GLANDULAR FEVER.

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Glandular Fever may be described as an acute infectious disease characterized by fever, general enlargement of the lymphatic glands, and changes in the blood, especially mononucleosis and the presence of heterophile antibodies.

The disease has had a curiously thorny path in its struggle for recognition as an acute infection *sui generis*. This is the more strange as the disease is by no means rare, occurs in epidemics in schools and other institutions, and nowadays is diagnosed on clinical grounds with little difficulty.

Historical.

The disease was first described in 1889 by Pfeiffer in Germany under the title "Drüsenfieber." He gave a good description of the common type as it occurs in children. But he stated definitely that the axillary and inguinal glands were not enlarged and it was not until 1894 that Desplats recognised the frequency with which these were involved. This was an important observation as it proved that the glandular enlargement is due to a general infection and is not merely an enlargement of the cervical glands secondary to some tonsillar infection. In 1896 Park West described an epidemic in America and in 1897 Dawson Williams wrote the first description in this country. But most of those who wrote on the subject considered that it was a form of influenza or that the enlargement of the cervical glands was secondary to some tonsillar infection. The entity of the disease was not accepted and the condition caused little interest.

By the commencement of the Great War the disease was dead so far as literature and recognition was concerned. During the War not a single article with this title appeared in the literature of any country, and Burnford is the sole observer who suggested the diagnosis in a group of cases. Yet we know now that epidemics of considerable severity occurred among the troops, and it is quite easy to recognise the diagnosis from the description given by some of those who were attacked. But during this series of years articles were published from time to time recording cases of innocuous lymphocytosis, practically always diagnosed as leukæmia in which recovery had occurred. When A. J. Hall published such a case in 1915 Parkes Weber called his attention to other cases in the literature and it was then recognized that they belonged to some entity not yet separated.

In 1920 Sprunt and Evans in America published a series of cases in which they recognized the development of what they named "infectious mononucleosis." They were probably unfamiliar with Pfeiffer's disease to which no reference was made. In March 1921 Morley and I recorded a case which we had diagnosed as Glandular Fever in the previous year and in which we had found lymphocytosis. This was the first case recording lymphocytosis in Pfeiffer's glandular fever.

In the course of the next ten years the identity of infectious mononucleosis and glandular fever was gradually accepted and the existence of so characteristic a feature as an absolute lymphocytosis lead to its increasing diagnosis.

During this period there were long discussions on the Continent as to the nature of a condition known as monocytic angina. These cases were first recognized in Fever Hospitals to which they had been sent with a diagnosis of diphtheria and in which the existence of an absolute lymphocytosis was originally found by chance examination. The dispute among the German authorities was very largely as to whether the cells were lymphocytes or monocytes, the connection with glandular fever being entirely overlooked. Indeed, it is only in the last four or five years that glandular fever has been accepted in many Continental countries. Monocytic angina has not played a great part in the literature of this country or of America where it has been accepted as a form of glandular fever.

Up to 1930 the disease was only known as an acute enlargement of glands occurring in children, and as the milder types among adults, mainly recorded in America.

In 1930 an extensive epidemic of glandular fever occurred in this country which differed widely from previous epidemics. The patients were mainly adults and there was a long prodromal period of two or three weeks during which rashes occurred in many cases. In the types already known eruptions are so unusual that their existence had been completely denied, though it is now known that their frequency was overlooked owing to their transitory nature. A further characteristic of the 1930 epidemic was the long duration and the severity of the constitutional symptoms. This epidemic would appear to be the fully developed course of glandular fever of which the forms previously known in children and monocytic angina may be regarded as variations or abortive types. There were many local epidemics in different parts of the British Isles which were very largely diagnosed as typhoid in spite of their negative agglutination reactions. But the blood contains an even more curious feature than the absolute lymphocytosis, the discovery of which so surprised hæmatologists and clinicians. In 1932 Paul and Bunnell in the course of a routine investigation discovered the existence of heterophile antibodies in the blood of cases of glandular fever. The test is quickly performed in any reasonably equipped laboratory and appears to be practically pathognomonic for glandular fever.

It will now be seen that we can recognize three groups of glandular fever, first the glandular type as described by Pfeiffer, (2) an anginose type usually described as monocytic angina on the Continent, and (3) the febrile type which was first fully recognized in the British epidemic of 1930.

The disease exists in all temperate zones. There is no satisfactory proof of its presence in the tropics but it may be confused with the many other glandular enlargements which occur in those parts. It is infectious but not highly so, and it is unusual to see more than one case in a family household. On the other hand, nearly everyone is susceptible, and when two or three cases occur in a school and mass infection is at work a large majority of the children will be affected.

The virus is at present unknown. In the 1930 epidemic Bland showed that infection could be transmitted to rabbits by injections of blood taken from cases early in the disease, and that it could be transmitted from one generation of rabbits to another. It has recently been shown that the blood of such rabbits contained the characteristic heterophile antibodies (Bernstein). Bland believes that the virus is a protozoon of the order toxoplasma.

The incubation period is most commonly between five and twelve days but there is evidence that it may be considerably longer, even up to twenty days or more.

Clinical Pictures.

(1) **Glandular Type.** This form is commonest between the ages of six and fifteen years. No age is immune but in adults it is usually contracted from children and occurs in a mild abortive form.

There is a prodromal period of one to four days with the usual symptoms of pyrexia and malaise. The symptoms may attract little attention and apparently may be completely absent. There may be some complaint of sore throat but it is rarely severe. The cervical glands nearly always enlarge first and the enlargement may take place with great rapidity. It is not unusual to find a large visible mass present in the evening when the nurse is quite confident that nothing was visible in the morning. The most characteristic glands are deep to the sternomastoid, about the middle of its length and just below the angle of the jaw, but any of the glands of the neck may enlarge. There may be some discomfort on moving the head but there is rarely any appreciable tenderness on palpation. Occasionally there is pain and a spasm of the neck muscles and there may be torticollis for a few days. The axillary and inguinal glands are commonly though not invariably enlarged.

In the neck the enlargement is usually unilateral at the onset.

The spleen becomes palpable in about half the cases but is rarely greatly enlarged. The liver may also be palpable and is sometimes tender.

There has been considerable discussion as to whether the parotid glands are involved. Personally I am satisfied that I have never seen an instance in which the parotid over the jaw was enlarged.

The constitutional symptoms are slight although the temperature often rises to 103°F. or 104°F. with the enlargement of the glands. In spite of this the patient does not appear or apparently feel particularly ill. Rashes are most unusual in this type. On examination of the fauces there may be general reddening and the tonsils may be enlarged but, as Pfeiffer observed, the enlargement of the glands is out of proportion to the faucial manifestations.

The main enlargement of the glands tends to subside in the course of three or four days and with it the temperature settles and the constitutional symptoms pass. But the glands may be palpable for many weeks or even months.

The blood changes may now be referred to. The lymphocytosis develops with the enlargement of the glands and attains a maximum in a day or two. In the majority of cases the total white cells are not greatly above the upper limit of

normal, although to this there are many exceptions. Most of the counts are in the neighbourhood of 12,000 to 15,000. Over 30,000 is rare and 40,000 to 50,000 may be regarded as the maximum. The percentage of lymphocytes is usually between 60 and 80 per cent. though figures above 90 per cent. have been recorded on many occasions. Yet the proportion never reaches the extreme figures of 99 per cent. and over, which are frequently observed in lymphoid leukæmia. The pathology of the mononuclear cells is interesting and differs widely from that seen in lymphoid leukæmia. The predominant cell is usually a large mononuclear, with almost clear cytoplasm and a somewhat irregular nucleus with an appearance often described as foamy. The blood picture usually changes rapidly and in the course of a further day or two there may be numerous varieties of mononuclear cells present. These are probably normal and abnormal cells derived both from lymphoid and reticulo-endothelial tissues. Such a picture of mixed types and rapid variations is not seen in lymphoid leukæmia. As the condition returns to normal there is an increase in the number of small lymphocytes.

It is important to remember that the initial change in the blood is a polynucleosis and that this occurs in the prodromal periods of any type of glandular fever. As in the case of the lymphocytes, the counts are often within the higher limits of normal but such figures as 30,000 white cells with 80 per cent. of polynuclear cells are occasionally recorded. The polynucleosis passes away as the glands enlarge and the lymphocytosis develops. But unless this initial polynucleosis is recognized and remembered errors of diagnosis will frequently be made on the examination of the blood.

The course and prognosis in this type may be said to be uniformly good although recrudescences and relapses are not uncommon. A slight degree of debility and anæmia frequently develops a few weeks later and may last for six to twelve months. An interesting illustration of this was in a boys' school in which an epidemic of no great severity occurred in the Easter term. In the next term the school lost every one of their cricket matches.

(2) Anginose Type. This is seen most commonly between the ages of 15 and 25 years. No age is immune, but in infants and younger children it rarely attains the severity seen in young adults.

There is a long prodromal period often lasting two or three weeks during which malaise gradually develops and there is increasing complaint of sore throat. Finally a membrane develops with great rapidity and the patient becomes acutely uncomfortable. The membrane is not strictly confined to the tonsils and may extend on to the uvula and in appearance, colour and distribution is often indistinguishable from diphtheria with which naturally it has frequently been confused. The cervical glands are always palpable at the time that the membrane is present but rarely to the extent which is found in the glandular form, and the characteristic glands beneath the sternomastoid are not always recognizable. This is partly due to the frequency of oedema. The axillary and inguinal glands are also frequently enlarged and the spleen usually becomes palpable. The temperature is often 104°F. or 105°F. and the pulse is rapid. But in spite of these features the patient does not appear to be especially ill and there is no tendency to collapse, although naturally the condition of the fauces with the laryngeal oedema causes grave discomfort. The membrane never spreads to the nose or to the larynx and laryngeal obstruction is unknown.

The membrane tends to persist for several days but without increase of constitutional symptoms, thus differing widely from the course of diphtheria. As the membrane separates, the temperature usually falls rapidly and the constitutional symptoms improve, though sometimes pyrexia may continue at about 100° F. for several days or even a week or two. In rare cases pneumonia may develop, but otherwise there are no serious complications. The glands in many cases appear to be on the point of suppuration, but actually this is a rare event. Recovery is complete.

(3) Febrile Type. This may be regarded as the fully developed course of glandular fever. It is seen in its most characteristic form in young adults. In children it is less common and less severe.

Three stages may be described (1) *Stage of Invasion*. The onset is usually comparatively sudden with headache, pyrexia, and general malaise. Sore throat is rare. The temperature is irregular and there is nothing pathognomonic in this stage, the glands not being palpable. This stage usually lasts from three to seven days, but may be longer. (2) *Stage of Eruption*. A rash commonly develops on the fourth or fifth day, but may be delayed as late as the tenth. In its characteristic form it may be described as a maculo-papular eruption which closely resembles and may even be indistinguishable from typhoid. The rash consists of small pink or pinkish-brown spots which fade on pressure, are few in number and are scattered over the trunk and back. There is usually only one crop which fades in about four days, but other crops are not unknown. A rash is not invariably present but it may be recognized in nearly all adults. With the onset of the eruption the temperature rises to 103°F. or 104°F. Constitutional symptoms become more marked and there may be recurrent rigors and very severe sweating. This stage lasts for two weeks or more, and the patient may become greatly exhausted, especially when anti-pyretics are administered. It is about this time that the Wassermann reaction may be temporarily positive. (3) *Stage of Glandular Enlargement*. The glands commonly enlarge about the end of the third week, though it may be distinctly later. With the enlargement of the glands the temperature again rises to 103°F. or 104°F., having fallen towards the end of the previous stage. Sore throat is rare, and the constitutional symptoms do not become more severe. Gradually the glands and the temperature subside, and after several weeks convalescence sets in. Recurrences are very common and may lengthen the duration to many weeks or many months. The last stages of the febrile course are often exhausting and the patient may be left in an extremely debilitated state, but the ultimate prognosis is almost uniformly good and fatalities are extremely rare.

Variations in Type. Between these three groups as described all varieties may be recognized. The type known in America as Infectious Mononucleosis is a mild febrile form which occurs with considerable frequency among medical students and nurses. It is not commonly seen in this country, although I have met with several cases, especially recently.

Rashes. Besides the maculo-papular eruption already referred to, a rubelli-form type may occur which is possibly a confluent form of the macular eruption. It is most common in young children, but no age is exempt. It may be identical with the eruption of true rubella, and the difficulty in diagnosis is increased by the fact that the occipital glands are sometimes enlarged in the atypical forms.

Complications. *Suppuration of the glands* is very rare in glandular fever. This is often a striking feature in the anginose form in which the glands appear to be on the point of suppurating, but usually subside without further trouble. *Hæmaturia* was mentioned by Pfeiffer in his original communication. Its frequency and importance has become exaggerated as it is certainly rare, and many large epidemics have occurred without a single instance. It appears to be quite innocuous and I have watched several cases over a course of years without having seen nephritis develop. *Epistaxis* is by no means uncommon in the early stages in growing children and it may be sufficiently severe to cause anxiety.

Other hæmorrhages are rare, but on one occasion I have seen rectal hæmorrhage in a child. Purpura has been recorded. Jaundice was a fairly common manifestation in the 1930 epidemic in adults, but is very rare in children. It has no bad diagnostic signification. Conjunctivitis is by no means uncommon at the onset but subsides without further difficulty.

The presence of Heterophile Antibodies in the Blood.

This curious phenomenon was discovered by Paul and Bunnell in 1932. Heterophile antibodies are hæmolysins and agglutinins to sheep's red cells in the blood of a human being. They are known to be present following injection of horse serum. In the course of a routine examination Paul and Bunnell found that they were present in the blood in glandular fever and in no other known disease. This has been confirmed by large numbers of investigations subsequently. A very few atypical results have been recorded, but it may practically be taken that a titre of over one in sixty-four is pathognomonic of glandular fever.

Diagnosis.

A reasonable familiarity with the clinical manifestations, the changes in the cells, and the use of Paul and Bunnell's test, should remove much of the difficulties in diagnosis in the future.

Treatment.

Treatment is in general symptomatic. In simple cases of the glandular type patients should be kept in bed until the temperature has been normal for a few days and the mass of the glands has subsided. The glands should be covered with cotton wool and kept warm. The prolonged febrile type leads to great exhaustion and needs careful nursing and attention on the usual lines.

It is unknown how long cases remain infectious, but probably the greatest degree of infectivity is in the early stages.