"fortresses." One may almost say that there are no new "fortresses" left to storm, since all the abdominal viscera are now the subject of the surgeon's frequent attention; certainly there can be nothing in the next quarter of a century to compare with the victorious advance made during this in the treatment of acute abdominal crises by the general adoption of early operation.

Having personally witnessed this twenty-five years' progress, as I have, and glorying in it, as I do, I naturally decided to select this as the subject of my presidential address to you, and to illustrate it by reference to the statistics of the Manchester Royal Infirmary—an institution around which the whole of my professional life has revolved, and of which I am, we all are, intensely proud. And if I have failed to arouse in each one of you something of the profound faith and enthusiasm in the progress of abdominal surgery which I myself feel, then I must ask you to ascribe such failure, not to any inherent defect in the theme itself, but to the inadequacy of my descriptive powers to do even the most rudimentary justice to this truly wonderful chapter of surgical progress.

HODGKIN'S DISEASE IN MAN AND ANIMALS.*

BY

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Synonyms.—Hodgkin's lymphogranuloma, lymphadenoma, lymphogranulomatosis, or granulomatosis maligna.

Nomenclature has been a stumbling-block, for the terms "lymphosarcoma" (Virchow) and "pseudo-leukaemia" have been applied to what we understand by Hodgkin's disease, whereas quite a distinct and different significance now attaches to these two words. Cohnheim in 1865 employed the term "pseudo-leukaemia" to a condition in which the enlarged lymphatic glands showed the histological structure in leukaemia while the blood did not—in fact, to what would now be called aleukaemic leukaemia, the aleukaemic phase of leukaemia, or probably better aleukaemic lymphadenosis. Lymphadenoma, which in this country is synonymous with Hodgkin's disease, has the disadvantage that in America and France it is sometimes employed for what would be more accurately described as lymphadenosis, since it does not run the inevitably malignant course. Except for the drawback of the change it might be well to adopt the term, used for seventeen years by H. M. Turnbull, and also employed by Ewing, of "Hodgkin's lymphogranuloma."

Incidence.—As the nomenclature is a source of confusion, and the clinical diagnosis, especially from lymphosarcoma, difficult, the Registrar-General's returns may not settle whether the disease is becoming commoner, as some have thought, but they show an increase in the last ten years, from 280 deaths in 1913 to 371 in 1923.

Criterion of Hodgkin's Disease.

As the cause of Hodgkin's lymphogranuloma is unknown, it is necessary to fall back on its histological structure as the only means of defining exactly what is meant by the name; indeed, the diagnosis of a given case can be made with certainty only on its microscopic characters, for the clinical features and the response to treatment, especially to radiations, though strongly suggestive, cannot be regarded as final courts of appeal. The histological appearances, described independently and almost simultaneously by F. W. Andrewes and Dorothy Reed in 1902, are so well known that it is unnecessary to do more than mention them—namely: (1) diffuse alteration of the structural architecture of the gland as a whole, showing (2) a diminished number of lymphocytes; (3) endothelial hyperplasia; (4) "lymphadenoma cells"; and (5) sometimes well marked eosinophilia. The blood changes are not patho-

gnomonic; there is often a leucopenia, especially in the earlier stages and in the cases of predominant splenic enlargement; when the disease is widespread a polymorphonuclear leucocytosis is common, and in rare instances there is a well marked eosinophilia, the significance of which is not clear.

Valuable as microscopical examination of an excised gland is, biopsies are not free from fallacies, for although there is lymphadenoma elsewhere the gland excised may show nothing more than indefinite lymphoid hyperplasia due to simple inflammation or compensatory for the destruction of other lymphatic glands. But Webster found that biopsies gave more positive results in Hodgkin's disease than in cases ultimately proved to be lymphosarcoma.

Nature of Hodgkin's Disease.

Lymphadenoma has been thought to be (1) a neoplasm, (2) a transition between a neoplasm and an inflammatory formation, and (3) as seems most probable, an infective granuloma, though the responsible virus, in spite of the descriptions of the tubercle bacillus (C. Sternberg; Fraenkel and Much), a Gram-positive pleomorphic diphtheroid bacillus (Bunting and Yates), and a spirochaete (White and Proeschner), has not yet been established.

The view that Hodgkin's disease is a neoplasm rests on several considerations, and perhaps chiefly on the assumption that in its early stage it is confined to existing lymphadenoid tissues, and that later it generalizes like sarcoma and invades tissues, such as muscle and bone, which do not contain any lymphoid tissue; this generalization, however, is quite compatible with the characters of the infective granulomas. The second reason is that in the late stages the histological characters may become those of a sarcoma—"Hodgkin's sarcoma," as Ewing (1922) calls it. If and how often this sequence has been actually proved by biopsy and necropsy I do not know; it is said by Ewing to occur often in mediastinal lymphadenoma, but these are just the cases in which a biopsy may be impracticable. Now the various kinds of cells seen in the early stage are much more like the inflammatory changes in the infective granulomas than the structure of a sarcoma, even though a mixed-celled. But Mallory groups together under the term "lymphoblastoma," as true tumours, Hodgkin's disease, lymphoid leukaemia, and lymphocytoma. It is a rather different and difficult question whether Hodgkin's lymphogranuloma becomes transformed during its course into Hodgkin's sarcoma, or whether the condition is sarcomatous from the start and becomes more virulent with the progressive impairment of the patient's resistance. On the analogy of chronic irritation as an antecedent of carcinoma and of the rare occurrence of sarcoma and carcinoma in the same growth, it would be reasonable to believe that a gland originally the site of chronic inflammation may later become sarcomatous, and Ewing (1913) has observed this sequence of events in cases in which repeated operations have shown the elimination of the original granulomatous lesion. But it would appear to be an open question whether the sarcomatous change occurs in the cells of Hodgkin's lymphogranuloma or in the tissues around, the latter process being analogous to the occurrence of a squamous-celled carcinoma in the site of cutaneous lupus.

Situation of the Disease.

The primary site of lymphadenoma is usually regarded as the cervical glands, as shown by the statement that these are first affected in from 50 (Ziegler) to 76 per cent. (Bunting) of the cases. But it does not follow that the glands first palpably enlarged are necessarily those first attacked; on the rather slender basis of fourteen cases Symmers has insisted that primary enlargement starts in the abdominal or in the abdominal and thoracic glands ten times more often than in the cervical, and Ewing confirms this. Its starting-point is of practical importance as determining the extent of the area to be treated by x rays or radium. A remarkable feature of Hodgkin's disease is that, although its first and main site is in the lymphadenoid tissues of the body, including the spleen, the mesenteric and the retroperitoneal lymphatic glands, it very rarely attacks

* An opening paper of a joint discussion of the Sections of Medicine and Comparative Medicine at the Royal Society of Medicine on January 26th, 1926.

the lymphoid tissue of the alimentary canal. It is true that cases, such as G. N. Pitt's collection of twenty-five cases, have been described, but it is significant how few have been recorded since 1902, when the histological characters were established.

Satisfactory evidence that Hodgkin's disease has ever been transmitted to animals is wanting; Bunting and Yates, after repeated injections of their diphtheroid bacillus isolated from lymphadenomatous glands, obtained appearances in five *Macacus rhesus* monkeys resembling "the early changes of Hodgkin's disease as seen in man": but this is rather ambiguous, for the lymphocytic hyperplasia which Bunting describes in the early stage of Hodgkin's disease resembles inflammation. Other observers have failed to confirm this. Inoculations of material from lymphadenomatous glands into monkeys have given negative results (Longcope; Cunningham and McAlpine; Stewart and Dobson). Stewart and Dobson described "a peculiar giant-celled reaction, probably of foreign body type, around the implanted material," which is of some significance in relation to the early changes of lymphadenoma reported by Bunting and Yates. C. C. Twort found that guinea-pigs frequently reacted to inoculation of pieces of lymphadenomatous tissue by the production of transient local nodules which histologically were entirely of an inflammatory nature.

HODGKIN'S DISEASE IN ANIMALS.

The chief interest of to-night's discussion, at which we welcome our colleagues of the Section of Comparative Medicine, is the question of the occurrence in animals of Hodgkin's disease as established by the histological appearances now accepted as characteristic in man. It is described as occurring in the so-called lower animals, but how far is this based on clinical rather than on microscopic evidence either by a biopsy or necropsy? In 1903 John McFadyean, under the title "Five cases of Hodgkin's disease in the lower animals," quotes F. W. Andrewes's account of the histological picture, and adds: "If the characters above mentioned are essential to Hodgkin's disease or lymphadenoma, the cases which I am about to describe have no title to be called by these names." This frank admission applies to nearly all the few recorded cases of lymphadenoma in animals that I have come across, which might more safely be headed lymphoma; thus in Hodgson's brief account of "Hodgkin's disease in a pig" the glands microscopically "showed simply an excess of lymphocytes above their normal structure." In G. Simons's case of Hodgkin's disease in an Aberdeen terrier there was no *post-mortem* examination; in Reed's case of Hodgkin's disease in a horse the microscopic appearances of the glands were "a hyperplasia of the cellular elements and an increase in the gland stroma." Hobday's case in a dog, however, was examined after death by Sir John McFadyean, who is quoted as stating that "it was a typical case" without any further details. There does not appear to be any reason why Hodgkin's lymphogranuloma should not occur in animals, but more information is required about the microscopic appearances of cases so diagnosed on clinical grounds.

DIAGNOSIS.

The greatest difficulty in the differential diagnosis of Hodgkin's disease is the clinical differentiation from the variously named primary sarcomas of lymphoid tissue—lymphosarcoma, malignant lymphocytoma, endothelioma. In many cases this can only be done by microscopic examination of an excised gland.

Cases of secondary malignant growth in the cervical and supraclavicular glands may imitate Hodgkin's disease when the primary growth in the mediastinum, or even the oesophagus, is latent and the chest is not skigraphed. I have seen a case which, after imitating Hodgkin's disease, became one of cancer en cuirasse, so that a small primary carcinoma of the mamma probably escaped detection. I have twice seen the following condition suggest Hodgkin's disease: a primary malignant hypernephroma of the left adrenal or kidney producing a tumour, taken for an enlarged spleen, and secondary glands above the left clavicle.

There are certainly a number of chronic enlargements of a hyperplastic or inflammatory character, though of undetermined origin, which clinically are regarded as Hodgkin's disease, and in which the doubt about the diagnosis only arises when a biopsy or necropsy upsets the clinical opinion. These may be toxic or probably due to a low-grade infection. Ledingham found that the virus of vaccinia, and possibly of small-pox, may set up changes in the cells of the reticulo-endothelial system resulting in an acute granuloma. In chronic infection of the urinary tract by *B. coli* I have seen glandular enlargement suggesting Hodgkin's disease. Brill, Baehr, and Rosenthal described splenomegalia lymphatica hyperplastica, a condition showing generalized and gigantic hyperplasia of the lymph follicles of the lymphatic glands and of the Malpighian bodies in the spleen: the blood count was normal, and the condition was rapidly cured by x rays; but before this was found out splenectomy was performed in two cases (one followed by death). Cases described as infectious mononucleosis and glandular fever run a short course, and so are not likely to give rise to much difficulty in diagnosis.

Tuberculous adenitis may come before us in three forms in connexion with the clinical diagnosis from lymphadenoma; the first is common and often commonplace, the second very rare, and the third so exceptional as to have aroused some scepticism (F. P. Weber; Lyon; Sprunt). (1) Tuberculous glands in the neck often simulate lymphadenoma, especially when the glands show tuberculous large-celled hyperplasia without necrosis or caseation. (2) Generalized tuberculous adenitis may, as MacNalty showed, be accompanied by the relapsing fever described in lymphadenoma by Murchison (1870), Pel (1885), Ebstein (1887), and often, regardless of strict priority, called the Pel-Ebstein syndrome, for Morgagni in 1769 briefly recorded an example. This generalized tuberculous adenitis, when it occurs, may be associated with visceral infection—for example, of the lungs (MacNalty)—though the absence of splenic enlargement, which occurs in about 75 per cent. of generalized lymphadenoma, is of some diagnostic value. In very rare instances, of which Crip and Narr could not find more than a very few recorded cases, the infection appears to be confined to the glands; in their patient and in another recovery occurred. (3) The condition, little if at all accepted in this country, described as adeno-lipomatosis, in which fatty growth occurs around lymphatic glands which may be tuberculous, a process regarded as an effort to localize the disease. In fat persons in the early stage of lymphadenoma the question of diagnosis from adeno-lipomatosis has arisen, at any rate in my mind.

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