TUBERCULOUS PERIFOCAL INFILTRATIONS (INCLUDING EPITUBERCULOSIS).

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Introduction.

Many problems of Medicine have been obscured by the application or misuse of a name. An example of the former is afforded by the subject of this article. "Epituberculosis" was the name given by Eliasberg and Neuland to phenomena which they described in 1921, and which they believed they were reporting for the first time. Actually, as will appear in the course of the present article, what they described were no more than particular cases of the general phenomenon of "perifocal infiltration" which runs through the whole life-history of tuberculosis.

This fact having been recognised, it is proposed to drop the term "epituberculosis" in favour of "perifocal infiltration" which describes the phenomena under consideration, and which has a definite and unmistakable meaning.

The example of the latter is afforded by the term "allergy" which will be introduced into this article. "Allergy" was a word coined to express a definite concept which was quite precisely defined by its originator, v. Pirquet. It has been wrenched from its original meaning and restricted so that it covers no more than a fraction of the field for which it was originally intended. In the present article, it will be used in its earlier and wider sense.

Pathology.

Before dealing with the clinical and radiological appearances of perifocal infiltrations, a short account of the known facts of the primary infection by tubercle bacilli is necessary.

It has been shown that the sequence of events following primary infection is the same in each case. A small lesion is set up at the point of entry of the bacilli which is characteristic in its histological structure; the anatomically related lymph-glands are infected within a few hours, and the lymphatic tract running between these two points is also infected. This whole inflammatory system, the "primary focus," the lymphangitis and the infected glands make up what Ranke called the "primary complex." This term, it should be mentioned, is an anatomical one, and has no significance in itself for the location, course or prognosis of the disease. The primary complex may form the source from which metastases or infiltrative processes may arise, or may heal up so completely as to leave behind little or no trace. It is usually possible to find it post-mortem, but success in finding it is directly proportional to the skill of the searcher and the care and length of time devoted to the search.

It has been shown that the reaction of the body to inoculation with tubercle bacilli or their products during the first 4-12 weeks after the formation of the primary complex, is in no way altered by the existence of the complex. This indifference on the part of the host to the presence of the tuberculous invader has been given several names—Primary Tuberculous State, Primary Allergic State and Negative Anergy. On the average, about 6 weeks after the formation of the complex, the body reaction undergoes profound and permanent change. The body
becomes sensitized and the introduction of tuberculous toxins now causes a sharp reaction at their point of entry (local reaction), some reaction around the primary complex (focal reaction), and even a general reaction of the whole body if their quantity is sufficient and the degree of sensitivity is high. If the toxins are introduced by absorption from the primary complex, the local and focal reactions coincide. In addition, the tissues have the power of arresting and destroying the newly-invading toxic substances, whether they be bacilli or their products, at their point of entry. This altered reaction is what is properly known as "allergy." Allergy consists, as just indicated, of at least two elements—hypersensitivity and immunity. The whole further history of the disease can be explained in terms of the interplay of these two factors, although the conditions governing this interplay are often obscure.

The terminology of the stages of syphilis has been applied to tuberculosis. On this analogy, the period between the lodging of the bacilli in the body and the onset of hypersensitivity has been described as the primary stage; that period immediately following, in which the hypersensitivity dominates the picture, has been called the secondary stage, and this is followed after an indefinite interval by a tertiary stage in which the immunity processes predominate.

Perifocal infiltrations are manifestations of hypersensitivity and therefore belong to the secondary stage.

It has been shown pathologically that the majority of town-dwellers have been infected with tubercle bacilli, and that the majority of these infections are located in the lungs. When the lungs of a child become sensitized to tuberculous products, the absorption of these products from the primary complex or from any other point from which they may be liberated—e.g., a focus of reinfection or an injection of tuberculin—will cause a reaction around the primary complex which may give rise to a clinically recognisable "perifocal infiltration."

The term "perifocal infiltration" was first applied to the radiological appearance of these reactions. It was then employed for the pathological condition underlying the radiological. The exact nature of the infiltrations is uncertain in spite of many attempts to determine it. The condition is benign for the most part, and does not come to autopsy. On needling the chest, tubercle bacilli have been found in the withdrawn fluid in several cases. Spence(2) found them twice in successive punctures of one case. On account of the improbability of the primary focus being exactly found by means of a needle, he concluded that the process was an ordinary caseating one. Against this view must be set the especial characteristic of these infiltrations—ability to resolve. This is so striking and so much in contrast to the usual behaviour of a caseous lesion, that the two cannot be considered identical. The presence of bacilli cannot, furthermore, be considered as necessarily indicating a caseous lesion. In support of this, the analogy may be drawn between these perifocal infiltrations and acute pleural effusion. It has been shown that 25-30 per cent. of the latter have living and (for the guinea-pig) pathogenic bacilli in the pleural fluid. Yet for these cases to proceed to form empyemata is almost unknown. Bacilli can, therefore, be present without giving rise to caseous lesions.

Better evidence of the nature of these infiltrations than that of Spence, is given by a case of Rubinstein's(3). The radiogram in his case suggested an interlobar empyema. On this assumption, the chest was opened, and when the diagnostic error was discovered, a piece of lung was taken for section. Round-celled epithelioid fibroblastic elements were found, together with a smaller amount of
alveolar epithelium and giant-cells. A thin layer of young connective tissue was found surrounding the lesion. No bacilli were present. The condition was therefore an exudative-pneumonic one.

When this case was published, it was soon realized that similar pathological conditions had previously been described under various names—Grancher’s splenopneumonia, Virchow’s pneumonia, Lennec’s gelatinous infiltration, Buhl’s desquamative pneumonia. The evidence appears to be in favor of grouping all these conditions together.

To sum up, perifocal infiltrations are probably inflammatory reactions of an exudative type and they may at times contain bacilli. For their formation one must imagine an interplay of antigen (bacilli or their break-down products), and sensitized tissue.

**Clinical Manifestations.**

The clinical history of perifocal infiltrations is often slight. In the primary tuberculous stage there may be a little fever at about the fourth week. The tuberculin test is at this time negative and as yet no infiltration exists. About the sixth week there may be definite malaise, fever, cough and loss of weight and appetite. The tuberculin test is at this time just becoming, or has just become, positive. These symptoms abate after about 10–14 days. The child may continue to be somewhat "out of sorts," but apart from cough and the loss of 2–3 lbs. of weight there is little else the matter.

The physical signs are usually indefinite, but some evidence of a consolidation of one or more lobes of one lung may be obtained.

Unless the case is now fully investigated, or unless the catastrophe of miliary tuberculosis or meningitis supervenes, the cause of this loss of health may never be discovered. This is probably the course of the disease in the majority of cases. Recovery ensues, and the patient seems none the worse for the infection.

In other cases, relapse occurs one or more times, particularly after intercurrent infection such as measles, and ill-health may continue for a considerable period.

In general, the younger the child the more severe are the symptoms; at any time there may be the insidious onset of miliary disease or meningitis.

Two clinical manifestations may be associated with the formation and presence of perifocal infiltrations. The first of these is erythema nodosum. About 90 per cent. of cases occurring in childhood are tuberculous in origin, and the majority of these show perifocal infiltrations on X-raying the lungs.

The second of these associated lesions is phlyctenular conjunctivitis. Here the association is much less close. About 70 per cent. of the cases are found in patients with fresh or relapsing tuberculous lesions, of which many are perifocal infiltrations.

The appearance of either of these so-called "paratuberculous lesions," should be considered ground for investigation for the presence of tuberculosis.

**Diagnosis.**

1. **Clinical.** This is seldom simple. The first requirement is a positive tuberculin reaction. The only cases where this rule is not always true are those which have had measles during the preceding 2–3 months. This group is of particular importance in that it has long been recognized that measles seems to
have a specifically depressant effect on the defence mechanisms of the body, and an attack of measles predisposes to the acquisition or activation of the disease. The usual tuberculin test in clinical use is the Mantoux intradermal reaction.

The clinical signs and symptoms are not often of assistance. If signs of consolidation of a lung are present, this information is of value; but their absence does not affect the diagnosis.

Contrary to the usual teaching, the temperature cannot be regarded as a reliable guide to the presence of the tuberculous infiltration. In the early and acute stages, and in the first few days of each relapse fever is usually present, and may be as high as 103°. For the most part, however, it is slight or absent. It is no more frequent in the tuberculous than in the non-tuberculous child.

2. Radiological. On account of the paucity of physical signs, the X-ray examination is necessary to the diagnosis. Indeed, as has already been pointed out, perifocal infiltrations were first discovered as the result of radiological examination.

The X-ray picture is diagnostic only in a minority of cases. The best examples of these completely characteristic forms are the "bipolar stage" described by Redeker (Fig. 1.), the triangular shadow described by Sluka and others (Fig. 2.), and a third unnamed picture (Fig. 3.) to be described below.

The bipolar stage appears when one area of infiltration surrounds the parenchymatous focus and another surrounds the hilar region. These two areas are joined by a narrow band of infiltration which surrounds the infected intervening lymphatic path. The whole shadow has a somewhat dumb-bell shape. Such shadows are not often seen on the X-ray plates, because the usual antero-posterior and even the lateral positions may fail to take the shadow at the correct angle. Where the suspected cases are repeatedly screened as a matter of routine, this stage is more frequently met. Theoretically, all cases should, in healing, pass through this stage, but it is only in a minority that it is actually observed. Conversely, it may be assumed that all cases in which the bipolar stage is observed, are cases of healing primary complex.

Sluka's triangle is a triangular shadow the base of which lies at the hilum and the apex of which lies in the middle zone of the lung fields. It is most frequently
seen on the right side. One side of the triangle is formed by the line of the thickened and inflamed pleural septum between the upper and middle lobes. If the patient is placed in the lordotic position, this appearance is accentuated because the interlobar septum then shows as a surface instead of as a line.

The third picture which can be regarded as typically tuberculous is a triangular shadow occupying the upper zone on either side (Fig. 3.). This is caused by consolidation of the upper lobe accompanied by some collapse. It will be remembered that more or less massive caseous glands are to be found in the region of the hilum corresponding to the infected lung area. These may be of sufficient size to cause partial collapse of a lobe by pressure on the bronchus. It is seldom that the collapse is complete. The lower and lateral boundary of the shadow is formed by the interlobar septum between the upper and middle (on the left side, upper and lower) lobes. The collapse causes the septum to be drawn up so that it lies at an angle to the normal (approximately horizontal) position.

Apart from these special forms, the radiological picture of a perifocal infiltration does not differ essentially from that of other pneumonias. The shadow seen may be of any size, from a small infiltration surrounding the hilum to complete consolidation of the whole of a lung. It is these massive forms which have been rather unnecessarily distinguished by the name of "epituberculosis."

3. Other diagnostic methods. Certain ancillary methods may be of considerable help in establishing the diagnosis. The most valuable of these is undoubtedly gastric lavage. Between 40 per cent. and 50 per cent. of these cases have bacilli in the sputum. The only practical way of obtaining sputum from these patients is by lavage of the fasting stomach. When the sputum so obtained is inoculated into a guinea-pig, the bacilli, if present, will be demonstrated. A positive finding is, of course, diagnostic.

Some help may be obtained from the sedimentation rate. This is usually, but not always, raised.

Another investigation which may assist is the determination of the monocyte-lymphocyte ratio. American authors have pointed out that in tuberculosis this is raised. This investigation must, however, be used with care. There is evidence to show that the ratio should be interpreted rather as an indication of the resistance of the patient at the moment of taking the blood, than of the activity or diagnosis of the case.

The peripheral blood-count is of little value.

It should be mentioned that these blood investigations are, properly speaking, non-specific. They can assist, but not make the diagnosis.

Course and Prognosis.

The prognosis of perifocal infiltrations is in the main benign. The most striking characteristic of these processes is their capacity for resolution.

The possibilities can be tabulated as follows:

(a) Complete.
(b) With calcification of the primary complex (formation of a Ghon's tubercle).
(c) With formation of an indurative scar. ("Induration fields" of the German authors).
(2). Recurrent relapse, finally progressing as in groups 1 or 3.

(3). Generalization as miliary tuberculosis or meningitis.

(4). Aspiration bronchopneumonia due to cavitation of the primary focus, or rupture of a caseous gland into a bronchus (usually occurs only in the very young).

(5). Juvenile phthisis.

Group 1. If the majority of cases of perifocal infiltrations are followed through radiologically, the infiltration will be seen to disappear in the course of a few weeks or months. Resolution begins at the periphery and progresses towards the hilum.

The factors determining the incidence of the sub-groups (a), (b) and (c) are not clear. Age plays some part here—the younger the child the more frequently does calcification make its appearance. Complete resolution is, on the whole, more frequently seen in the older children. Induration may occur at any age, but it is usually found in the older children. Whichever form the final picture takes, the infiltration as such disappears, and the residuum, if any, is due to the scarring of the primary focus or to the lymphangitis.

Group 2. Relapse may be caused by intercurrent infection, especially measles, or by further exposure to infection with bacilli—e.g., in contacts. These relapses are called "secondary infiltrations." When seen radiologically, they are indistinguishable from the primary infiltrations, and only the knowledge of the previous primary infection allows the distinction to be made. As far as is known, this distinction is not of clinical importance.

The final fate of these cases may be resolution as in group 1 or generalization as in group 3. When resolution occurs, some induration is usually to be seen remaining.

Group 3. The causes of unfavourable prognosis are often obscure. Under the age of two years, the most important factor is the age itself. The younger the child, the more dangerous is the disease. Apart from this, the main causes of serious complications are (a), intercurrent infection, particularly measles, pertussis and other catarrhal illnesses; and (b), continued contact with cases of open phthisis (reinfection).

Discussion of groups (4) and (5) lies outside the scope of this article.

It has been estimated that not more than 5 per cent. of the cases of perifocal infiltration which occur are ever diagnosed. Of these, only a few have a serious outcome. It may therefore be asked why it should be considered of such importance. The reason is that although only a few of the diagnosed cases become seriously ill, it is probable that all fatal cases pass through this stage shortly before the onset of the final illness.

Treatment.

There is no specific treatment for tuberculosis in childhood any more than in adult life. Certainly no active measures are required. Sanatorium life is desirable on several grounds. Firstly, the patient is under control. This is an important factor with children. It is notoriously difficult to restrict at home the activities of
a child who feels himself perfectly well, and most children with perifocal infiltrations complain after the first two or three weeks of nothing more than cough.

Secondly, in an institution the patient can be shielded from intercurrent infections, such as measles and pertussis, which predispose particularly to activating the disease.

Thirdly, the patient can be removed from possible contact with sources of infection and so protected from superinfection with tubercle bacilli, which is actually the most prolific cause of the grave forms of tuberculosis in childhood.

Fourthly, the child can be prevented from itself becoming a source of infection for other children. The gravity of this factor is uncertain. Since bacilli can be found in the (swallowed) sputum of quite small children with perifocal infiltrations, these patients can, theoretically, spread the disease by coughing. They can therefore infect other children.

Against sanatorium treatment can be set two objections. The first is that the children may become "institutionalized." The second is the stigma attaching to the word "sanatorium." The advantages considerably outweigh the disadvantages.

No surgical treatment is required for perifocal infiltrations. Artificial pneumothorax has been tried extensively on the continent but has been abandoned. There is no indication for its use. Gold salts, valuable in certain cases of phthisis in adults, are absolutely contraindicated in the highly reactive state of the body which conditions the appearance of perifocal infiltrations.

Symptomatic treatment should be applied according to the requirements of each case.

**Prophylaxis.**

The problem of prophylaxis of perifocal infiltrations is that of the prophylaxis of tuberculosis. Control of cases of "open" phthisis, and systematic examination of contact children, using the tuberculin test and X-rays, are the principal means at our disposal. Unfortunately, it must be said that the thoroughness with which these means are used often leaves much to be desired.

**REFERENCES:**

(1) Eliasberg and Neulant, Jahrbuch für Kinderheilkunde, 1921, xcll—xciv.

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