DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPHATHY

DR. .V CAPTUR
Demonstrator in Medicine,
Royal University of Malta,
Assistant Physician, St. Luke's Hospital.

The aim of this paper is primarily to help the senior medical student in learning methods of diagnosis and applying them in his clinical work — in other words my intention is to familiarise the student in the philosophy of medical diagnosis.

The diagnostic field of lymph node enlargement is vast and a nightmare both to the clinician and pathologist. The first requisite is to know what the causes of lymph node enlargement could be, hence I am beginning by a classification which to my mind is as good as any other. This is followed by the clinical features of each particular disease, by the investigations which are of help in the diagnosis and finally by the pathological picture of the enlarged gland.

Enlargement of Lymphatic Glands.

A. Infective

(a) *Acute.* 1. *Tonsillitis.*
2. *Diptheria.*
3. *Scarlet fever.*
4. *Rubella.*
5. *Measles.*
6. *Glandular fever.*
7. *Plague.*
8. *Typhus.*
9. *Septic skin conditions.*

(b) *Chronic.* 1. *Tuberculosis.*
2. *Syphilis.*
3. *Boeck's sarcoid.*
4. *Chronic skin infection.*

B. Neoplastic.

(a) *Reticulo-endotheliosis* (Reticulosis)

(b) *Lymhoblastomas:*

1. *Follicular lymphoblastoma*
2. *Lymphosarcoma—*
   i. small-cell type. (malignant lymphocytoma)
   ii. large-cell type. (reticulum-cell sarcoma)
3. *Hodgkin's disease.*
4. *Mycosis fungiodes.*
5. *Lympho-epithelioma.*
6. *Benign lymphoma.*

(c) *Leukemias*—1. *Lymphocytic.*
2. *Myelocytic.*
3. *Monocytic.*

(d) *Secondary deposits.*

Clinical Features.

Acute infectious adenopathy. Multiple masses that appear rather suddenly, associated with fever and malaise, are usually an infectious adenopathy. If the process is bilateral, and especially if there is evidence of considerable constitutional reaction, one of the acute infectious diseases must be thought of. The node may increase in size rather rapidly and become tender. They are discrete, firm, but not hard, and move freely in their bed. The overlying skin is normal. The deep cervical chain is involved usually, although glands of other areas may become enlarged.

In the child such disease as an acute *upper respiratory infection, scarlet fever, diphtheria* and *measles* must be considered. In scarlet fever especially, one of the first diagnostic signs is bilateral cervical adenopathy associated with sore throat and the typical strawberry tongue. In measles, the Koplik's spots are pathogno-

monic. With German measles (*rubella*) the occipital and posterior cervical glands are the first to become enlarged. In diphtheria the marked inflammatory involvement of the tonsillar region with membrane formation should at once point to the necessity of a culture. With tonsillitis, if unilateral, the enlarged glands, are, as a rule, confined to the side involved.

In the presence of a subacute or chronic oral infection such as *Vincent's angina* a cervical adenopathy may present for many days or weeks, even months.

In childhood due to the large amount of lymphoid tissue in the upper respiratory tract and also probably because of the susceptibility to lymphoid hyperplasia, an adenopathy without causative factor is common. It is found in the undernourished child living under poor dietetic and hygienic conditions. Vitamin deficiency is usually present. Such children are prone to develop low grade infection especially of the nasal and pharyngeal mucous membrances.

Frequently very early in the course of *acute infectious hepatitis,* before jaundice is present, a soft tender liniabean-sized gland can be felt along the posterior border of the sternomastoid muscle low in the right side of the neck (Barker's node). At this stage of the disease, the only other physical findings will be a tender liver and a small localised area of tenderness in the right costovertebral angle.

In *acute infectious mononucleosis,* quite frequently the glands in the posterior triangle on one side become enlarged and soon such an adenopathy may be found on the opposite side. In some instances there is marked involvement of all the cervical as well as the axillary and inguinal glands. The glands often become painful. Such a syndrome appearing in a child or a young adult with a history of exposure to the disease and fever with an absolute high mononuclear leucocyte count makes the diagnosis quite likely. The diagnosis may be verified by a positive heterophile antibodies test, the patient's serum agglutinating sheep erythrocytes in higher dilutions than normal. In some instances the spleen and, at times, the liver may be enlarged. The disease runs a course of from 2-4 weeks.

In *bubonic plague,* the adenopathy comes on 48 hrs. after a child with high fever, extreme prostration and headache. There is present a high white count. The diagnosis can be made by aspiration from a gland and culturing.

Regional adenopathy may also occur in acute skin conditions e.g. erysipelas.

Chronic infectious adenopathy.

Tuberculosis. Onset insidious, often only one area being involved. The onset may be synchronous with malaise, sweats, and a low grade fever with loss of weight. In the beginning the nodes are discrete, freely movable and not tender. There is a tendency for a progression in the glandular involvement so that other regions are affected; however, in most instances the site of maximum reaction is one area. Here the glands increase in size rapidly and tend to become agglutinated to form an irregular mass. With agglutination the mass tends to become fixed not only to the skin but surrounding deep structures such as the sternomastoid muscle and the deep blood vessels. In some cases the overlying skin becomes bluish red and softening of the mass may be noted. At times this secondary change may take place quite suddenly, being accompanied by anorexia, headache and rise in fever signifying a secondary pyogenic infection. Rupture of the abscess often occurs and following this the mass decreases in size considerably; however, a residual mass and a chronic draining sinus remains in

most instances. Direct smear from the discharge may rarely reveal the tubercle bacillus. Unless there is virulent secondary pyogenic infection, guinea pig inoculation from the discharge may prove positive. In those cases where the glands do not break down but remain discrete the only means of an accurate diagnosis is through biopsy. The recognition of active tuberculosis elsewhere in the body is of paramount importance in every unproven case.

Syphilis. In the young or middle-aged adult, bilateral cervical adenopathy associated with involvement of the axillary and inguinal glands and especially the epitrochlear glands must suggest syphilis. The postauricular glands are often the first to become enlarged. Such an adenopathy occurs usually during the second stage of syphilis and may be associated with sore throat, mucous patches and headaches. The Wasserman reaction is positive and a skin rash not infrequently is present. The glands remain discrete and never break down. In some instances a biopsy may become necessary.

Boeck's Sarcoid. Originally described as sarcoma-like nodular lesions of the skin, sarcoid is now recognised as a generalised systemic disease in which there is most commonly involvement of lymph nodes, lung, bone marrow, spleen, liver, paortid and other organs. Etiology unknown. It has been considered as an atypical form of tuberculosis — but not proved. Closely related conditions in which sarcoid lesions are found include regional ileitis and nuesparotid fever (Hurfordt's syndrome).

Neoplastic adenopathy.

1. *Reticulo-endotheliosis (reticulosis).* Rare condition in which there is diffuse hyperplasia of the reticulo-endothelial system to the point of replacement of normal structures. It may occur at any age but it is more frequent in infant and young children. The characteristics include splenomegaly, hepatomegaly, anaemia, purpura, and bony changes such as rarefaction and cyst formation. A fatal ending is reached in ten weeks to ten years.

2. *Follicular lymphoblastoma.* It is a relatively benign disease of lymph nodes and spleen, in which the characteristic feature is a marked increase in number and size of lymph follicles. It occurs in adults, the average age being over 40. The blood picture is normal and constitutional symptoms mild. Ascites is a common accompaniment. The tissue is peculiarly radio-sensitive, and the prognosis is for longer survival than in most other lymphomatous diseases. Many cases have a late malignant phase. The lymph nodes are enlarged, firm, and discrete. The spleen is usually greatly enlarged.

3. *Lymphosarcoma.* Malignant tumour which can arise from any aggregate of lymphoid tissue. It may occur at any period of life, but the average age is about 45 yrs. Constitutional symptoms and blood changes are lacking in the early stages. External lymph node enlargement is the most frequent beginning, and the cervical nodes are most often affected. The gastro-intestinal tract is frequently involved. The tumour tissue is highly radio-sensitive. Lymphosarcoma probably arises from the undifferentiated mesenchymal stem cell of lymphoid tissue. Lymph follicles are composed of two types of cells, the small lymphocyte arranged about the periphery and the large reticulum cells of the germinal center. Differentiation may be different in degree and direction, so that two types of lymphosarcoma may be distinguished, a small cell type and a large cell type.

4. *Hodgkins disease.* This involves lymph nodes or lymphoid tissue elsewhere, as in the alimentary tract, spleen and rarely bone-narrow. Etiology unknow. Most popular conceptions

are that it is (i) a chronic infective granuloma or (ii) a true neoplasm. The belief that it is an atypical from of T.B. has been abandoned. A fatal ending occurs after an average duration of 2 yrs., but length of life varies from a few months to ten years. Males are affected more than twice as frequently as females. It may occur at any age but the higher incidence is in young adults.

The beginning is usually a painless enlargement of a group of lymph nodes, most frequently in the neck. Blood changes are inconstant but there may be a moderate polymorphonuclear leucocytosis, with lymphopenia, and eosinophilia is occasionally present. Anaemia develops in later stages. Fever of the "Pel-Ebstein" type is present. The nodes are at first discrete, but in late stages matted together. Diagnosis is usually made by biopsy of a lymph node.

5. *Mycosis fungiodes.* Is considered by some to be a lymphoblastomatous disease of the skin related to leukemia or lymphosarcoma, and by others to be an infective granuloma. In early stages, there is an ecsematoid eruption, followed by a tumour phase.

6. *Lympho-epithelioma.* Is a highly radio-sensitive malignant tumour arising in the naso pharynx ,in which there is intimate association of lymphoid tissue and immature squamous epithelium.

7. *Leukemia.* Is a condition of lawless evergrowth of white blood cells and proceeds to a fatal ending. It is probably best regarded as a neoplastic change in the blood forming tissues, with the excess of white cells, many of which are immature or abnormal forms. Those unusual cases in which excessive or abnormal white cells are not found in the blood are referred to as aleukemic leukemia. According to the type of white cell involved, the leukemias are classified as lymphatic, myeloid, and moncytic. Each of these may be acute or chornic, but the acute types are difficult to distinguish from each other. There is a different age incidence from the various types. Acute leukemia has its maximum incidence in the first decade, chronic myeloid leukemia between 25—45 yrs. and chronic lymphoid leukemia between 46—60 yrs.

(i) *Acute leukemia.* May begin suddenly and run a rapid course of a few weeks or months. Early stage may be aleukemic, but later the white blood count becomes very high, though less than the extreme figures of chronic leukemia. Anaemia and thrombocytopenia are often severe. The majority of white cells in the blood are myeloblasts or lymphoblasts, distinction between these primitive cells being difficult and unreliable.

(ii) *Chronic myeloid leukemia.* There is a great increase in granular leucocytes in the blood, and many immature cells (myelocytes and myeloblasts) are responsible in blood smears. The total white count may become very high, reaching 500,000 or more per c.mm. in some cases. Platelets also may be increased, but R.B.C. progressively diminish in number. The course of the disease may extend over several years before the inevitably fatal end. The essential lesion is a myeloid hyperplasia throughout the bone marrow. The spleen becomes enormously enlarged. Lymph nodes are slightly enlarged.

(iii) *Chronicle lymphatic leukemia.* The white count is lower than in the myeloid type. It is usually around 100,000 and often 90% or more are lymphoid cells. Red cell reduction and anaemia occur in late stages. The lymph nodes all over the body are enlarged.

(iv) *Monocytic leukemia.* Includes two varieties: (a) The Naegeli type is characterised by immature cells inter-

mediate between myeloblasts and monocytes. (b) The Schilling type, when the immature cells resemble monocytes and reticulo-endothelial cells.

INVESTIGATIONS

1. *History.* Past history. Family history. History of present condition.
2. *Age.* Infancy and adolescence: T.B. and Glandular fever.
   Middle age: Hodgkin's.
   Lymphosarcoma.
   Leukemia.
   later: Leukomia.
3. *Lymph glands.* Localised with fever and tenderness:—
   i. Pyogenic
   ii. Tuberculosis.

   Localised without fever and tenderness:
   i. Lymphosarcoma.
   ii. Syphilis.
   iii. Hodgkin.

   Generalised enlargement with fever:—
   i. Acute phase of Leukemia.
   ii. Syphilis.
   iii. Hodgkin.

   Generalised enlargement without ferev:
   i. Chronic leukemia.

   Fluctuant nodes:— i. Tuberculosis.
   ii. Pyogenic

   Discrete and elastic: i. Leukemia.
   ii. Hodgkin's.
4. Fever. i. Septic type: Inflammation.
   Acute Ieukemia.
   ii. Pel-Ebstein type: Hodgkin's
   iii. Low-grade type: Tuberco-
   losis.
5. *Splenomegaly.*
   i. Large spleen and generalised enlargement: Leukemia.
   ii. Moderate spleen and cervical adonopathy: Hodgkin.
   iii. Slight spleen: Glandular fever.
   Lymphosarcoma.
6. *Blood Picture.*
   i. Normal; Early neoplastic. (probability)
   ii. Leucocytosis: Infection.
   iii. Mild anaemia
   Monocytosis Tuberculosis.
   Lymphocytosis
   iv. Marked anaemia
   Lymphopenia Hodgkin.
   Leukopenia
   v. Marked leucocytosis
   Lymphocytosis Leukemia
   vi. Normal R.B.Cs and W.B.Cs.
   Eosinophilia Syphilis.
   Lymphocytosis
   vii. Normal R.B.Cs.
   Marked lymphocytosis
   Glandular fever.
   Reider nuclei.
7. *X-Ray Chest.*
   Mediastinal Adenopathy:—
   Hodgkin.
   Lymphosarcoma.
   Leukemia.
8. *X-Ray sinuses and Exam. of nasopharynx.*

   To detect primary growth if there is one.
9. *Wasserman Reaction.*
10. *Paul-Bunnel test.*
11. *X-Ray Bones.* X-Ray evidence of bone infiltration (osteoscherrtic leukemia), accounts for the occasional severe pain that accompanies leukemia or Hodgkin's disease.
12. *Biopsy of gland.* Most important to establish diagnosis with certainty.

(a) *Lymphadenitis.*
Macro. Swollen and tender. In pyogenic infection suppurration occurs.
Micro. The sinuses are filled by polymorphs or mononuclear cells.

(b) *Glandular fever.*
Micro. Throughout pulp, in the sinuses, and on the edge of the germinal centers are large numbers of the specific large mononuclear cells.

(c) *Tuberculosis.*
Macro. In both proliferative and caseous, the glands are at first

enlarged, firm and discrete ,while their cut surface is grey and translucent. The caseous variety is later characterised by small, soft, yellow, opaque areas.

Micro. Basic lesion is the tubercle follicle. The centre is occupied by endothelial cells (faintly acidophilic, non-granular cytoplasm and oval, feebly stained, vesicular necleus.). These are surrounded by lymphocytes and plasma cells. Each follicle also generally includes one or more plasmodial masses. These giant cells may be situated amcngst the endotheloid cells or at the endotheloid and lymphocytic zones. It may occupy the centre of the follicle.

(d) *Follicular lymphoblastoma.*

Macro. Enlarged. Firm and discrete (until late).

Micro. The essential change is a tremendous increase in number and size of the germinal centres which are surrounded by a narrow rim of small dark mature lymphocytes. The condition is easily distinguished microscopically from the other type of lymphoblastoma by the maintenance and exaggeration of the follicular architecture.

(e) *Lymphosarcoma.*

Micro. Essential feature is disruption and obliteration of the architecture of the lymphoid tissue by the cellular overgrowth. Pleomorphism is not a feature, most of the cells being similar in appearance. (small cell or large cell.) Mitoses are present, but not abundant.

(f) *Hodgkin's*

Macro. At first discrete but later matted together.

Cut surface has a greyish, translucent, 'fish-flesh' appearance.

Micro. (i) Pleomorphism of cellular tissue, with loss of normal architecture.

(ii) Sternberg or Dorothy Reed cells (large hyperchromatic cells).

(iii) The presence of eosinophiles.

(iv) Fibrosis.

Pleomorphism is prominent and there is a mixture of the specific cells, giant cells, plasma cells, lymphocytes, leucocytes and eosinophiles. Fibrosis is important in distinguishing Hodgkin's from other lymphoblastomatous conditions such as lymphosarcoma and lymphatie-leukemia.

(g) *Chronic lymphadenitis.*

Micro. Hyperplasia of the reticuloendothelial cells, large numbers of the endothelial cells becoming swollen, rounded and cast off into the greatly dilated lymph sinuses, an appearance to which the name of "sinus catarrih" is given.

(h) *Sarcoidosis (Boeck's Sarcoid).*

Micro. Difficult to decide from tuberculosis. The giant cells are larger from those of tuberculosis and there is generally no surrounding lymphocytic infiltration. Silver stains show a delicate reticulum which is absent, owing to destruction, in T.B.

(i) *Syphilis.*

Micro. The histology is not characteristic i.e. a proliferation of epitheloid cells, lymphocytes and plasma cells. In the primary and secondary forms, the demonstration of the spirochaeta pallida is usually easy.

(j) *Reticulosis. (histiocytic medullary reticulosis)*

Micro. Cellular proliferation in the medulla, which consists principally of phagocytic histiocytes containing R.B.Cs. and nuclear debris.

(k) *Lymphatic Leukemia.*

Micro. The nodes are crowded with lymphocytes which entirely obliterate the usual architecture.