GLANDULAR FEVER.

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GLANDULAR FEVER was first described by E. Pfeiffer in 1889 under the title "Drüsenfieber." It may be defined as an acute infectious disease principally of children, characterized by rapid enlargement of the cervical glands and by a less constant enlargement of the liver, spleen, axillary, inguinal and other glands. The disease is rare, but there is some reason to believe that a considerable number of cases are occurring at the present time.

The largest epidemics are those recorded by Park West, 96 cases; Botschkowsky, 54 cases; Byers, 33 cases; Stark, 30 cases; Tschajagajew, 24 cases. Korsakoff has reported 29 cases observed over a course of years.

Pfeiffer stated in his original article that the disease occurred in small epidemics, and especially in "house epidemics"; when one child of a family was affected the others rarely escaped. Subsequent observers have agreed that it is infectious. Fisher records 8 cases in one family, and Chapman 5 in his own household. Park West observed an epidemic in a country district in Ohio, and saw 96 cases in the course of three years, besides hearing accounts of at least 40 others. The 96 cases occurred in forty-three families, about 20 children in the affected families not being attacked. He states that the epidemic spread irregularly, the houses attacked not being in any special contiguity or social connexion with each other. Von Starck's 12 cases occurred in eleven families, Haas's 12 cases in ten families, and Schiller's 11 in nine families. Schäffer's 21 cases occurred in the space of four months in an institution for children, but there is no statement as to the total number of inmates. Numerous sporadic cases are also on record. Authorities agree that it is more common in the spring months.

CLINICAL FEATURES.

The incubation period has been noted by many observers and may be stated to be 5 to 10 days, most commonly 7 or 8 days. The extreme limit may be longer.

The disease is principally one of childhood. Botschkowsky had the experience, apparently unique, of observing an epidemic of 54 cases in a battalion of soldiers. Apart from this, it is probably correct to say that at least 80 per cent. of recorded cases were under the age of 12 years, and the majority between the ages of 5 and 9 years. Park West's youngest patient was 7 months and the eldest 13 years. He had no case in an adult. Robertson has reported a case in an infant of 6 months. The youngest of Schäffer's cases was 4 months old and the eldest 16 years.

Adults, however, are certainly not immune. In the series of 464 cases there are 20 adults (excluding Botschkowsky's epidemic), the majority being young mothers of affected children; three patients were over 40 years of age. In adults the condition tends to be very mild and malaise slight, though Korsakoff saw a severe case with nephritis. There is no record of its occurrence during the war. The condition is, however, easily overlooked and may be mistaken for aberrant mumps, though one of us (H. L. T.) spent eighteen months in a hospital for infectious diseases in France without recognizing its entity or calling to mind its existence.

The onset is sudden, with the usual symptoms of an acute pyrexial attack in children: restlessness, loss of appetite, constipation, furred tongue, rapid pulse, and occasionally vomiting. Abdominal pain is sometimes present, and may be severe.

Enlargement of the Lymphatic Glands.

This may be present with the earliest symptoms or develop rapidly within twelve to forty-eight hours. The glands constantly affected are the cervical glands, deep to the sterno-mastoid muscle about the middle of its length. The enlargement is marked, and produces a definite swelling of the neck. On palpation several discrete glands are felt, often the size of walnuts. Robertson records glands as

large as a hen's egg in an infant of 7 months, and states that they were painless. The skin is not reddened, and the tissues are not oedematous.

The cervical enlargement is commonly unilateral at the onset. The glands on the opposite side frequently, but by no means invariably, enlarge later, usually within two to four days of the onset, but occasionally not until the first side has subsided to a varying degree. In Schäffer's series of 21 cases the cervical enlargement was unilateral throughout in 11, bilateral from the onset in 3, and affected first one side and then the other in the remaining 7. Some authors state that the left side is much more commonly affected than the right, but there is no definite agreement on this point. Other glands in the neck may enlarge subsequently, but to a much less extent. The initial enlargement is below the level of the angle of the jaw, and the position and general condition of the swelling differs from that of glands secondary to infections of the tonsils, teeth and nasopharynx.

The parotid and submaxillary glands are not affected. The submaxillary glands were enlarged in one case of Schäffer's and in one of Trautmann's, but not in others of their series. The parotid was enlarged in one case of Hörschelmann's, but it is doubtful if this group was really glandular fever. Enlargement of the parotid, submaxillary, epitrochlear and many other glands is referred to by Haas, but without quoting instances. By no other writers are they stated to be enlarged; nearly all have specifically mentioned their absence, and it may be accepted that the parotid and submaxillary salivary glands are not affected. The submaxillary lymphatic glands and possibly the pre-auricular gland may, however, be enlarged.

Enlargement of the axillary and inguinal glands has been noticed by most observers. Park West states that they were palpable in 75 per cent. of his cases, and enlargement has been recorded by Trautmann, Bellotti, Korsakoff, Haas and many others. Pfeiffer, in 1889, said that they were not affected, but Von Starck had noticed them in his series of 12 cases in 1890. Schiller did not find them in his 11 cases, and a few recorders of individual cases noted their absence. It may, however, be accepted that they are palpable in the majority of cases, but never attain the size of the deep cervical glands.

Pain and tenderness of the cervical glands may be entirely absent; there is usually some pain on movement of the head, but palpation of the glands even in the acute stages may be painless. Some pain and difficulty in swallowing may be complained of, and is referred not to the fauces, but under the level of the isthmus of the thyroid.

Enlargement of the mesenteric glands has been much discussed, and involved with this is the occurrence of abdominal pain. Pfeiffer noted pain in the abdomen as one of the characteristics, and stated that it was localized exactly in the mid-line below the umbilicus. Others have not supported this exact localization, and it may evidently be more generalized, but its presence has been repeatedly recorded. Byers does not mention its presence or absence in his group of 33 cases, but with this exception it is referred to by all others who have observed many cases. Park West states that some degree of abdominal pain or tenderness occurred in about 75 per cent. of his 96 cases. The pain may be very severe, as in specific cases published by Dawson Williams, Rudolf, and others.

The mesenteric glands may be definitely palpable. Many writers have not referred to them, but Korsakoff, Haas, Bellotti, and others record their presence. Jones states that they are palpable in 40 per cent. of cases. Park West said that he felt them in 37 of his 96 cases, and believed that the number would be larger if he had examined the earlier patients more carefully.

There is some evidence that the *peribronchial glands* may be affected. Von Starck in 1890 recorded the occurrence of a paroxysmal cough resembling whooping-cough, but without the whoop, and suggested that this was due to the pressure of enlarged peribronchial glands. Similar paroxysmal coughs have been noted by several French writers (Moussous, Comby, and Labbé); on the other hand, nearly all the writers state that no cough occurred and that no abnormal signs were present in the lungs. It may be accepted that the lungs are unaffected.

The only recorded autopsy is Korsakoff's. There was definite enlargement of the axillary, inguinal, peribronchial and mesenteric glands, but in this case the cervical glands had suppurated.

OTHER SIGNS AND SYMPTOMS.

The condition of the tonsils and pharynx has been closely observed. Pfeiffer's attention appears to have been attracted to glandular fever owing to the disproportion between the size of the glands and the changes in the fauces. A slight reddening of the pharynx, he says, is the most that is present, and frequently there is no obvious change. Subsequent writers have fully confirmed his observation; thus Park West, Byers, Stark, Korsakoff and Schäffer record absence of tonsillitis in any of their cases, which make a total of 209. Stark's 30 cases occurred amongst children of the London area in whom diseased conditions of the tonsils and pharynx notoriously are very common. Park West states that in his series there were 29 cases with some reddening of the pharynx, and 4 had definite pharyngitis. It may be accepted that usually there is no obvious abnormality of the fauces, but that occasionally there is slight reddening of the pharynx, which bears no relation to the size of the glands.

No rash accompanies the condition; Heubner, who spoke at the same meeting as Pfeiffer in 1889, stated that in some similar cases he had seen urticaria was present. Korsakoff, in 1905, says that herpes labialis occurred often in his series, but the only other recorded case is one of Schäffer. Erythema multiforme is recorded in two cases by Tschakowski; scarlatiniform eruptions occurred in one case of Botschkowski, and in one case of Hörschelmann. Thornton published a case of glandular fever associated with erythema nodosum; this patient was a child of 5½ years, in whom a mitral systolic murmur was present on first coming under observation, and it is impossible to exclude the occurrence of rheumatic fever. There is no record of any other rashes, and these exceptions are obviously negligible in a series of 464 cases, mainly in children.

It may be accepted that there is no eruption associated with glandular fever.

Epistaxis may occur at the onset, which is not surprising if we are to regard glandular fever as an acute specific infection. It is, however, rare. The first instance was recorded by Chapman in 1897, among 5 cases in his own family, epistaxis occurring in 4. It also occurred in 2 cases of Trautmann's, in two of Schäffer's, and in 1 of Rudolf's. It is mentioned by Tschakajew and Comby. There is no record of other cases. When it takes place it is apparently profuse.

Vomiting occurs occasionally at the onset.

The pulse may be rapid, while the temperature is high, but cardiac complications do not occur.

Constipation was mentioned by Pfeiffer as being severe. It may terminate with diarrhoea or with the discharge of slimy motions at the end of the first week. The early writers refer to this sequence as almost a characteristic symptom of glandular fever, and considered that convalescence commenced with the discharge of mucus. Constipation, while evidently common, is by no means invariable, and it is doubtful whether much stress should be laid on it.

The liver and spleen are enlarged in a considerable proportion of cases. Pfeiffer noticed that in the severer cases both were palpable, and the majority of subsequent writers have confirmed this. Park West noted that the spleen became palpable in 57 of his 96 cases, and that the liver was enlarged in 87. Korsakoff did not note any definite relation between the enlargement of the spleen and the severity and duration of the illness. There is some disagreement as to the frequency with which the spleen is palpable. Byers, recording 33 cases, does not mention the liver or spleen, and possibly may have overlooked them. Stark mentioned the spleen only once in 30 cases, nephritis being present in this instance. Schäffer states that the liver and spleen were not palpable in any one of his 21 cases. On the other hand, Jones, who refers to 20 cases, states that the spleen was palpable in 80 per cent. and the liver in 90 per cent., and Schiller felt the liver and spleen in each of his 11 cases. Such differences may be partly due to variations in different epidemics and series of cases. Probably it is partly due to individual observers, since it is well known that the recognition of the tip of the spleen is frequently a matter of difficulty and doubt.

From a general study of the literature it appears undeniable that the spleen is palpable in a considerable number of cases, which may be placed at about 50 per

cent. Pfeiffer states that it usually becomes palpable at about the fourth day, but there are no other observations for checking this opinion. In our case it was just felt on the third day and easily palpable on the fourth.

The temperature usually rises to 101° to 103°, occasionally it may be as high as 104°. It corresponds roughly with the size and duration of the marked glandular enlargement, usually being maximum on the third or fourth day, then falling rapidly and becoming normal early in the second week. When the onset is unilateral the temperature may fall as this side subsides, and then rise again as the opposite side enlarges or if it recurs on the same side. Schäffer noticed such relapses in 10 cases. In mild forms there may be no rise of temperature, as noted by Schäffer and others. In Botschkowsky's 54 cases in adults 10 were apyrexial. The fall may be so rapid as to suggest a crisis, as in some cases of Park West and Von Starck, but usually it is more gradual.

Bacteriological investigations have been principally directed to cultures from the fauces, and, as may be expected, they resulted in the growth of streptococci, staphylococci and pneumococci, with influenza bacilli in a certain number of cases. The earlier observers dealt very fully with these investigations, but little importance will now be attached to them.

Cultures from the glands themselves have been made only in a few cases in which suppuration occurred, and in these streptococci have always been present. In Korsakoff's fatal case streptococci were found in the heart blood and other sites in cultures taken twelve hours after death. The glands had suppurated and the child died with the symptoms of septicaemia. Tschakowsky claimed that in 3 cases he isolated influenza bacilli from the blood during life. As Schäffer points out, these results must be accepted with caution, as it is stated that the bacilli were isolated on a simple agar medium without blood, and subsequent subcultures were grown on the same medium. Schiller found influenza bacilli, together with streptococci and staphylococci, in the pus from a gland. Loude and Froin in one case isolated pneumococci from the blood. The patient's father had had lobar pneumonia three weeks previously, and they suggest that this was a direct infection.

A general review of the bacteriological investigations reveals nothing specific.

There are very few records of examination of the blood, and these are either scanty or made in cases in which suppuration of the glands had occurred. Jones gives the following results in two cases:

Case 1.—On sixth day, leucocytes 14,900 per c.mm.; on ninth day, leucocytes 8,900 per c.mm.; red cells 4,000,000 per c.mm.; haemoglobin 90 per cent.

Case 2.—On eighth day, leucocytes 7,000 per c.mm.

In one of Rudolf's cases the glands subsided but enlarged again a month later and suppurated. When it was suspected that pus was forming frequent blood counts were carried out, but "showed no leucocytosis."

Just before the operation the blood count was: Leucocytes, 7,000 per c.mm.; red cells, 4,500,000; haemoglobin, 80 per cent.; polymuclear neutrophils, 60 per cent.; no abnormal cells. After the operation the number of leucocytes was "about doubled" for a few days.

These are the only instances in which definite blood counts are referred to, and no other details are given. Many observers mention the subsequent development of anaemia and its obstinate character.

Complications are rare. Nephritis is the most important. It was mentioned by Heubner in remarks made at the meeting at which Pfeiffer read his original article, and has been referred to by many subsequent writers. When it occurs it is frequently, usually in severe cases, stated to be a "haemorrhagic nephritis." The onset is at the commencement of the illness or within a few days. There is no record of the occurrence of oedema. All writers agree in stating that nephritis never becomes chronic, but the evidence is scanty and cannot be regarded as conclusive. The summary of the statistics given in articles in which both the total number of cases and the number of cases of nephritis is given shows 17 instances of nephritis in a total of 270 cases—an incidence of 6 per cent. There is no record of the occurrence of purpura or of any other form of haemorrhage except the initial epistaxis.

Suppuration of the glands is a very rare occurrence, indeed the earlier writers deny that it ever took place. Only 9 instances are recorded in the literature. One of these, Korsakoff's, was fatal. In all cases in which bacteriological investigations were made streptococci were present; staphylococci or other organisms are also mentioned occasionally. In Rudolf's case the glands subsided, but enlarged again one month later and then suppurated. In all recorded cases the suppuration was confined to the cervical glands.

Otitis media is recorded in 4 cases—in 2 of Schäffer's and in 2 of Durno's. In one of Schäffer's cases the glands had suppurated. There is no mention of otitis media elsewhere in the literature.

Pulmonary complications are confined to the observations of a paroxysmal cough referred to above. Coryza is mentioned by one or two writers, but most observers definitely refer to the absence of any catarrh. There is no record of the occurrence of orchitis, and the diagnosis of pancreatitis has never been made.

PROGNOSIS.

The prognosis is favourable. The enlargement of the glands usually reaches its maximum about the third or fourth day, and after a further two or three days the glands rapidly diminish in size. At the end of one to two weeks there is no visible swelling, the temperature is normal, and definite symptoms of malaise have passed away. Recurrences are not infrequent, and, as has been mentioned above, there may be either an enlargement of the glands on the opposite side to that originally affected or a return of swelling on the same side. Such recurrences are accompanied by pyrexia and prolong the acute stage.

The slowness of convalescence has attracted the notice of many observers. The glands, though no longer visible, often remain palpable for many weeks or even months. Anaemia is frequently referred to as developing during convalescence and persisting for a considerable time. The general health is poor during this period. Complete recovery finally takes place. No second attacks have been recorded.

Only four fatal cases are recorded in the literature. In Park West's fatal case the child had been previously in poor health. Bellotti had two fatal cases in children, aged 1½ and 3 years; both began with the ordinary symptoms and the glands subsided, but cachexia developed and was finally fatal. In Korsakoff's case the cervical glands suppurated.

This is the only instance in which an autopsy is recorded, and, unfortunately, findings are complicated by the probability that death was due to septicaemia. The cervical, peribronchial and mesenteric glands were greatly enlarged, and the axillary and inguinal glands slightly. Microscopic sections of the glands were said to show hyperplasia of the parenchyma, with signs of inflammation. There was no evidence of tuberculosis or lymphadenoma; ecchymoses were present on the pleura; in the left pleural cavity was 8 oz. of fluid. The spleen was enlarged. The kidneys were in a condition of glomerulonephritis. Streptococci were present in the pus of the cervical glands before death, and twelve hours after death were isolated from the axillary glands, liver, spleen, kidneys, bone marrow, and heart blood.

The following is the account of a case which has been under our observation:

C. G., male, aged 8 years. First seen on July 1st, 1920. Previous health very good. Measles in April, 1920. Had been somewhat irritable for three or four days previously. The parents noticed swellings in the neck on June 30th, and on July 1st the father noticed that the glands were enlarged "all over the body." Slight nausea on previous day, but no vomiting. The general condition was good. He had a good colour and no evidence of anaemia. There was no sore throat. On examination: The lymphatic glands in the neck were markedly enlarged. Deep to the sterno-mastoid and about the middle of its length on both sides were several glands about the size of walnuts, causing a definite prominence in the neck, especially on the right. There was no superficial oedema, and the glands on palpation were discrete, suggestive of the condition found in Hodgkin's disease. Palpation was almost painless. On the right side the superficial submaxillary

lymphatic gland was greatly enlarged and bulged away from the jaw. It could be distinguished from the deeper lying salivary gland. The other glands in the neck were also enlarged, but to a much less degree. The axillary glands were enlarged on both sides. In the groin there were two large glands on the right side and smaller ones on the left. In the abdomen two large mesenteric glands were easily palpable just to the right of the umbilicus and slightly below it, and they were somewhat tender. It was thought that the tip of the spleen could be felt. There was no purpura or haemorrhages. The tongue was slightly furred. The fauces showed no abnormality and the mouth was quite clean. The heart and lungs were normal. The urine contained no albumin or sugar, and remained normal throughout. There were no septic foci in the scalp, ears, or elsewhere except one carious molar on the left side, which was painless. The temperature was 100°. On July 3rd the temperature was 103°, but the general condition remained good, and the boy was hungry and wished to be allowed to get up. All the glands were larger and the spleen was now definitely palpable. On July 4th the temperature fell rapidly, almost suggesting a crisis. The glands in the neck were distinctly smaller, but the spleen

was now nearly two finger-breaths below the costal margin. The other glands were unchanged. The bowels were opened freely on this day, constipation having been present previously. On July 5th the glands in the neck were again smaller and continued to diminish rapidly from this date. The remaining glands, however, diminished more slowly. By July 11th the patient felt perfectly well and was allowed up. The glands

were still diminishing and the spleen was only just palpable. On July 18th the spleen was no longer felt. The glands in the groin appeared slightly larger and the other glands about the same as a week previously. The child appeared somewhat paler than before, and the mother said that he was easily tired.

Subsequently progress was uninterrupted, but the glands, even at the present time, remain palpable. The blood counts are recorded in tabular form. The percentage of lymphocytes is very striking. It rose to a maximum on July 5th and then probably commenced to diminish, at first rapidly and then more slowly, and it is now approaching normal. The large and small lymphocytes are classified together, but throughout large lymphocytes predominated, and on July 5th formed

Examination of Blood.

Date.	Erythrocytes.	Haemoglobin.	Leucocytes.	Polynuclear Neutrophils.	Eosinophils.	Lymphocytes.	Large Hyaline.	Mast Cells.
1920.		%		%	%	%	%	%
July 1 ...	—	—	15,000	23.0	1.0	74.5	1.0	0.5
July 3 ...	4,830,000	90	14,400	19.0	0.8	77.4	2.4	0.4
July 5 ...	4,850,000	—	—	12.2	0.8	84.6	2.0	0.4
July 11 ...	4,850,000	—	9,000	24.6	1.4	71.0	2.2	0.8
July 18 ...	5,200,000	—	7,800	36.0	1.0	58.0	4.5	0.5
July 25 ...	4,800,000	90	8,100	35.5	1.5	59.5	2.5	1.0
Aug. 1 ...	4,750,000	90	10,000	40.0	2.5	55.0	2.5	—
Sept. 15 ...	5,100,000	100	—	43.4	1.6	50.4	4.2	0.4
1921.								
Jan. 8 ...	5,300,000	100	16,000	57.8	1.4	38.2	2.0	0.6

72 per cent. of the total white cells. There were no abnormal leucocytes and no abnormal erythrocytes. Apparently there was a slight but persistent anaemia. The Wassermann reaction was negative.

Other children in the family were not affected, but the patient was isolated early in the attack.

It is probable that a patient under the care of one of us at the Great Northern Hospital was also an example of glandular fever.

This was a boy, aged 7 years, admitted on December 8th, 1920. Malaise had commenced twelve days previously, and after two days the glands in the neck were noticed to be enlarged. They subsided rapidly, and after a few days in bed he was allowed to get up, when it was noticed that the urine was "blood red," and also that the face was swollen. The red urine lasted about a week. On admission he looked pale and the glands in the neck were palpable. The fauces were clear. There were a few small glands in the axillae and groin. The

urine contained albumin and casts. The blood count on December 16th was as follows:

Leucocytes	...	...	...	13,500 per c.mm.
Polynuclear neutrophils	...	...	...	60 per cent.
Lymphocytes	...	...	...	35 "
Eosinophils	...	...	...	2 "
Large hyalines	...	...	...	5 "

A trace of albumin was still present on discharge on December 31st. There were six other children in the family, none of whom were affected.

A third case has also been under observation at St. Thomas's Hospital, but the glands had almost subsided when the patient was first seen. The blood and urine were normal. Another child in the family had been similarly attacked about a week previously.

ETIOLOGY AND PATHOLOGY.

The nosology of the disease presents several questions. Is it an acute infectious disease? If so, is it a specific disease or an aberrant form of some common fever?

The evidence that it is infectious is sufficient to be accepted as proof. Pfeiffer stated that it occurred in small, limited epidemics and in house epidemics, and while numerous sporadic cases have been recorded, there is sufficient evidence that his statements are correct. Fisher, in 1897, noted 8 cases and Chapman 5 cases in one family, and numerous instances are recorded in which several members of a household have been attacked. It has been observed frequently when this occurs that the interval between successive cases is about seven days, all the members not being attacked simultaneously. For example, this was the interval between the two cases in Rudolf's family, and Park West states that when two children of a family are affected, the second case most commonly commenced on the seventh day after the first.

Examples of more widespread epidemics have been given above, the largest being Park West's 96 cases in forty-three families widely scattered over a large area. Park West noticed that the infection spread irregularly.

The view that it is an acute infectious fever is consistent with the general course of the illness, with the occasional occurrence of epistaxis, with the occurrence of nephritis, and with the observation that treatment has no effect on the course of the acute stage.

Admitting that glandular fever is infectious, the question arises whether it is a specific disease or a variant of some common fever. The similarity to mumps is superficial rather than real. Evidence has been given above that the parotid and submaxillary salivary glands are not affected in glandular fever, and there is no recorded instance of orchitis. In mumps the swelling frequently commences behind the jaw just below the ear, but it is characteristic of glandular fever that the site of the enlarged glands is definitely lower than this—that is, about the middle of the length of the sterno-mastoid muscle. A decisive argument for the distinction of the two diseases is the number of instances in which children with glandular fever have previously or subsequently had an attack of mumps. This occurred in 54 of Park West's cases, and Byers also notes that several of his 33 cases had previously had mumps. With regard to exanthemata, rashes do not occur in glandular fever, and even in the larger epidemics no intermediate cases have been recorded.

The mode of spread in epidemics is sufficient to eliminate syphilis, although in the diagnosis of a sporadic case it might have to be considered. There is no record of any Wassermann reaction. The general type of the glandular affection is unlike syphilis, which does not tend to produce a very marked enlargement of the cervical glands. Again, the mode of spread is unlike tuberculosis. In Korsakoff's fatal case the glands examined showed no signs of tubercle. There is no other record of a microscopic examination of a gland.

Many of the earlier writers considered that glandular fever was a form of influenza. At the present time no one knows what influenza is, but it is noteworthy that the last article on glandular fever in the literature was published in 1914, and it is consequently justifiable to assume that it is not influenza as we have known it in recent years.

With regard to infection from the fauces—another suggested cause—it has been pointed out above how very little change is recognizable at this site. Tonsillitis is practically unknown. Pharyngitis is very uncommon and rarely exceeds slight reddening, yet several authorities have upheld the theory of pharyngeal infection. Trautmann argues on anatomical grounds that the glands

affected are those supplied by lymphatics from the pharyngeal tonsil. Most of these writers have ascribed the infection to streptococci on the strength of their presence in cultures from the nasopharynx. This cannot be accepted as an argument of any weight in view of the now known frequency with which streptococci occur in this position. The great enlargement of the cervical glands and the enlargement of the spleen and other glands, together with the rarity of suppuration and the very low mortality, is not consistent with a streptococcal origin. Even when some pharyngitis is present, it is characteristic of glandular fever that the size of the cervical glands is out of proportion to the symptoms and signs in the fauces.

Most French writers refuse to accept glandular fever as a disease *sui generis*. Thus Gallois regards it as only "a special form of influenza," and Labbé as a "cervical adenitis due to a naso-bucco-pharyngeal infection similar to any other acute adenitis." Combemale believed it to be Hodgkin's disease, but the subsequent history of the patients, which in some cases has been watched over prolonged periods, is against this view. Von Starck, noting the occurrence of constipation and of final diarrhoea, discusses the possibility of an auto-intoxication from the bowels. Subsequent writers have often quoted him as accepting this origin, but reference to his article shows that he rejected it.

It appears that glandular fever must be accepted as an acute infection and as a general and not merely a local infection. Further, there is no evidence to connect it with any of the better known acute infectious diseases, and we agree with those who regard it as a disease *sui generis*.

Various epidemics have been recorded which more or less resemble glandular fever. Breinl, Priestley and Fielding, described in 1914 an endemic glandular fever which occurred in North Queensland, and was known locally as Mossman River fever. Many hundreds of cases have occurred since 1877. Adults are principally attacked, and it is rare in children. The onset is gradual, with pyrexia for ten or more days, the glands enlarge slowly, and the axillary and inguinal glands are mainly affected. At the onset the blood is normal, but about the end of the first week leucocytosis develops, the white cells being 12,000 to 15,000 per c.mm., with 45 per cent. of lymphocytes, and there is some degree of anaemia. The mortality is under 1 per cent. The glands show a simple adenitis. It is supposed that the infection is spread by mosquitos. It is evident that this is not glandular fever of the type which we are discussing.

Several writers have described outbreaks of epidemic cervical adenitis, especially Sharp, Pruen and Kirkland in 1913 and 1914. The changes in the fauces were marked, tonsillitis was common with exudation or even membrane formation, but diphtheria bacilli were not present. Tonsillar abscess was not infrequent. The cervical glands alone were affected and the spleen was not enlarged. Kirkland says that blood cultures, when positive, and swabs from the throat, showed streptococci. These epidemics would appear to be a definite infection of the tonsils with secondary enlargement of the cervical glands, and the clinical symptoms and course do not agree with glandular fever.

DIAGNOSIS.

Diagnosis has to be made from mumps, acute cervical adenitis secondary to septic foci, acute leukaemia, exanthemata, acute lymphadenoma, syphilis, tubercle, and possibly influenza.

From mumps, glandular fever is distinguished by the position of the initial and main enlargement of the glands being below the angle of the jaw, and by the freedom of the salivary glands, the parotid and submaxillary. The tissues of the neck are not oedematous, and much pain is rare. A previous attack of mumps may have occurred. It must be noted that, though the salivary glands invariably escape, certain lymphatic glands in proximity to them may be involved, producing the impression that the salivary glands are affected. Thus, in one of our cases, the superficial submaxillary lymphatic gland was greatly enlarged and produced a large prominence on the jaw, but examination easily proved that this was not the salivary gland. Possibly the pre-auricular lymphatic gland may sometimes be enlarged, and no doubt an erroneous diagnosis of mumps might be suggested.

Should a blood count be made, the combination may be present of enlarged cervical and other lymphatic glands, enlarged liver and spleen, together with a certain degree of leucocytosis and a greatly increased percentage of lymphocytes. Such a group of phenomena was actually present in one of our cases, and naturally suggested the possibility of acute leukaemia. It is not uncommon in the early stages of acute leukaemia, especially the lymphoid type, for the leucocytes to be only slightly or not at all increased in number. It was noteworthy that the severe symptoms associated with acute leukaemia were entirely absent. The general condition was good, the mouth was clean (oral sepsis is practically invariable in acute leukaemia), there was no vomiting, no purpura and no haemorrhages. Further, the degree of anaemia was very slight, and the stained red cells were normal, neither nucleated cells nor abnormal forms of any type being present, nor were any abnormal leucocytes recognized.

It is almost inconceivable that acute leukaemia could produce such a picture. It was our opinion from the first that this case was glandular fever, but as neither of us was aware of having seen an instance previously, and as we could find no information on the condition of the blood we hesitated to give a good prognosis for some days. There can be little doubt that similar cases sometimes have been regarded in the past as acute lymphoid leukaemia and probably have been recorded as cures. Many of those who have had much experience in diseases of the blood will be able to recall such events. It is well known that marked lymphocytosis also occurs in whooping-cough.

The distinction of glandular fever from acute cervical adenitis secondary to septic infection may be difficult, but there are numerous points of difference which, taken together, should lead to a correct diagnosis. Attention may be directed to the absence of septic foci in the fauces, scalp, ear and elsewhere in glandular fever, to the site of the main glandular enlargement, to the freedom of the skin and subcutaneous tissues, to the rapidity of diminution of the cervical glands and of the fall of temperature, to the rarity of suppuration, and also to the good general condition which may be combined with general glandular enlargement, a palpable spleen and a very high percentage of lymphocytes. The diagnosis from acute tuberculous adenitis might, presumably, have to await the progress of the case.

From scarlet fever and other exanthemata glandular fever is distinguishable by the large size of the cervical swelling, by the absence of changes in the tonsils and fauces, and of toxic symptoms, and by the absence of rash.

TREATMENT.

In the acute stages only symptomatic treatment is necessary. If the cervical glands are painful, compresses, hot or cold, may be applied, or glycerin of belladonna. Constipation should be treated by simple remedies, and there is no indication for the drastic methods recommended in the past.

As convalescence is often prolonged, as some degree of anaemia may develop and a poor state of health may persist for several months, care must be taken, especially with delicate children, and tonics of iron and cod-liver oil and malt should be administered. There is no reason to believe that nephritis becomes chronic, but our knowledge of this complication at present is scanty, and it is advisable to treat it with the same care as an ordinary nephritis.

Glandular fever must be regarded as infectious, and patients should be isolated. A period of fourteen days may be suggested for isolation and a similar period for quarantine.

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ON UNUNITED FRACTURES.

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A FRACTURE which shows no evidence of bony union at the end of twelve months may be regarded as a case of non-union. To treat any disorder efficiently it is necessary to obtain a clear idea of the condition to be remedied and its cause, for the treatment will largely depend upon the removal of the cause.

The Condition to be Remedied.

Normal bone, like all other tissues, is constantly undergoing a steady process of absorption and reformation, the resulting structure accommodating itself to the function to be performed. The inflammatory process of bone is modified by the vessels being enclosed in rigid channels. This delays the formation of granulation tissue and also the removal of damaged tissues. To overcome this disability Nature appears to have provided a special mechanism for absorption—namely, osteoclastic. It would appear that the same processes which stimulate the osteoclastic element very often coincidentally stimulate the bone-forming process—that is, osteoblastic—into activity. Bone is only a specialized type of connective tissue, and osteoblasts in early stages are indistinguishable from fibroblasts; it is not surprising that fibrous union is not uncommon. It is well known that the pituitary and also thyroid gland secretions have an important influence upon bone formation. Pituitary secretion particularly produces a hypertrophy of interstitial growth of bone.

The chief features noted on examination of the ununited fractures are: atrophy of the bone; loss of vascular supply; sclerosis of surrounding soft tissues and the bone ends.

Causes of Non-union.

The causes of non-union may be conveniently divided into two main groups.

Group I.

- Some upset between the osteoclastic and osteoblastic elements possibly due to derangement or abnormal internal secretions.
- Disuse.
- Defective blood supply.