HODGKIN'S DISCOVERY OF LYMPHO-GRANULOMA 100 YEARS AGO

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It is now a hundred years since Thomas Hodgkin, in a masterly way and with astonishing clearness, endeavoured to separate out the definite disease which we now know as Hodgkin's disease or lymphogranuloma. The clinical accounts of that time naturally do not include all that we now know of the disease, but the description of his original seven cases shows that it was a chronic disease, often associated with fever, leading to cachexia, in which for the medical diagnosis the most important signs were extensive enlargement of lymph glands and often enormous enlargement of the spleen. The necropsy findings supported the idea of a single disease; in all the cases there was great and widespread enlargement of lymph glands; the enlarged glands were hard, sometimes of almost cartilaginous hardness, and were similar to each other in substance and free from necroses; the spleen was generally very considerably enlarged, and contained whitish, hard, mostly large foci of a substance resembling that of the lymph glands. In several cases there were similar nodules in the liver.

In spite of the absence of microscopical examinations the essential features of lymphogranuloma were described, which I would classify in the following way:

1. Chronic febrile disease.
2. Widespread but not quite generalized lymphatic glandular enlargement without necroses (excepting in two cases with local complications).
3. Enlargement, often enormous, of the spleen, which contained peculiar foci or large nodules.
4. Similar nodules in the liver.

In regard to the differential diagnosis of lymphogranuloma, the following come into consideration:

(a) *Leukaemic Processes*.—These appear to be excluded in Hodgkin's cases, because in leukaemia nodules in the liver and spleen never occur, but only diffuse hyperplasias. In only one of Hodgkin's cases (Case 4) does the question of possible leukaemia—lymphadenosis—arise, as the glandular enlargement was unusually widespread and there was a meningeal infiltration. But I think the case must have been one of lymphogranuloma, as the cachexia showed that the disease had lasted a long while and there were many small white patches in the spleen, whilst in chronic lymphadenosis the hyperplasia is always diffuse.

(b) *Tuberculous Processes*.—These can be excluded, as in them great and widespread enlargement of lymph glands and spleen (tuberculous pseudoleukaemia) is certainly extremely rare, and doubtless never occurs in the absence of regressive changes (caseation) in some part or other. I know of no case in the whole literature of the subject in which a tuberculous pseudoleukaemia corresponded to the picture of Hodgkin's seven cases. It was the extent and size of the glandular and splenic enlargements that enabled Hodgkin to exclude tuberculosis in his cases. We know that in many cases of lymphogranuloma lard-like yellowish necroses occur, but such cases in Hodgkin's time would have been regarded as tuberculous, and his description of the new disease was therefore saved from confusion with tuberculous processes.

(c) *Syphilitic enlargements of spleen and lymphatic glands* are doubtless never as great as the enlargements described in Hodgkin's cases. For many years not a single case of tertiary syphilis has been described which, owing to the degree and extent of the glandular enlarge-

ments, could be termed "syphilitic pseudoleukaemia," and the older cases described under that heading are very doubtful ones, as I have explained in my textbook on *Blood Diseases*.

(d) *Glandular enlargements from sarcoma and carcinoma* can be certainly excluded in Hodgkin's cases, as in real tumour cases the spleen is not enlarged and contains no, or only very few, or only microscopic nodules.

We see, therefore, that Hodgkin's observations are of cases which, through much later intensive work, have been separated out as Sternberg's disease, lymphogranuloma, or malignant granuloma. The genius of Hodgkin is proved by the fact that by correct considerations he excluded diffuse hyperplasias in spleen and liver (that is, leukaemic processes), and also tuberculous processes, syphilitic processes, and changes due to malignant tumours. This was an extraordinary accomplishment in the state of knowledge one hundred years ago, and that we wish to commemorate to-day.

Later on, indeed, many authors did not follow Hodgkin's reasonings. They neglected the importance of the splenic enlargement that was present in all but one (Case 6) of Hodgkin's cases, and under "Hodgkin's disease" they included all kinds of lymphatic glandular enlargements.

Thus Hodgkin's clear conception of the disease was neglected, and the term "Hodgkin's disease" lost its significance and came to mean merely chronic lymphatic glandular enlargement of high degree. This was quite contrary to the conclusions of Hodgkin himself, who had wished out of the large number of enlargements of lymph glands and spleen to select this special group as a special disease.

Abstract of the seven cases communicated by Hodgkin in his paper "On some morbid appearances of the absorbent glands and spleen," *Medico-Chirurgical Transactions*, London, 1832, xvii, 68 (paper read on January 10th and 24th, 1832):

Case 1.—Boy, aged 9 years. Pains in back last nine months. Terminal ascites. Scrotal oedema. One brother had died recently of phthisis. Patient himself was cachectic. *Necropsy*: Old pleural adhesions (right), with recent pleuritis; scarring at apex of right lung; a few small nodules scattered in both lungs; bronchial glands enlarged and indurated. Fresh sero-purulent peritonitis (probably secondary, after paracentesis); enlarged mesenteric glands (up to the size of pigeon's egg), of semi-cartilaginous hardness and streaked with black; liver of normal size, containing a few white firm nodules somewhat larger than peas; spleen enlarged, containing numerous nodules; enlarged and indurated para-aortic and pelvic glands.

Case 2.—Boy, aged 10 years, ill for thirteen months, with considerable enlargement of the spleen, which diminished at times and then again increased. Glandular swellings on both sides of the neck. Terminal abdominal distension, scrotal oedema. *Necropsy*: Greatly enlarged lymph glands in neck, paratracheal, bronchial, and para-aortic, and also in pelvis. These glands were pale, poorly vascularized, of almost cartilaginous hardness, without any areas of softening. Old pleuritic adhesions. Ascites. Liver apparently normal. Spleen four times the normal size; mammillated surface; on section sprinkled with nodules of similar consistence to that of the lymph glands.

Case 3.—Man, about 30 years of age, admitted to hospital because of cachexia and terminal ascites. Previously treated for secondary syphilis with large quantities of mercury. Scrofulous-like ulcers in armpits and neck. *Necropsy*: Some calcification at the pulmonary apices; pleural adhesions over right lung. A little ascites. Liver hardened, pale, and permeated with a hard white substance, partly diffuse, partly in pinhead-sized nodules. Spleen twice the normal size, and full of granules like early miliary tubercles, but if anything smaller. Some of the mesenteric glands enlarged and containing firm white material, so also some of the para-aortic, inguinal, axillary, and bronchial glands. The axillary glands were in a condition of suppuration, and partly ulcerated.

Case 4.—Man, about 50 years old, pale, not wasted, but of cachectic countenance. Clinically all the lymph glands were enlarged, especially in the axillae and neck, averaging a pigeon's egg in size. Abdomen distended. *Necropsy*: Circumscribed whitish infiltration of the pia mater. Lymphatic glands enlarged, white on section, of rather soft consistence, and having the appearance of morbid hypertrophy rather

than new growth. Large retroperitoneal lymph glands. Liver pale, large, and slightly granular. Spleen very large; on section lighter and more reddish than normal, with innumerable small white spots, without nodules. Heart hypertrophied.

Case 5.—Middle-aged man, who had been ill for a long while, especially with chest troubles. In the hospital there were swollen cervical glands. *Necropsy*: Considerable enlargement of cervical and submandibular glands. Part of one lung was airless and firm, as in white hepatization. Fresh inflammation of one pleura. The liver was more than seven pounds in weight, not much altered on section, like a fatty liver, of dark green to yellowish colour. Spleen four or five times the normal size, firmer than usual, in some parts containing little specks of rather soft consistence. Great enlargement of retroperitoneal glands. Some of the abdominal glands showed ecchymoses. The thoracic duct contained blood.

Case 6.—Man, about 50 years old, fell ill about two years previously with fever; enlargement of the glands on both sides (one side before the other) of the neck, then in the axillae and groins; pallor and ascites. *Necropsy*: Cervical, axillary, and para-aortic glands greatly enlarged; those on the left side of the neck and in the left axilla were the largest; all these glands were of similar structure, without softening, pale, covered by soft membrane; some were of semi-cartilaginous hardness. Liver rather small, with an irregular and uneven surface, in which there were two or three white nodules. Spleen of moderate size, and free from adventitious deposit. Omentum corrugated. Yellowish ascitic fluid in peritoneum.

Case 7.—Specially communicated under the title, "Cancer cerebri-formis of the lymphatic glands and of the spleen." Man, about 30 to 40 years of age, who for three or four months had had enlargement of submandibular, cervical, axillary, and inguinal glands. Died in Paris in a few days from difficulty in swallowing. *Necropsy*: Masses of enlarged glands from chin to axilla, varying in size and degree of vascularity, each of them enclosed in a capsule; the contents were "brain-like." Similarly altered inguinal and para-aortic glands. Behind the stomach a retroperitoneal conglomerate glandular mass of the size of an adult's head, in the middle of which was a haemorrhage. The vena cava inferior and aorta passed through this mass. Similar alteration in the tonsils. Spleen full of nodules of the brain-like substance, containing fine blood vessels. Apparently there was nothing special in the thorax (not seen by Dr. Hodgkin himself), nor in any other organs.

IMPERIAL CANCER RESEARCH FUND

ANNUAL REPORT

There will be no annual meeting of the Imperial Cancer Research Fund this year. The thirtieth annual report of the Fund, published this week, was submitted to and adopted by the Executive Committee at a meeting held on November 2nd, and has been approved by the president, the Duke of Bedford.

Tribute is paid in the report to the services of Sir Frederic Andrewes, representative of the Royal Society, who died earlier in the year: Professor M. Greenwood has been appointed as his successor. Another severe loss has been that of Sir William Watson Cheyne. Sir Humphry Rolleston has been re-elected as the Royal College of Physicians member, and is chairman of the Executive Committee. Sir Percy Sargent and Mr. Wilfred Trotter represent the Royal College of Surgeons, while Dr. F. C. Minett has been appointed a member of the Pathological and Publications Subcommittee in place of Sir John McFadyean. Dr. F. R. Selbie and Dr. A. F. Watson have been appointed members of the scientific staff. Dr. Petro Jonescu of Jassy, Professor F. Pentimalli of Rome, and Dr. T. Cherry of Melbourne have been given facilities for voluntary work in the laboratories. Sir Frederick Hallett, who has been compelled by illness to resign his post as secretary, has been granted a pension. During the financial year ended June 24th, 1932, the treasurers report that expenditure amounted to a little over £14,000. The

present state of finance has not allowed an increase in the scientific staff, though it is pointed out that the requirements of the work are as great now as they ever have been. A capital sum of £20,000 is promised by the executors of the late Miss E. Wills-Allen for the establishment of a memorial fellowship. The Royal Colleges of Physicians and Surgeons have granted a further lease of the laboratories now occupied by the Fund for a period of seven years, on payment of a premium of £3,700.

In his director's report, Dr. J. A. Murray refers to the work already published in the tenth scientific report (see *Journal*, October 22nd, p. 766), the preparation of which occupied most of the time of the staff during the past year. Publications from the laboratories during the year which are not incorporated in that report comprise two papers by Professor Chambers and Dr. Ludford on micro-dissection and micro-injection of normal and cancer cells grown *in vitro*, Dr. Cramer's survey on the comparative study of cancer, and Dr. H. G. Crabtree's critical essay. A summary of the latter, which occupies the remainder of the annual report, is given below.

METABOLISM OF THE CANCER CELL

The fundamental discovery of Professor Warburg in 1923 created a new outlook in cancer research. The cancer cell was shown to behave abnormally in the essential chemistry of its life processes. Every ten hours it produced an amount of lactic acid equal to its own dry weight, the energy freed as a result of this process being available for the cancer cell's activities. The cancer cell uses the two processes of respiration and glycolysis, and therein lies its distinction from the great majority of normal body cells in higher organisms. Using Warburg's technique, with thin slices of surviving tissue placed in small saline-containing glass vessels attached to manometers, it is now possible to measure respiration and aerobic and anaerobic glycolysis simultaneously. Warburg has, in fact, elaborated methods for the study of tissue metabolism which are quite new and of great ingenuity.

Cancer is an exhibition of an unlimited, incoordinated growth, which implies a constant storage of chemical energy. Respiration and glycolysis constitute the primary energy-yielding reactions, and it was on these that Warburg focused his attention. His cancer work arose in the course of physiological studies of the oxidation processes in sea-urchins' eggs. At the moment of fertilization the respiration increased to six times the value found in unfertilized, quiescent eggs—that is, the transition from "resting" to development was shown in a tremendous acceleration of the reactions supplying energy to the cell. The cancer process is essentially a transition from normal "resting" tissue to rapidly proliferating tissue, and a similar acceleration of respiration was expected. When tested experimentally, however, this proved not to be the case. Even when various substances of importance in nutrition were placed at its disposal no increase in respiration occurred in the cell, but its glycolysing powers were discovered. Meyerhof had already shown an empirical relationship between the formation of lactic acid and the consumption of oxygen. In the first tumours studied by Warburg an exactly similar relationship was found. The discovery of high glycolysis in the cancer cell was naturally followed by a comparison of its metabolism with that of other rapidly growing tissues. Embryonic cells showed as high anaerobic glycolysis as the cancer cell, but in the presence of oxygen glycolysis completely disappeared. In these normal growing cells the vital oxidations effectively prevent the accumulation of lactic acid. Why, then, does glycolysis persist in cancer cells when ample oxygen is available? The conclusion was inevitable that the respiration by tumours was too small to prevent aerobic glycolysis. This idea prevailed until the author (Dr. Crabtree) studied a whole range of mouse and rat tumours, and found that the conception of tumour respiration being too small in all cases proved untenable. In tumour cells two types of defective respiration are