A CONTRIBUTION TO THE STUDY OF FEVER IN LYMPHADENOMA, WITH SPECIAL REFERENCE TO SEVENTEEN REPORTED CASES OF TERMINAL RECURRENT FEVER IN LYMPHADENOMA AND SARCOMATOUS DISEASE.

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(Plate VIII.)

The pathology of lymphadenoma is so little understood that the description of any phenomena occurring in the course of the disease, offering somewhat anomalous features, is welcome, from the possible light it may throw upon the etiology of this malady. I am indebted to the courtesy of Dr. Sydney Ringer and Mr. R. J. Godlee for permission to publish the details of a case of lymphadenoma with recurrent fever occurring in University College Hospital, and to Professor Osler for references to the earlier reported cases.

Case 1.—G. C., a commissionaire, was admitted to the hospital with a mass of enlarged glands on the left side of the neck, lying underneath and on either side of the sterno-mastoid muscle, and reaching from the ear to the clavicle (Plate VIII.).

In the above case all the characters of lymphadenomatous glandular invasion were present. The glands were freely movable, being in the earlier stages free from attachment to one another or to the skin; as a rule they were not tender, but one or two near the clavicle showed some tenderness, were softer than the others, and the skin in the neighbourhood was distinctly red. The blood examination revealed nothing abnormal, beyond the fact that there was an increase in the total leucocytes (16,000 per c.mm.); the relative proportion of the various leucocytes was normal. Shortly after admission the temperature rose, reaching a height of 102°, the girth of the neck increased, and the tenderness of the glandular swellings was intensified. The case was then transferred to Mr. Godlee's care, and a number of glands were...
removed; no suppuration was found in any of the glands, though yellow-white areas were seen, showing a tendency to caseation. The wound healed quite normally, and the patient was discharged much relieved. A little more than two months later, the patient was again admitted under Dr. Ringer's care, with the history that since his last visit to the hospital he had had seven attacks of fever, in which he shivered, vomited, and had occasionally some diarrhoea. In the intervals between the attacks the glands in the neck shrank so that he could easily button the collar of his commissionaire's tunic; during the attacks this was quite impossible. The spleen was now found to be enlarged, and there was swelling of the left arm. On June 1 the temperature gradually rose, reaching 104°6 on the 4th of the same month, and then gradually subsided, reaching normal on the ninth day from the onset of fever. A similar attack occurred between June 19 and 29 (vide charts). On both occasions there was a measurable increase in the girth of the neck; in the latter attack, the upper part of the glandular mass had become much softer and smaller, the lower part larger and very much more tender, the skin over it becoming quite purplish in colour, and appreciably warmer to the hand than the surrounding part. There was no marked alteration in the blood at this time. Towards the latter part of July another slight rise took place.
having much the same accompaniments as in the former attacks. The patient then left the hospital, returning again in October very much wasted, with increased glandular enlargement on the right and left sides of the neck in both axillae and groins, and signs were present of involvement of the mediastinal and retroperitoneal glands. Blood examinations showed about 80 per cent. of the normal red blood corpuscles and 55 per cent. of hæmoglobin; there was also an increase in the leucocytes. The temperature was raised, but reached the normal in about nine days. A fourth and much more protracted period of pyrexia commenced on November 2 and lasted to the 22nd of the month, death following shortly after.

At the autopsy the enlarged glands in some places were adherent to one another; the spleen was greatly enlarged, and showed the "hard-bake" deposits met with in lymphadenoma. In no case was suppuration met with in any of the glandular masses, whether found in the neck, axillæ, mediastinum, or retroperitoneal tissues; the glands on section revealed the characters met with in lymphadenoma. A few lymphadenomatous masses, as large as peas, were found in the liver. Tubercle bacilli could not be demonstrated in the deposits found in the spleen.

The special points of interest in the above case were the periodic rises of temperature, accompanied by severe constitutional
disturbances, such as anorexia, vomiting, diarrhoea, and on some occasions rigors; in addition, local changes were obvious in the glandular masses; they enlarged during the pyrexia, shrinking again with the fall of temperature; and there were also present a marked intensification of redness, pain, and heat of the skin near some of the masses. No suppuration was found at the operation or at the autopsy. No evidence of the malarial parasite had been found in the blood during the periodic fever. The earliest recorded case at all similar to the above is reported by Hodgkin (1) in his paper on, "Some Morbid Appearances of the Absorbent Glands and Spleen." In Case 7, mention is made of a young woman, aged 25, who was supposed to have malaria; two attacks of fever were observed, intermittent in character. At the autopsy a deposit was found in the spleen and another in the kidney; the description suggests that the case was one of lymphadenoma. Wunderlich (2) later described a case in which, with a rise of temperature, there was an associated increase in size of the enlarged glands and spleen, with a shrinkage when the temperature fell; this, however, was only noted once. Murchison (3) in 1870 described a case of lymphadenoma in a girl aged 6, with periodic rises of temperature. Three years later, Sir William Gowers (4) called attention to three types of temperature met with in lymphadenoma, and he mentioned a case under Wilson Fox's care, in which there was intermittent fever with a marked increase in the size of the glands during the pyrexial period. Gowers found fever was present to a greater or less degree in about two-thirds of all cases of lymphadenoma; in thirteen out of forty cases the temperature was terminal, in twenty-seven it appeared to be a characteristic of the disease even in earlier stages. In 1885, Pel (5) gave the first detailed account of this clinical type of disease; he also mistook such a case for typhoid fever with four relapses, and also noted the enlargement of the spleen with a rise of temperature and contraction during the apyrexia; indeed, he makes this a means of diagnosis from typhoid fever, in which disease, as a rule, the spleen remains large during the interval of apyrexia. Osler (7), writing in the same year, refers to Case 1 of his series of private patients; this was a case of lymphadenoma, showing ague-like paroxysms, with rigors and hot and sweating stages; the temperature rose to 104°, and the glandular enlargements became more marked; he does not refer to the occurrence of redness of the skin with tenderness in the neighbourhood of the enlarged glands. In 1887, Ebstein (8 and 9) described similar cases under the name, "Das chronische Rückfallsfieber, eine neue Infektions-krankheit." Ebstein's first patient had attacks of fever about once a month. Ebstein noticed that the rise of temperature was, as a rule, gradual, but that the fall was more sudden; the average duration of the fever was thirteen to fourteen days, the periods of apyrexia, ten to eleven days; on one occasion only was
any complication found which could account for the rise of temperature. Ebstein also noted that the appetite of his own patient and of the one described by Murchison was enormous during the periods of normal temperature, and was much disturbed during the paroxysms of fever. Ebstein also noted periodic enlargement of the spleen. As opposed to Pel, who would rather look upon such cases as merely "special infectious forms of so-called pseudo-leukaemia," Ebstein preferred to call them cases of "chronic recurrent fever," referring them to some unknown bacterial origin. Ebstein did not agree with Pel in thinking that the excessive appetite in the periods exempt from fever was a cause of the subsequent rise of temperature. Neither Pel nor Ebstein were able to find any definite etiological factor. Renvers (19) followed with a description of another case, under the name of "Lymphosarcomatosis, with Recurrent Fever," and objected to Pel's nomenclature, because the actual infection was unknown. The first efforts to detect an organism in such cases were made in the year 1888. Maffucci (11) found streptococci and bacilli in the enlarged glands of patients dying of this disease, and a micrococcus and short bacillus were found by Majocchi and Pecchini (12) in all parts of the body affected. Cardarelli (13) also found a typhoid-like organism, and he described a form of pseudo-leukaemia occurring in young children, in whom there were present attacks of fever at irregular intervals throughout long periods; there were also progressive cachexia and a hard splenic tumour; the spleen was extirpated in one case, the child notably improving, losing the attacks of recurrent fever. In 1889, Kast (14), in discussing the relationship of body temperature in general to malignant tumours, referred also to a case of a boy æt. 7, with involvement of the glands of the neck and of the inguinal and axillary glands. There were nine attacks of fever in five months; the case presented somewhat the features of typhoid fever, and later developed a yellow skin with urobilinuria. At the autopsy general invasion of the glands, liver, spleen, and kidneys was discovered, and the case was probably one of lymphadenoma, though Kast preferred to look upon it as a case of multiple sarcoma with recurrent fever. Kast concludes that intermittent, remittent, and recurrent types of fever may occur in cases of sarcoma and carcinoma, involving the stomach, etc. He thinks that the periodic rise of temperature is due to a periodic absorption of some toxic body. Similar cases were described in 1889 and 1890 by Hanser (15), Völckers (16), and Klein (17). Hauser raised the question, whether it really was not a fault in these cases that there was a mixed infection. Völckers noted the occurrence of syphilis in his own and Renvers' case.1 Klein was unable to find any organisms in the liver of his case, but streptococci were found abundantly in the cortex of the glands.

1 Loc. cit.
affected, less so in the medulla. Puritz (18) also described a case of sarcoma of the liver, in which there were periods of fever with afebrile intervals. The temperature charts do not, however, show such regular periods of pyrexia and apyrexia as in the cases described by Pel and Ebstein. Puritz thought that there was a great possibility that the accessions of fever were due to invasion by an infective agent. Stevens (19) has also described a case of Hodgkin's disease with a fluctuating febrile course; in three attacks there was noticeable enlargement of lymphatic glands; and in another there was intense pain over the spleen, coincident with the rise of temperature.

Fischer (20) published a paper in 1893 on the subject of "Malignant Lymphoma with Secondary Infection and Recurrent Fever." He does not favour the view that such cases form a special variety of lymphadenoma, but that such secondary infection may occur in other diseases, e.g. carcinoma and sarcoma. He admits the difficulty of trying to account for the periodic temperatures, and invokes a periodic temporary immunity. Fischer was able to make cultivations from the blood and lymphatic glands during the febrile attacks and in the intervals; he found Staphylococcus pyogenes aureus during the febrile manifestation, but failed to find any in the feverless periods; nor at the autopsy were any organisms recoverable from the glands by culture or inoculation. In opposition to Langhans, Fischer does not believe in the subvarieties of lymphadenoma—one characterised by hard enlarged glands, the other by soft ones, for in his case both kinds were met with; a similar condition was found in Dr. Ringer's case. Fischer makes no reference to the redness and tenderness, like that present in the skin in Dr. Ringer's patient. Westphal (21) also contributes a very exhaustive paper on the fever met with in lymphadenoma. He gives details of twenty-one cases, and these comprised cases in which the fever was continuous or remittent, or intermittting. The twelfth case described had recurrent attacks of fever, and at the autopsy no complication was found, so that this case may well be considered as an example of simple lymphadenoma with recurrent fever. A very remarkable case was described by Hammer (22) of "Primary Sarcomatous Osteitis with Chronic Recurrent Fever." According to Hammer, the variations in temperature are not a sign of infection, but merely a characteristic of sarcoma or cancer; other possible explanations are that the fever in such cases is merely a specific reaction of the individual attacks, or that each rise of temperature coincides with a fresh metastasis; and, finally, that the periods of temperature are due to the localisation of the tumours to certain blood-forming organs. Hohenemser (23) prefers to call such cases examples of multiple sarcomata, and remarks upon the occurrence of diarrhoea and urobilinuria in such cases; he, however, only considers such manifestations as accidental. From the clinical
point of view the diagnosis has to be made from typhoid fever and tuberculosis. Hohenemser quotes Strümpell on the rarity of relapses in typhoid fever beyond two or three occasions, whereas in this malady several relapses are known; and, further, in multiple sarcoma with recurrent fever the patient is quite well in the intervals between the periods of fever. In tuberculosis periodic temperature is rare. Hohenemser concludes with a résumé of the characters of this form of malady:—(1) Recurrent fever is a well-marked symptom; (2) the disease is clinically and anatomically separable from lymphadenoma (?); (3) blood alterations are not very marked; (4) the spleen and liver are enlarged, and there is general glandular swelling; (5) Urobilinuria and peptonuria are met with; (6) etiology is unknown, but tuberculosis can be excluded.

In 1895, Delbet (24) announced the discovery of a bacillus in a case of lymphadenoma, which produced generalised lymphadenoma in a dog, inoculated with material derived from a lymphadenomatous gland. The evidence, however, is slender, and only one dog was inoculated successfully. In further reference to the question of bacterial invasion, to explain the periodic rises of temperature, Stengel (25) quotes Verdelli, who stated that twenty-nine of such cases examined for organisms showed positive results. Stengel, however, thinks that such invasion is purely terminal. As already stated, several writers prefer to call cases of lymphadenoma, with a specially malignant and rapid course, cases of sarcoma; but, as Stengel remarks, it is often quite impossible to distinguish between what is known as cases of lymphadenoma and lymphosarcoma. Billroth's dictum, that in the former there is a tendency to spread to adjacent glands, and in the latter to adjacent tissues, is not of practical value, for the characters are common to both types. The confusion existing in the nomenclature of such diseases is well shown in Göppert's résumé (26), where he says that lymphosarcoma must include—(1) ordinary splenic lymphadenoma; (2) ordinary splenic lymphadenoma of children; (3) the aleukæmic stages of leukæmia.

Fischer (27) in 1897 again returned to a discussion of the subject, and still maintains the view of considering such cases as "malignant lymphoma," an independent disease with an unknown etiology. Before a definite diagnosis can be given, tuberculosis must be excluded, and he also admits that tuberculosis of other organs can exist synchronously with malignant lymphoma. James Finlayson (28) has recently published details of a case which in its clinical course was very similar to Dr. Ringer's case, with the exception that there was no periodic enlargement of the lymphatic glands synchronous with the rise of temperature. The remarkable feature of Finlayson's case was the almost complete disappearance of the lymphadenomatous glands during the course of the disease.
An analysis has been made of sixteen cases collected from the literature, in which "recurrent fever" was a special feature occurring in the course of certain diseases; it is, however, admitted that all the cases described are not simple lymphadenoma, in fact there is considerable doubt about the cases described by Vöckers, Puritz, and Hammer. The remaining thirteen cases, together with the case described in this article, may be considered cases of lymphadenoma. The question, practically as unsettled to-day as it was when Pel and Ebstein first described their cases, is whether we should consider cases of lymphadenoma with recurrent fever as a special form of lymphadenoma or as a special disease. Considering the number of cases of lymphadenoma which pursue an afebrile course for months and even years, or do not show attacks of recurrent fever, it must be acknowledged that, in the form of lymphadenoma with recurrent fever, some other agency must be at work; so much has been done of late years in the investigation of "terminal infections" in chronic disease, that it is almost impossible to think otherwise of the recurrent fever met with in lymphadenoma, than that it too is due to a similar bacterial invasion.

It is difficult to say during what period of time before death an invasion by organisms may be considered terminal. In the series of more or less undoubted cases of lymphadenoma, already referred to, the intervals elapsing between the onset of fever and death were as follows:—Murchison's case, two and a half months; Pel's first, second, and third cases, respectively five months, five months, and fourteen months; Ebstein's case, eleven months; Renvers', eleven months; Kast's, five and a half months; Hanser's, twelve months; Fischer's, fourteen months; Hohenemser's, three months; Westphal's, twelve months; Finlayson's, roughly about five months; Dr. Ringer's case, eight months. These periods amount on an average to a little over seven and a half months. Seeing that cases of lymphadenoma may last for years, and that when once "periodic fever" has commenced it persists till death, it may be allowed that such terminal infections may take place as long as twelve or even fourteen months before death.

As to the bearing of these cases upon the pathology of lymphadenoma, it must be admitted that the results are quite negative, and rather tend to show that uncomplicated lymphadenoma is not due to an infection of any of the ordinary organisms like staphylococci or streptococci, since in only a very limited number of cases have such organisms been found, and even in these the effect has been very different in producing recurrent fever in a few cases, and in others fever without any marked periodicity. Lymphadenoma, as Sir William Gowers has pointed out,¹ may be accompanied by moderate continued fever throughout the illness; out of forty cases, twenty-seven were found to possess such elevation of

¹ Loc. cit.
temperature, the remaining thirteen being free from fever except towards the end of the illness.

That the specific agent causing lymphadenoma, whatever its action may be, is not responsible for the periodic fever, is shown in the analysis of the cases reported by Völcker, Puritz, and Hammer; periodic fever has been described in cases of malignant disease of the liver and stomach; and similar features are met with in the malarial form (so called) of malignant endocarditis, in pernicious anaemia, leucocythaemia, and other blood diseases.

It is almost beside the mark to refer to the fact that in all cases of periodic fever occurring in lymphadenoma, there has not been a positive bacteriological observation; the positive cases are so numerous now that one may almost conclude that the negative ones are merely the result of some fault in technique.

In Dr. Ringer's patient, and in eight of the other cases analysed, periodic attacks of fever occurred, accompanied by enlargement of the spleen or lymphatic glands. This feature has always been a puzzling one, and so far no adequate explanation has been given; enlargement of the spleen in other infectious diseases is well known. A point of further interest is that in Dr. Ringer's case, not only did the glands enlarge, but they became painful and the skin over them became reddened with the rise of temperature; neither at the operation nor at the autopsy on Dr. Ringer's case was suppuration demonstrable. It is possible that the glands become invaded by the organisms found so frequently in the skin, and are able to deal with them without the occurrence of suppuration; the fact that thirteen of the seventeen cases analysed showed well-marked enlargement of the superficial glands, lends some support to this view.

In further résumé of the above cases, urobilinuria was found in five cases, and a doubtful form of jaundice in two others. Twelve of the undoubted cases of lymphadenoma occurred in males and two in females, as in uncomplicated lymphadenoma the male sex preponderates. The number of febrile attacks varies from one or two to as many as thirty-three, noted in Hammer's case; the attacks of fever varied from two or three days to as many as thirty-two days. The average duration of life from the onset of the illness was a little over twelve months.

Consideration of the above cases impresses the view that "lymphadenoma with recurrent fever" is not a special form of disease, that such cases are due to a terminal infection occurring any time during the last year of life of some patients affected with lymphadenoma; that the nature of the bacterial invasion is different in different cases, and that in some cases proof of a bacterial invasion is wanting; that in a considerable number of cases of lymphadenoma with recurrent fever, there is a great constitutional disturbance with elevation of temperature, rigors, vomiting, and diarrhoea, anorexia, and malaise; that in some cases

[Continued on page 512.]
**Analysis of Seventeen Cases of Terminal Recurrent Fever.**

| No. of Case | Author and Title of Case | Occupation, Age, and Sex | Enlargement of various Organs during Life | Periodic Enlargement of Organs, etc., Synchronous with Rise of Temperature | Duration of Illness, from Onset to Death |
|-------------|--------------------------|--------------------------|------------------------------------------|------------------------------------------------------------------------|----------------------------------------|
| 1           | Murchison (5).           | Girl, aet. 6.            | Superficial Glands: Cervical axillary; groin also tender. | Yes, spleen tender. | Cervical glands enlarged, producing dulness behind sternum, which increased with rise of temperature. | 2½ years. |
| 2           | Pel (6). "Pseudo-leukaemia" (infectious form). | Male, aet. 25, paper-hanger. | No. | Yes. | Spleen enlarged, with rise of temperature. | 4-5 months. |
| 3           | Pel (6). "Pseudo-leukaemia" (infectious form). | Male, aet. 32, naval officer. | Yes. | " | Spleen enlarged with rise of temperature. | 1 year. |
| 4           | Pel (6). "Pseudo-leukaemia" (infectious form). | Sailor, aet. 41. | Yes, supraventricular and inguinal. | " | Same phenomena noticed as in Case 2, probably (p. 640, l. c.). | 13-14 months. |
| 5           | Einstein (6). "Chronic recurrent fever." | Male, aet. 19, mechanic. | No. | " | Spleen regularly enlarged with rises of temperature. | About fifteen months. |
| 6           | Renvers (10). "Lympho-sarcoma with recurrent fever." | Male, aet. 31, conjuror. | " | " | Spleen enlarged with rise of temperature. | About fourteen months. |
| 7           | Kast (14). "Chronic recurrent fever and multiple sarcoma." | Boy, aet. 7. | Yes. | " | Spleen becomes distinctly larger during febrile attacks, and shrunk subsequently. | Acute illness, lasts 6½ months. |
| Reference | Details |
|-----------|---------|
| Individuals | Fever Details |
| Hanser (15) | Chronic recurrent fever (Ebstein). |
| Voelckers (16) | Sarcoma with recurrent fever. |
| Klein (17) | Pseudo-leukemia with cirrhosis of the liver and recurrent fever. |
| Puritz (18) | Sarcoma with so-called recurrent fever. |
| Fischer (19) | Malignant lymphoma with recurrent fever and secondary infection. |
| Westphal (20) | Case 12 of series. Pseudo-leukemia. |
| Hammer (21) | Primary sarcomatous osteitis with chronic recurrent fever. |
| Homememer (22) | Recurrent fever with multiple sarcomata. |
| James Finlayson (23) | Hodgkin’s disease. |
| Case described in this contribution | Lymphadenoma with periodic fever. |

**Male, age 25.**
- Yes, splenic dulness increased, but spleen not palpable.
- No mention.

**Male, age 30.**
- No mention.
- No mention.

**Widow, age 31.**
- Yes, especially inguinal and crural.
- No mention.

**Woodman, age 29.**
- Yes (probably).
- Not enlarged.

**Male, age 34.**
- Yes, glands quite free from tenderness.
- No.

**Barber, age 25.**
- Yes, axillary left cervical.
- Yes.

**Miller, age 41.**
- Yes, three months before death.
- Yes.

**Clerk, age 28.**
- Yes, painless.
- No alteration noticed in size of glands.

**Coachman, age 49.**
- Yes, cervical, axillary, inguinal.
- No.

**Soldier, age 41.**
- Yes, cervical, axillary supracondylar, inguinal.
- Permament enlargement of glands well marked in periods of elevated temperature.

| Age | Duration |
|-----|----------|
| 10 months |
| About one year |
| 18 months |
| 1 year |
| Acutely at 10 months |
| Acute illness, 3½ months |
| About eight months |
urobilinuria is a marked symptom; that in some of the cases the superficial lymphatic glands, and even the spleen, become very tender and enlarged during the attacks; and that the skin over the enlarged glands may become reddened and show increase of local temperature. Finally, that the prognosis in such cases is, as a rule, hopeless, and that the duration of life, after the onset of the periodic attacks of fever, averages about seven and a half months, but may be as much as twelve or fourteen months.

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THE TOXÆMIC BASIS OF GENERAL PARALYSIS.

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Among the numerous theories of the causation of general paralysis which prevailed prior to the commencement of the past decade, the most widely accepted was the theory of “premature involution.” According to this theory, the disease was regarded simply as a premature senile decay of the cortical ele-