SPONTANEOUS REGRESSION OF THE GLANDS IN HODGKIN'S DISEASE

BY

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In view of the recent emphasis on the treatment of Hodgkin's disease, it is timely to remember that the enlarged glands may regress spontaneously. The purpose of this paper is to report three cases (Cases 1-3) in which this occurred and to refer to others collected from a survey of the hospital records.

In the first patient the regression was so striking and the restoration to apparently normal health so remarkable that the diagnosis was doubted even though supported by a gland biopsy. Only after a recurrence was it accepted. Shortly afterwards the second patient was admitted with a similar story. Meanwhile the diagnosis in the third patient had passed through a similar cycle to that of the first.

A review of the records of the Royal Victoria Infirmary from 1948 to 1952, inclusive, revealed 29 acceptable cases in which to study the occurrence of this phenomenon. All underwent biopsy or necropsy. Five showed it clearly and six less definitely.

Case Reports

Case 1.—A farmer aged 46 attended first on October 2, 1952. One month previously he had developed glands in his neck associated with sweating bouts and persistent itching. Apart from the enlarged glands there and in his groins and axillae, nothing abnormal was found on clinical or laboratory examination. On October 18 he was pyrexial, with further involvement. On gland biopsy the case was reported as being more like Hodgkin's disease than anything else. One month later he said that he was better and that the glands had disappeared. They were, however, just palpable. The diagnosis was doubted and the question of the histology raised, but the pathologist maintained his position. A fortnight later the patient was readmitted with stridor, the glands having enlarged again. All the superficial groups were affected, but particularly the cervical. A final diagnosis of Hodgkin's disease was made and radiotherapy given. On February 17, 1953, he was readmitted with symptoms and signs of bone involvement and marrow replacement. He died three days later. *Necropsy*:—Lymph glands: abdominal mainly involved, pink or mottled red. The liver and spleen were large, the latter being soft, with an early infarct but no Malpighian bodies. *Histology*:—The spleen showed a pleomorphic mixture of lymphocytes, plasma cells, large mononuclears, occasional polymorphs and eosinophils, scanty Dorothy Reed cells, and primitive reticulum cells. The lymph nodes were similar, with some haemorrhages. The marrow showed no haemopoietic tissue but small collections of cells resembling those in the spleen. The liver showed a non-specific picture. *Comment*:—The appearances are like those of Hodgkin's disease, but are not absolutely classical.

Case 2.—A schoolboy aged 14 was admitted as an emergency case on January 2, 1952, complaining of swellings in his right groin for two weeks. His temperature was 103.8° F. (39.9° C.). He was ill and drowsy. He had marked tender enlargement of all the right inguinal glands. There was a small uninfected scratch on the right calf and no lymphangitis. Blood cultures were sterile and his white-cell count was 4,600 per c.mm. He was treated with antibiotics, but his temperature seemed to settle fortuitously. The glands decreased to about half their original size, but

in August others appeared elsewhere. Section showed Hodgkin's disease. He was readmitted on November 26 with visceral as well as glandular involvement. He responded to nitrogen mustard therapy, but subsequently died at home.

Case 3.—A farm labourer aged 36 was admitted on June 7, 1952, as a case of Hodgkin's disease for a gland biopsy. His story was of malaise, night sweats, and a cough of recent onset. His temperature was 99.4° F. (37.4° C.). Most groups of glands were enlarged, and his spleen was palpable two fingerbreadths down. He had signs of collapse at the right base. Chest x-ray examination showed enlargement of the right hilar and paratracheal glands. After pyrexia for five days the swelling of the spleen and glands subsided along with the temperature. He was discharged with a tentative diagnosis of glandular fever in spite of a negative Paul-Bunnell test and differential white count. His general condition improved. He was readmitted with a recurrence and a remittent temperature up to 102° F. (38.9° C.). The glands had enlarged, as were the spleen and liver to four fingerbreadths. The chest x-ray report stated that there was "marked decrease in the glandular shadows but not complete resolution." Biopsy showed Hodgkin's disease.

Case 4.—A miner aged 50 was admitted on March 5, 1952. Eighteen months previously he had noticed lumps first on the right and then on the left side of his neck. They subsided without treatment. Four months before admission they enlarged again. With the glandular enlargement went general symptoms. He was pyrexial, with discrete enlargement of all groups of glands except the posterior cervical and the axillary. Section of a gland showed appearances more like Hodgkin's disease than anything else.

Case 5.—A housewife aged 29 was admitted on February 4, 1952. Her main complaint was of pain substernally after meals and night sweats. She was pyrexial, with epigastric tenderness but no significant glandular enlargement. Chest x-ray examination showed hilar lymphadenopathy. A Mantoux test was positive at 1:1,000, but her sputum was negative for *Mycobacterium tuberculosis*. Tuberculosis or reticulosis was the provisional diagnosis. Following readmission for haemoptysis on February 26, she had a large tender gland above the left clavicle. Biopsy was postponed because she developed a cold and then because the gland disappeared. Subsequent biopsy of a recurrence showed appearances more like Hodgkin's disease than anything else.

In the remaining six cases the decrease in size was not so dramatic, and in two there was a possible focus of infection.

Discussion

There is no reference to this phenomenon in most recent textbooks. Horder and McNee (1950) describe Hodgkin's disease as "characterized by painless, progressive enlargement of the lymph nodes." Cecil and Loeb (1951) make a similar statement, and say that the onset may be associated with oropharyngeal infections, but there is no proof of their connexion. Longcope (1927) states that "the correct conclusion may not be arrived at until the subsidence of the swellings (glands) with complete recovery excludes Hodgkin's disease." It was such statements as these which made our original diagnoses suspect.

Again there are few papers in which it is mentioned. Wallhauser (1933), in a review mainly concerned with pathology, merely says that he has known regression to occur. Symmers (1948), in a paper of similar nature, does not hint at it; nor does Gilbert (1939), although many varied presentations are discussed. Slaughter and Craver (1942) mention a case in which it probably occurred.

Among clinical reports, Baker and Mann (1939) and Goldman (1940) also ignore it. Middleton (1937) briefly mentions it, but without histories. This emphasis upon the progressive enlargement of the glands in Hodgkin's disease seems to be derived from Dorothy Reed's classical paper

in 1902. She, however, was faced with the problem of definition of the disease and therefore had to choose strict criteria for the cases for her studies.

As early as 1911 MacNalty recognized that there was a definite form of Hodgkin's disease associated with a relapsing fever. He noted that sometimes when the temperature became normal the spleen and glands decreased in size. This seems to have been widely forgotten in recent years, although Rolleston (1925) quotes MacNalty.

Hodgkin (1832) himself recorded a case in which the spleen and right glandulae concatenatae (cervical glands) were considerably enlarged, but "under the treatment employed these tumours, as well as that in the situation of the spleen, were at times very considerably reduced in size." This patient, Ellenborough King, was accepted by Fox (1936) as being a true example of the disease on histological grounds. The variations were probably spontaneous. Murchison (1870), who recorded the recurrent febrile episodes now erroneously accorded the eponym of Pel-Ebstein, comments on it clearly. Gowers (1879) stated that "a remarkable diminution in size of the glands may occur," and he refers to the "alternating pyrexia," thus avoiding inaccurate eponymity. Barron (1926) records a case in which the glands subsided, followed by a relapsing fever without a local recurrence.

Variation in the size of the spleen with the temperature is perhaps better appreciated. Whittington (1915) and Baldridge and Awe (1930) each recorded such a case. Jackson and Parker (1947) note that "it is not so well known that an enlarged spleen may diminish in size without any treatment whatsoever." However, they attribute diminution in size of the lymph nodes to the elimination of secondary infection, and add that their virtual disappearance should not be taken as proof that they merely represent chronic inflammation. In support, they give a history, and comment on whether the glands which decreased in size were actually involved with Hodgkin's disease at the time or not. Elsewhere they quote histories, and four more of these contain definite statements of variation in size without treatment, although the diagnosis had not yet been confirmed. Hoster and Dratman (1948) in a comprehensive review, do not refer to it in the clinical section, although elsewhere they quote it in favour of the inflammatory nature of the disease.

Whenever regression of the glands or spleen is recorded and explained, either secondary infection is invoked to account for it or it is implied that the disease may not have been present in these glands. I submit that regression of the glands may occur as part of the natural history of one form of the disease. In Case 1 the diagnosis was thought to be Hodgkin's disease from the biopsy before the decrease in size occurred. Nor was there evidence of infection. It is unlikely that several groups of glands should regress as in Cases 1 and 3 if a local septic focus is the cause. Indeed, where only one group of glands has been involved there is not always a convincing source (Case 2).

The commonest group of glands affected appears to be the posterior cervical and not the tonsillar and superior cervical. It would be reasonable to expect the latter if secondary infection played an important part (Baker and Mann, 1939). Jackson and Parker (1947, p. 67) contrast the rarity of involvement of the tonsils by Hodgkin's disease with its frequent infections. They therefore deny a direct relationship, and suggest that they serve only to light up dormant disease or to draw attention to already enlarged glands. Case 5 shows how this may occur. There was no suggestion of an infection in Cases 1, 3, or 4, while in Case 2 both groups of inguinal glands were enlarged, which would be unusual for such a local lesion.

The reason for the decrease in size is unlikely to be necrosis, as it coincides with restoration to apparently normal health, whereas patients with necrotic neoplasms are usually ill. The enlargement of the glands in Case 1 prevented a proposed further biopsy. So far as our knowledge extends, such behaviour is seen only in some of the leukaemias apart from infections.

The reason for the high incidence of this phenomenon in the series under survey is uncertain. There is nothing to suggest sex, abnormal selection, geography, or inadequate records as a reason. Whatever it is, this phenomenon, which clearly has received insufficient attention in the past, is an important feature of one form of the disease. Such an occurrence is no reason for doubting the diagnosis.

Summary

The glands in a patient with Hodgkin's disease were observed to undergo almost complete regression without treatment.

Out of 29 cases, 5 showed the phenomenon clearly and a further 6 less well.

The cursory attention that this occurrence receives in the literature is noted; there is no evidence that elimination of secondary infection, adduced as a possible explanation, is responsible.

It is submitted that regression of the glands in Hodgkin's disease, often associated with an alternating fever, is an occasional but important variant of its natural history.

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REFERENCES

- Baker, C., and Mann, W. N. (1939). *Guy's Hosp. Rep.*, **89**, 83.
 Baldridge, C. W., and Awe, C. D. (1930). *Arch. intern. Med.*, **45**, 161.
 Barron, M. (1926). *Arch. Path. Lab. Med.*, **2**, 659.
 Cecil, R. L., and Loeb, R. F. (1951). *Textbook of Medicine*, p. 994. Philadelphia.
 Fox, H. (1936). *Guy's Hosp. Rep.*, **86**, 11.
 Gilbert, R. (1939). *Amer. J. Roentgenol.*, **41**, 198.
 Goldman, L. B. (1940). *J. Amer. med. Ass.*, **114**, 1611.
 Gowers, W. (1879). In J. R. Reynolds's *System of Medicine*, **5**, 306. London.
 Hodgkin, T. (1832). *Med.-chir. Trans.*, **17**, 68.
 Horder, Lord, and McNee, J. W. (1950). In *A Textbook of the Practice of Medicine*, edited by F. W. Price, 8th ed., p. 914.
 Hoster, H. A., and Dratman, M. B. (1948). *Cancer Res.*, **8**, 1.
 Jackson, H., and Parker, F. (1947). *Hodgkin's Disease and Allied Disorders*. New York.
 Longcope, W. T. (1927). In Osler and McCrae's *Modern Medicine*, **5**, 255. London.
 MacNalty, A. S. (1911). *Quart. J. Med.*, **5**, 58.
 Middleton, W. S. (1937). *Ann. intern. Med.*, **11**, 448.
 Murchison, C. (1870). *Trans. path. Soc. Lond.*, **21**, 372.
 Reed, D. M. (1902). *Johns Hopk. Hosp. Rep.*, **10**, 133.
 Rolleston, H. (1925). *Lancet*, **2**, 1209.
 Slaughter, D. P., and Craver, L. F. (1942). *Amer. J. Roentgenol.*, **47**, 596.
 Symmers, D. (1948). *Arch. Path. Lab. Med.*, **45**, 73.
 Wallhauser, A. (1933). *Ibid.*, **16**, 522, 672.
 Whittington, T. H. (1915). *Quart. J. Med.*, **9**, 83.

The fifth annual report of the medical officer in charge of the student health service at the Queen's University of Belfast contains an account of some student health services in the United States. The University of Minnesota, for instance, has one of the most advanced student health services in the world. It has been in existence for 32 years and is responsible for the medical care of 17,000 students. The staff consists of a director, an assistant director, 13 whole-time physicians (three of whom are psychiatrists), and 50 part-time physicians and consultants. The staff also includes a sanitary engineer and four sanitary inspectors responsible for the public health of the university campus. The service maintains its own laboratory, x-ray and ophthalmic departments, dental clinic, and a separate 50-bed hospital. The present hospital building was built four years ago and is magnificently equipped. The student health service is self-supporting and receives no funds from the general university budget. Each student pays a fee of five dollars a quarter, which entitles him or her to the initial medical and x-ray examination and four days in hospital. Fees are charged for special examinations, drugs, dental treatment, and any stay in hospital above the allotted four days. The main aim of the service is the care and treatment of the individual student during illness, and the service is used by about 80% of the student population. It is less expensive to the student than private or other hospital services.