyperplastic cell may follow. The classification now proposed assumes that any one of the unknown aetiological factors will act on medulla or follicle or sinus, since such special site of action has been established for the known aetiological agents producing changes in the lymphatic glands (syphilis, etc.).

TABLE II.—*Non-infective Enlargements of Lymph Nodes*

- (1) Reticulosis—hyperplasia of differentiated or undifferentiated mesenchyma
 - A: Medullary reticulosis:
 - (i) Primary:
 - (a) Undifferentiated. (b) Haemic (leukaemias). (c) Fibromyeloid (lymphadenoma). (d) Histiocytic.
 - (ii) Metabolic; generalized lipoidosis:
 - (a) Gaucher's disease. (b) Niemann-Pick disease. (c) Primary xanthomatosis.
 - B: Follicular reticulosis:
 - (a) Lymphoid. (b) Fibrillary.
 - C: Sinus reticulosis:
 - (a) Acute. (b) Chronic.
- (2) Primary neoplasms—reticulosarcoma

In medullary reticulosis the proliferating cells arise in the medulla of the lymph gland, spleen, and bone marrow. In follicular reticulosis the follicles of the lymph gland are affected and the proliferating cells have a follicular arrangement. In sinus reticulosis hyperplasia affects the littoral cells lining the lymphatic sinuses of the

lymph glands and the venous sinuses of the liver, spleen, and bone marrow. Subdivisions can then be made in these groups according to the types of cells produced. Some of the groups given in Table II can be further subdivided. For instance, the haemic medullary reticuloses are the leukaemias (or leucoses), myeloid or lymphatic or monocytic. Possibly, according to some opinions, the more accurate position for monocytic leukaemia would be in the sinus reticulosis group; this is a matter on which more knowledge is badly needed.

Having outlined the classification of the diseases affecting the haemopoietic organs, it remains to provide a clinical picture of each type and briefly to indicate the changes found in the lymph nodes.

Undifferentiated Medullary Reticulosis

It may be taken as a rule that where there is little differentiation of the primitive cells the clinical picture is an acute one. This type of reticulosis is an acute disease affecting children. The course averages about six weeks. The symptoms are typhoid-like. There is generalized enlargement of the lymph glands, splenomegaly, and hepatomegaly. The intestinal lymphoid tissue may be affected. The predominating cell in the enlarged gland is the reticulum cell. Sometimes fibrils are formed, but phagocytosis is not present. Roussy and Oberling (1934) described about sixteen cases. A similar disease occurs in adults, but is very rare. In adults the course tends to be subacute.

Haemic Medullary Reticulosis

This group includes the myeloid, lymphocytic, and monocytic leukaemias, or leucoses. Chronic and acute myeloid leukaemia need not detain us. In myeloid leucoses the hyperplasia seems to affect cells which have already become differentiated and can only differentiate to more adult members of the granulocyte series. As a rule, in this condition there is no evidence of any reticular hyperplasia in the lymphatic gland. In lymphatic leukaemia there is, however, evidence in nearly all cases of hyperplasia of cells without a fixed line of differentiation—that is, hyperplasia of the reticulum cells. The following case illustrates this in a most striking degree. In other cases lesser degrees have always been found on careful examination of the lymph glands.

CASE I

This patient, a man aged 57, was admitted to hospital with a history of enlarged glands of the neck, axillae, and groins for three years, necessitating periodic rests from work. Two and a half years before admission a white blood count showed 60,400 cells, with 92 per cent. of lymphocytes; a gland removed at biopsy was said to be typical of lymphatic leukaemia. On admission the white cells of the peripheral blood stream were all of a primitive type—oxidase-negative non-granular cells (see Table III). There was pleural effusion, and the liver and spleen were enlarged. Later, after prolonged x-ray treatment, the cells were for the most part small lymphocytes. At necropsy the mediastinal, cervical, abdominal, and inguinal glands were all enlarged. The liver was large, weighing 2,041 grammes. The spleen weighed 1,415 grammes, and showed very large grey Malpighian bodies in a reddish pulp. Microscopically, adult lymphocytes were present in the pulp. The Malpighian bodies were normal but large. Microscopically, some glands were packed with small lymphocytes, with obliteration of the normal architecture; others showed reticulum hyperplasia with development of fibre-bearing cells, and giant cells with twin mirror-image nuclei were present. One of the points of interest in this case is that before the post-mortem histological examination there

was no reason to suspect that the blood count, so typical of lymphatic leukaemia, did not give an accurate indication of the underlying tissue changes.

TABLE III

1936	R.B.C. (1,000's)	Hb %	W.B.C.	P.	Degen. Cells	Primitive Oxid. neg.	Lymph.
Feb. 15	3,200	52	700,000	0.5	36.0	63.5	—
" 26	3,100	52	438,000	3.0	36.5	60.5	—
" 27	3,260	54	500,000	2.0	40.5	57.5	—
Mar. 3	3,250	52	408,000	1.0	46.0	53.0	—
" 6	3,080	56	345,000	2.0	27.0	66.0	8.0
" 9	3,030	54	286,000	2.0	35.0	53.0	10.0
" 12	3,340	54	260,000	3.5	—	12.5	83.5
" 17	3,500	58	238,000	4.0	3.0	2.5	89.5
" 19	3,270	58	225,000	3.0	2.0	2.0	93.0

Treatment: Deep x-ray to spleen and chest. Frequent paracentesis.

There is some confusion in the literature of monocytic leukaemia as to the histological changes in the lymph gland and other organs, and at the present time it is not possible to formulate any opinion as to the true position of this disease. I have no personal experience of a true monocytic leukaemia. In a case of acute leukaemia with 10,500 white blood corpuscles per c.mm. 32 per cent. by vital staining were true monocytes and 41 per cent. small lymphocytes. The sternal puncture showed adult small lymphocytes. The case was diagnosed as acute mixed leukaemia, and the lymph glands showed hyperplasia of the sinus reticulum as well as medullary hyperplasia.

Fibromyeloid Medullary Reticulosis

This is the correct term in the suggested classification for that disease so long known as lymphadenoma or Hodgkin's disease. It is the best known of the primary reticuloses except those of the haemic group, and the clinical picture is well defined. The course is chronic. It is longer in duration than other reticuloses, with the possible exception of follicular reticulosis and Gaucher's disease. The lymph nodes in the cervical region are affected first as a rule, and the enlargement then spreads to the other groups. Splenomegaly occurs in about 70 per cent. of the cases; it is moderate and not constant. Massive involvement of the lung may occur in some cases.

The characteristic changes in the glands in fibromyeloid reticulosis are the proliferation and differentiation of the reticular syncytium. These changes have been described in great detail by Pullinger. The changes in the reticular syncytium and the cells derived from it may be summarized as follows:

The nucleus becomes enlarged and the cytoplasm becomes partially separated. The swollen cells then separate out as individuals. The cells may show vacuolation and retraction of the cytoplasmic processes, and groups of cells may be seen showing ill-defined cell boundaries with large nuclei, perhaps twin. Cells appear with well-defined twin nuclei, which in characteristic Sternberg-Read giant cells are mirror images of one another. These giant cells are often seen in Hodgkin's disease.

The characteristic of lymphadenoma is, however, differentiation of the cells; a filigree of reticulin fibrils is present, and granular cells, many of them eosinophils, are developed from the reticulum cells, a considerable diversity of cell structure resulting. In late stages the production of collagen may give rise to a very dense fibrous tissue with only a few reticulum cells remaining.

Histiocytic Medullary Reticulosis

Histiocytic medullary reticulosis is a condition which has probably been classified as "atypical Hodgkin's disease." Pullinger described a case in 1932. The glandular lesion was characterized by areas of haemorrhage and necrosis. Macrophages were present, with chromatin particles and, frequently, red blood corpuscles in their cytoplasm. Giant cells having small nuclei arranged at the periphery were also present. Occasionally reticulum cells with twin nuclei were seen. Cells with eosinophilic cytoplasm and darkly staining nuclei were abundant. Some of these showed mitotic figures. (These cells have been termed prohistiocytes by Robb-Smith, 1938.) Bodley Scott and Robb-Smith (1936) have included this case with three others in a paper on histiocytic medullary reticulosis. These authors have been able to find six other cases in the literature and to assign a clinical picture to the condition. Briefly, the clinical course is characterized by fever, wasting, generalized glandular enlargement, splenomegaly, and hepatic enlargement. Jaundice, purpura, and anaemia with leucopenia are common in the final stages. The average duration of the disease is fifteen weeks, all cases ending fatally.

Generalized Lipoid Histiocytosis

Gaucher's disease is familial, the average duration being about forty-five years. The condition is characterized by great splenic enlargement, and although there may be generalized enlargement of the glands it would be unusual for diagnosis to rest on the biopsy of a gland. It is not always realized that patients suffering from Gaucher's disease may live for "three-score years and ten" and die of the cerebral complication of atherosclerosis so common to the old without the metabolic disturbance being of clinical significance.

Follicular Reticulosis

Follicular reticulosis of the lymphoid type has been described by Brill, Baehr, and Rosenthal (1925) in America as follicular lymphoblastoma. It is a disease affecting adults, the average age being from 43 onwards. The course is typically remittent, lasting for four or five years. There is splenomegaly and enlargement of the lymph glands. The disease is characterized by serous effusion, and hypochromic anaemia is fairly constant. The clinical picture in some cases is that of hepatic cirrhosis with splenomegaly. Other cases, however, give the clinical picture of "splenic anaemia" with leucopenia and relative lymphocytosis. The lymph glands show on the cut surface numerous small white nodules. These are enlarged follicles, consisting of large lymphocytes. There is no reticulin increase, and occasional reticulum cells are present. In all about forty-five cases of the disease have been described. The American writers state that the condition responds well to irradiation.

CASE II

This case was diagnosed in life as reticulosis. The patient, a woman aged 58, was admitted for swelling in the abdomen. There was a ten-weeks' history of listlessness, dyspnoea on exertion, and swelling of the ankles. For six weeks there was enlargement of the abdomen with ascites, which was tapped, and at the onset constipation was present. She was admitted on May 24, 1938, and died on June 22, being under observation for four weeks. On admission the spleen was down to the umbilicus and the liver palpable. Glands were palpable in the axillae and groins. Paracentesis was performed on two occasions, 16 pints and 18½ pints of milky fluid being withdrawn. This was sterile and contained no fat. A blood

count showed: red cells, 5,160,000 per c.mm.; haemoglobin, 92 per cent.; white cells, 6,600 per c.mm.—75 per cent. polymorphs, 0.5 per cent. basophils, 0.5 per cent. eosinophils, 22 per cent. lymphocytes, 4 per cent. monocytes.

Post-mortem Examination.—There was oedema of the larynx, and ten pints or more of turbid fluid were present in the left pleural cavity. The lungs were collapsed at the base; the abdomen contained twenty pints or upwards of turbid fluid; the liver weighed 2,280 grammes and was firm and pale. The spleen weighed 1,120 grammes, was 22 cm. long, was dull pink with a thick capsule, and its cut surface was studded with white nodules. The lymph glands were all enlarged, were white, soft, and discrete, and numerous punctate white areas were present on the cut surface. The bone marrow showed similar small white nodules. Microscopical changes in the lymph nodes were recorded thus: "The white areas are the lymphoid follicles much enlarged. They consist of large lymphocytes, with occasional reticulum cells. There is no increase of reticulin fibrils in the follicles." This case was similar in many ways to one described by me in 1933.

CASE III

This patient, a Post Office worker, was under observation for five years. The onset of disease, with swelling of the glands in the groin, occurred when he was 43; later the glands in the axilla became enlarged. At the age of 47 he was admitted to hospital. He then had dental sepsis with ulceration of palate. The Wassermann reaction was negative. There was proptosis of the left eye, and enlarged glands were present about the left orbit and in the left cervical region. A biopsy on one of the cervical glands at this time showed follicular lymphoid reticulosis, with follicles consisting almost entirely of adult small lymphocytes. These glands disappeared under x-ray treatment. A blood count showed: 3,930,000 red cells per c.mm.; 68 per cent. haemoglobin; and 4,200 leucocytes, 74 per cent. being polymorphs, 2 per cent. basophils, 1 per cent. eosinophils, 4 per cent. monocytes, and 19 per cent. small lymphocytes. There was a recurrent enlargement of glands for a period of three years. As new groups of glands became enlarged and interfered with his work, x-ray treatment was given, the enlargement then subsiding. Three months before death he was admitted with generalized glandular enlargement and a cough. Death resulted from confluent bronchopneumonia with empyema.

Necropsy.—There was generalized enlargement of the lymph glands, and also a mass in the abdomen pressing on the right renal pelvis, causing hydronephrosis. The spleen was large, with a normal pattern. The glands showed small white nodules studded over the cut surface. Microscopically the glands revealed lymphoid follicular reticulosis, and in some of them there were adult and small lymphocytes in the follicles, as had been found in the biopsy material two years previously. In the mass in the abdomen the follicles consisted of large lymphocytes, and reticulum cells were also present. The feature of this case was the extraordinary sensitivity to x rays, whereby the disease was checked but not arrested. This was like a case of lymphadenoma, in that the one group of glands enlarged first, and the enlargement then took place in another group. The glandular enlargement was not generalized from the onset.

I believe that similar cases have in the past been regarded as radiosensitive Hodgkin's disease, and that this type of lymphoid follicular reticulosis is a clear-cut clinical entity.

Fibrillary Follicular Reticulosis

This disease is similar to lymphoid follicular reticulosis, but is evidently more rare. It occurs in adults. I described a case in a woman of 61 who was admitted to hospital with a diagnosis of hepatic cirrhosis with splenomegaly and generalized glandular enlargement. There had been recurrent ascites for eighteen months. The blood count was: red cells, 3,770,000; haemoglobin, 50 per cent.; leucocytes, 6,000, 47 per cent. being poly-

morphs, 5 per cent. monocytes, and 48 per cent. lymphocytes. The lymphatic glands, on naked-eye examination, showed numerous small white nodules. Microscopically these white nodules consisted of irregularly shaped reticulum cells with occasional binucleate forms. A great increase in reticulin fibrils was present in these follicles.

Primary Sinus Reticulosis

This group includes hyperplasia of sinus-lining or littoral cells. An acute type, running a clinical course of great rapidity, with jaundice and increasing anaemia, has been described by Debenedetti and Florentin (1931). It affects adults. The spleen and liver are enlarged, and in the lymphatic glands and elsewhere there is phagocytosis of the red blood corpuscles by the proliferating sinus-lining reticulum cells. Pryce and Reburn have described a similar case in this country.

There was also a chronic type which was originally described as occurring in the spleen (Stengel; Wolbach, 1911). When the lymph glands are affected the normal architecture of the gland is entirely destroyed: circular foci of cellular proliferation surrounded by a zone of peripheral fibrous tissue are scattered throughout the whole gland. The centre of each focus consists of proliferating cells of the histiocyte type, usually with one or more giant cells of the Langhans type. Occasionally the giant cells contain cytoplasmic inclusions. Necrosis has never been observed. Reticulin fibrils and collagen fibrils run in between the cells, as well as encircling the nodules, and fibrosis of the entire nodule results. The aetiology is quite unknown.

Conclusion

This concludes my survey of some of the conditions in which reticular hyperplasia is the underlying tissue change. I hope I have made it clear that well-defined clinical entities are represented by some of the groups into which the conditions have been classified. Cases of lymphadenoma, or Hodgkin's disease, lymphoid follicular reticulosis, myeloid leukaemia, histiocytic medullary reticulosis, Gaucher's disease, and some others fall into their correct position when the tissue changes in a lymph gland are subjected to careful analysis, and the clinical characteristics of other groups should be recognized as our knowledge of the reticular hyperplasias increases. The future should enable us to assign most conditions to their correct classes, but meanwhile the careful examination of lymph gland and bone marrow (preferably before treatment is begun) must take a prominent position in the diagnostic investigation of all cases.

It must be remembered that the ultimate object of classification is (1) to assist in the search for an aetiological factor, and (2) to provide a basis for information as to prognosis and the result of treatment. No real advance can be made until a definite cytological examination is carried out before treatment is begun.

REFERENCES

- Brill, N. E., Baehr, and Rosenthal, N. (1925). *J. Amer. med. Ass.*, **84**, 668.
Debenedetti, R., and Florentin, P. (1931). *Bull. Mém. Soc. méd. Hôp. Paris*, **47**, 739.
Maximow, A. (1927). *Hdb. des mikr. Anat. des Menschen*, vol. 2, Pt. I, p. 359.
Pullinger, B. D. (1932). *Rose Research on Lymphadenoma*, Bristol.
Robb-Smith, A. H. T. (1938). *J. Path. Bact.*, **47**, 457.
Ross, J. M. (1933). *Ibid.*, **37**, 311.
Roussy, G., and Oberling, C. (1934). *Wien. med. Wschr.*, **84**, 407.
Scott, R. B., and Robb-Smith, A. H. T. (1936). *St. Bart's Hosp. Rep.*, **69**, 143.
Wolbach, S. B. (1911). *J. med. Res.*, **24**, 243.