Original Articles

PSEUDO-TUBERCULOSIS OF THE LUNGS WITH EOSINOPHILIA, OR BENIGN EOSINOPHIL LEUKÆMIA

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Introduction

SEVERAL authors have recently described the syndrome of chronic bronchitis associated with a high eosinophil blood count, symptoms of asthma, fever and loss of weight; many cases display a fairly typical *x*-ray appearance. Frimodt-Möller and Barton (1940), who published the first extensive description of this disease, were concerned chiefly with its *x*-ray appearance, but they pointed out that the condition, being essentially benign, was in no way connected with tuberculosis. However, they made no suggestions for treatment of the disease.

In February 1943, I mentioned in this journal two cases of this disease which were cured by acetylarsan. Up to 1938 only a few cases had come to my attention, none with definite radiological changes, and all were cured by 'arseno-typhoid'. None showed filaria in the blood. The curative effect of arsenicals on massive eosinophilia had actually been known to me since 1933 when the first case of this type came under my observation.

This particular patient had consulted me for fever, accompanied by a very irritant cough and swelling of the inguinal glands. His blood count showed 57 per cent eosinophil cells, and his lung skiagram was without any definite pathological change. As there was no other explanation of this high eosinophil count, I assumed it represented a rare manifestation of filariasis and treated him with 'arseno-typhoid' injections. After a few injections the symptoms disappeared, the patient became well, and his eosinophil count remained normal under my observation for years.

In January 1943, Weingarten published a detailed account of this disease, but this publication did not reach India until several months later. His study was based on eighty-one cases observed subsequent to 1934, and since 1936 he has found that the organic arsenicals were a specific. His description of the disease provided a very uniform picture : it begins with slight fever, loss of appetite and weight, and after about one week the patients develop a dry cough, especially at night; in a great number of cases asthmatic symptoms appear. Weingarten pointed out that the *x*-ray evidence during this early period is very distinctive, and is characterized by a mottling of the lungs, but later this *x*-ray appearance is not necessarily so typical. Only a small number of Weingarten's patients were females, and in no case was more than one member of a family affected. Neither he nor Frimodt-Möller and Barton noted any example of this disease combined with tuberculosis.

In May 1943, Simeons described thirty-five cases observed in Bombay, many of which showed radiological evidence of infiltration of the lungs although others did not. Because of the absence of radiological evidence in many cases, Simeons prefers the term benign eosinophil leukæmia.

Another typical case was reported by Chaudhuri (1943) and Shah (1943), and the *Indian Medical Gazette* devoted an editorial (1943) to this syndrome.

Recent cases

The clinical picture in the literature to date is remarkably uniform. The impression is gained that fever and cough are certainly essential symptoms of this disease. However, recent observations on nineteen new cases seen since 1943 have led me to conclude that the clinical manifestations of the syndrome are much more variable than previous records have indicated, and that the only consistent features are the high eosinophilia and the invariably dramatic results of treatment with organic arsenicals. Even fever is not an essential symptom at any stage, and the disease does not exclude active tuberculosis. Lung symptoms may be entirely absent, yet there may be gross radiological changes. The disease has now been observed in two members of the one family. The onset of the disease may be quite sudden, indicated by violent asthmatic attacks. Finally, the treatment with arsenicals may be accompanied by acute febrile reactions or symptoms of profound general malaise.

These more recent cases may be illustrated by the records of the first two patients which follow, the first displaying the typical syndrome, the second atypical in character.

Case 1.—European male, aged 36 years, first consultation on the 20th May, 1943. First attack of 'bronchitis' in 1939 lasting for several months. Since November 1942, had a continuous cough, very little expectoration, often with fever and breathlessness, particularly at night. Lost two stones in weight since November 1942. Clinically, the patient showed typical asthma-bronchitis; radiologically the mottling of the lungs was typical; blood eosinophilia 66 per cent; total leucocyte count 28,000.

The patient was given 2 c.c. acetylarsan on the 21st May, 1943, and 3 c.c. on the 23rd, 26th and 29th May and 1st June. Four hours after the last injection, the patient's temperature rose to 103°F. with a severe ague. Next morning the temperature was normal; no malaria parasite was found in the blood. On the 5th June another injection of acetylarsan was given, but only 1 c.c. A few hours later the temperature rose to 104°F. Again no parasite was found. Treatment was stopped after a total of only six injections. On the 3rd June the eosinophil count had come down to 13 per cent. Since his last injection the patient has had no further symptoms; his lung skiagram has become normal and has remained so. He has gained 17 pounds in weight. Eosinophil count on the 8th April, 1944, 10 per cent.

The secondary effects of arsenical treatment were much more severe in another case in which

the clinical picture failed to conform to the more or less standardized description of this syndrome.

Case 2.—Indian Christian male, aged 24 years, first examined on the 12th August, 1943. No history of previous severe illness. He had noticed loss of weight for some time and also an increasing feeling of weakness. Ten days previously he suddenly felt dizzy and fainted. Clinical examination: poor general state of health, thoracic organs normal, no swelling of liver or spleen; inguinal glands on the right very much enlarged but not tender—this was thought to be attributable possibly to inflammatory changes of the glans penis which was covered by hardened epithelial debris which had collected under the foreskin. The patient denied ever having had intercourse. He was advised to remove this foreign matter with some warm oil. On examination on the 14th August the glans penis looked quite normal; the inguinal glands were unchanged. His blood count showed 26,800 white cells, 80 per cent eosinophil cells. *X*-ray skiagram of the lungs normal.

On the 16th August treatment with acetylarsan was begun. In view of the weak general condition, only 1 c.c. was given in the first injection, but on the 18th August 2 c.c. and on the 21st August 1.5 c.c. acetylarsan were given. On the 23rd August the patient was brought to me. He was unable to walk alone and reported that since the 22nd he had had fever and very severe pain in the limbs. He had lost all appetite, was unable to raise his arms or close his fists, tendon reflexes of arms and legs were unobtainable, very slight pressure on the muscles of the extremities and particularly along the course of the extremity nerves was very painful. The condition of the patient was so alarming that he was sent to the School of Tropical Medicine, Calcutta. His eosinophil count had already fallen to 45 per cent. In hospital a tentative diagnosis of lymphogranuloma inguinale was first suggested, the diagnosis being based on the combination of fever, swelling of the inguinal glands and myositis. When the Frei test proved negative, my original diagnosis of eosinophil leukæmia with severe reaction of the type known in syphilis as Herxheimer's reaction was accepted, and the patient was dismissed after one week of symptomatic treatment. Treatment was continued with carbarsone orally. On the 8th September the eosinophil count had dropped to 13 per cent, and the swelling of the inguinal glands was much reduced. The patient has been under my continuous observation to date. He has put on 6½ pounds, feels perfectly fit for work, and his eosinophil count still fluctuates between 10 and 20 per cent.

The case described next would almost certainly have been accepted as pure eosinophil leukæmia unless an *x*-ray skiagram had been taken. There was no clinical indication of the necessity for this skiagram as lung symptoms were completely absent, yet the *x*-ray skiagram displayed the most marked changes of all the skiagrams of my series.

Case 3.—Anglo-Indian male, aged 17 years. First consultation on the 30th December, 1943. For a period of two weeks he had experienced irregular fever, up to 101°F. and 102°F., with a feeling of weakness and with breathlessness when running. Despite the fever the patient had not reported sick, and had continued his strenuous duties and even physical exercises, but undertook the latter with difficulty as he soon lost breath when running or jumping. There was scarcely any cough. The spleen was found to be slightly enlarged, the breath sounds over the lungs were somewhat harsh, but there was no catarrh. A diagnosis of malaria suggested by the patient and his mother appeared very likely. However, blood examination showed no malaria parasites, but 38 per cent eosinophil cells in a 21,000 total count. *X*-ray screening of the lungs showed very strongly diminished translucency of both lung fields, and a skiagram showed numerous and rather large infiltration shadows spread over both lung fields (figure 1, plate XXIII). From the 2nd January to the 21st January, five injections of N.A.B. were given, 0.3 gm. each. Subsequent to the second injection the patient felt and continues to feel perfectly well. The swelling of the spleen has disappeared completely and an *x*-ray skiagram (figure 2, plate XXIII), taken on the 22nd February, 1944, showed the complete elimination of the pathological shadows. The eosinophil count is now 10 per cent; the total count is normal.

This baffling case, showing such extensive radiological changes of the lungs but with no clinical evidence of any lung affection, would probably not have been recognized as 'eosinophil lung' for some time. Possibly, however, some lung symptoms would have become evident after a few days, as it is not readily conceivable that such extensive changes as became evident in his skiagram could have remained latent for any length of time. Sooner or later he would presumably have experienced a sudden asthmatic attack, as in the following case.

This next case had been under my observation for some time when he suddenly developed a very severe asthmatic state, without any preliminary symptoms such as fever or cough. The *x*-ray skiagram showed very extensive changes which had not, of course, developed during the few days between the commencement of the attack and the date of taking the *x*-ray skiagram; they must have been in existence for some time before the sudden onset of asthma which led to the correct diagnosis.

Case 4.—Mohammedan male, aged 55 years, first consultation on the 2nd May, 1943. For a period of several years he had experienced a steady loss of weight, great thirst and increasing general weakness. Examination of the internal organs showed no pathological changes of importance; urine—specific gravity 1033, sugar 4 per cent, blood sugar 226 mg. per cent. The patient was put on diet and insulin. He gained weight fairly rapidly; blood sugar and urine sugar were well controlled. On the 13th May the patient suddenly developed a severe asthma attack, and during the following week his asthmatic fits were so continuous and troublesome that only frequent injections of adrenalin brought any relief. He was in continuous severe distress, not relieved by ephedrine. There was no fever. On the 20th May blood examination showed 47 per cent eosinophil cells, and an *x*-ray skiagram on the 21st May showed typical mottling of the lungs.

This case is of special interest, not only because of the sudden outbreak of severe asthma without preliminary symptoms and without fever, but more particularly because of the fact that his son, aged 5 years, was affected by the same disease. The boy had been suffering from cough with expectoration for a considerable time; an examination of the lungs indicated typical asthma-bronchitis; an *x*-ray skiagram showed typical mottling of the lungs, and there was blood eosinophilia of 19 per cent.

The following history is of a case in which a very sudden outbreak of a most severe type of asthma lasting for four years, again with no preliminary symptoms, and uninfluenced by the usual anti-asthmatic drugs, was dramatically cured by arsenic.

Case 5.—Mohammedan male, aged 43 years. This patient had been known to me for several years previous to April 1940, when he suddenly fell ill with severe asthmatic symptoms, unrelieved by the usual treatment.

He rapidly lost weight and was unable to continue his work in Calcutta. I saw him again on the 24th March, 1944. His asthmatic state had continued throughout the interval of four years, and on examination, he showed typical asthma-bronchitis, diminished breath sounds, and prolonged expiration. There was no swelling of the spleen. Blood examination—51 per cent eosinophil cells. From the 27th March to the 13th April five injections of N.A.B., 0.3 g., were given. After the third injection he suffered no further breathlessness, and examination on the 24th April gave normal breath sounds over the lungs, and there were no signs of bronchitis. The patient now feels perfectly fit, although eosinophilia of 21 per cent still persists.

Observations published to date agree that there does not appear to exist any connection between 'eosinophil lung' and tuberculosis of the lungs. Although apparently true in the vast majority of cases, this should not lead to the assumption that the one disease excludes the other, as is demonstrated by the following example.

Case 6.—Hindu male, aged 20 years. First consultation on the 3rd December, 1943, with a history of fever, cough, and breathlessness, particularly at night. The left tonsil showed several ulcers and typical sounds of asthma-bronchitis could be heard over the lungs. The patient was advised to rest and to take sulphanilamide tablets. When seen again on the 8th December, 1943, the tonsillitis had cleared up, but fever, cough, and breathlessness persisted. Blood examination showed 37 per cent eosinophil cells, and an *x*-ray skiagram of the lungs showed mottling of both lung fields, particularly below the left hilus. The broncho-vascular markings in both lung fields were strongly increased. The skiagram was not suggestive of tuberculosis, and in view of the marked eosinophilia, eosinophil infiltration of the lung was diagnosed (figure 3, plate XXIII). Under treatment with acetylarsan, breathlessness and bronchitis disappeared readily, but cough and fever persisted. On the 27th December, 1943, the eosinophilia had disappeared, and only 6 per cent eosinophil cells were found, but another *x*-ray skiagram (figure 4, plate XXIII) of the lungs showed diffuse loss of translucency below the left clavicle with a cavity, the mottling otherwise being less pronounced than on the previous skiagram. Sputum : T.B. positive.

The cases described above illustrate deviations from the accepted pattern of the syndrome 'eosinophil lung'. Other cases which I have observed more or less followed the typical clinical picture as described by Frimodt-Möller and Barton, Weingarten and Simeons. In a previous communication I suggested that a typical *x*-ray skiagram is not essential for diagnosis, just as a typical *x*-ray skiagram does not necessarily mean that the patient will exhibit cough and breathlessness. In several patients displaying typical clinical symptoms, I have failed to find an abnormal *x*-ray skiagram of the lungs. Amongst these patients was a European who had come to India in July 1942 on war service and was transferred to Calcutta in August 1943. On consulting me in November 1943, his disease had lasted for six weeks. It had obviously been recently acquired in India. All my other cases were in Indians or in Europeans who had been resident in India for many years. Assuming that the syndrome is caused by some agent peculiar to the tropics, the case of this particular European leaves a very large margin for the incubation period. Owing to the war, a large number of Europeans have come to this country, and it is likely that some may in time develop eosinophilia and lung symptoms; it is to be hoped that observations on such cases will be made available in due course.

Weingarten concludes from his observations that the disease he describes as typical eosinophilia is found chiefly amongst people living near the sea in India. Most of my cases were residents of Calcutta, but there were several exceptions. Two patients came from Raniganj, the climate of which is not as damp as that of Calcutta, and two patients came from Bihar. One patient, a Chinese, had brought the disease from Singapore. He came to India as an evacuee, and his clinical history dated back to his Singapore days. The syndrome has apparently been observed in Australia but is very rare ; under the diagnosis eosinophil leukæmia Fenner (1943) describes the case of a private, nineteen years of age, who had been treated for asthma for five years and showed a very high eosinophilia, his total blood count being about 60,000. *X*-ray therapy in this case remained unsuccessful, the specific effect of arsenicals apparently being unknown in Australia.

A noteworthy feature of the cases observed by me is that not one female patient occurs amongst them. Although it cannot be said that females do not suffer from this disease, it is certain that they are far less prone to attack than males.

Ætiology

Until very recently no acceptable suggestions as to the ætiology of the syndrome—high eosinophil count, associated with pulmonary symptoms —have been put forward. Frimodt-Möller and Barton as well as Weingarten postulated an allergic basis, chiefly because of the common asthmatic manifestations. This theory always seemed to be open to objections. It is difficult to accept a purely allergic basis, particularly in patients who present themselves as suffering from what is obviously an infectious disease accompanied by fever, swelling of the spleen or lymph glands and eosinophilia. It is also difficult to understand why allergic manifestations so variable in nature should be consistently cured by organic arsenicals.

In a recent publication Carter, Wedd and d'Abrera (1944) have contributed cogent evidence on the ætiology. In a large percentage of their cases which showed pulmonary symptoms they observed mites in the sputum, chiefly of the genera Tarsonemus, Tyroglyphus and Carpoglyphus. Some of the patients showed radiologically typical mottling of the lungs, others did not. Out of thirteen of their cases, five gave a normal blood picture, five others showed an eosinophilia from 6 to 12 per cent, and the remaining three cases showed from 38 to 66 per cent. Treatment with organic arsenicals was

curative. The authors suggest that the condition is caused, at least in part, by mite infestation of the respiratory system. This suggestion is certainly apposite in all those cases with respiratory symptoms, but in the present state of our knowledge it is not easy to see how mite infestation of the respiratory tract will cause fever, loss of weight, swelling of the spleen or lymph glands in those cases in which lung symptoms are entirely absent clinically as well as radiologically. Further, it is difficult to explain the absence of eosinophilia in such a large percentage of the above authors' cases so long as we regard high eosinophilia as essential, or even the leading feature of the syndrome. Also, it will be very difficult—apart from technical considerations—to prove mite infestation of the respiratory tract in cases showing lung symptoms but unproductive cough.

A high eosinophilia must be regarded as an essential part of the syndrome from the standpoint of therapy. High eosinophilia in combination with lung symptoms provides a definite indication for arsenical treatment. This treatment, however, failed completely to bring about any improvement in four patients who suffered from long-standing bronchitis with asthmatic symptoms and low eosinophil count, and on whom I tried this treatment as a control measure after the usual therapy directed against their asthma-bronchitis had failed previously. In every other respect these four cases might have fitted easily into the clinical picture of 'eosinophil lung'. Only observations on a very large number of cases of bronchitis with and without eosinophilia will prove how far infestation by mites is responsible for their clinical manifestation. For the present we may acknowledge that the above authors' contribution has at least thrown some light on this apparently quite common and often disabling condition.

Summary

The syndrome of tropical eosinophilia is discussed and a number of observations described which differ from previously published records.

It is shown that lung symptoms may be entirely absent, although profound radiological changes may be present.

Clinical symptoms may be severe although unaccompanied by radiological changes of the lungs. One case is described in which there were no lung symptoms but there was swelling of lymph glands and fever.

Some reactions during the course of treatment with arsenicals are described.

Occasionally the disease may start with the sudden outbreak of violent asthmatic symptoms, unaccompanied by fever.

The occurrence of the disease in two members of the one family is noted, and an example is quoted of its association with tuberculosis.

The syndrome appears to be more widespread over India than has been assumed so far.

Its recently-suggested causation by mite infestation is discussed.

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THE INFLUENCE OF INTRAVENOUS INJECTIONS OF QUININE ON THE MYOCARDIUM*

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Since Wenkebach (1918) discovered that quinine is capable of abolishing extra systoles as well as auricular fibrillation, the attention of cardiologists has been centred mainly upon the action of this drug on disturbances of heart rhythm; this attitude was still more pronounced because of the wide use of the quinine isomer quinidine, introduced by Frey (1918) into the therapy of auricular and ventricular extra systoles, fibrillation and paroxysmal tachycardias. A large number of investigations have been devoted to the understanding of the influence of quinine and quinidine on these pathological conditions (Hecht and Zweig, 1917, Singer and Winterberg, 1921, Otto and Gold, 1926, Levine and Stevens, 1928, Schwartz and Jezer, 1934, Scherf and Siedek, 1935, Kohn and Levine, 1935, Francaviglia, 1937, Eldahl, 1940, Horine, 1940, Riseman and Linenthal, 1941); but very few facts are to be found in the literature available to us about the electrocardiographic changes which are caused by intravenous quinine administration in cases of normal heart rhythm.

In what way and to what extent does intravenously injected quinine affect the heart muscle; in what proportion of cases is myocardial damage to be expected; is an apparently normal myocardium safer against toxic quinine effects than one which shows pathological signs prior to quinine therapy? These questions have hardly been investigated with modern methods under tropical conditions. It seems to be

*Since this article was received (August 1943), a paper bearing on the subject has appeared (*Journal of American Medical Association,* 1st January, 1944, Vol. CXXIV, p. 63) but is not available in the original. —Editor, *I. M. G.*

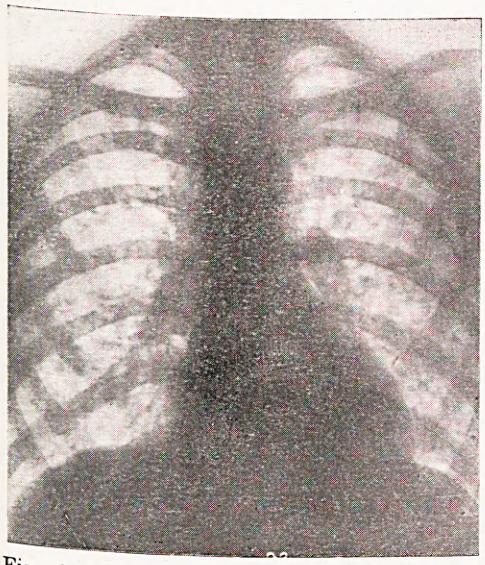

Fig. 1.—Anglo-Indian male, aged 17 years. Numerous and rather large infiltration shadows spread over both lung fields.

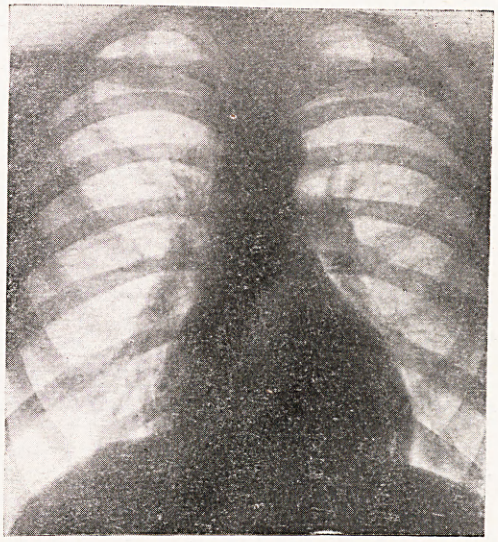

Fig. 2.—Same patient as in figure 1 after N.A.B. injections. Complete elimination of the pathological shadows.

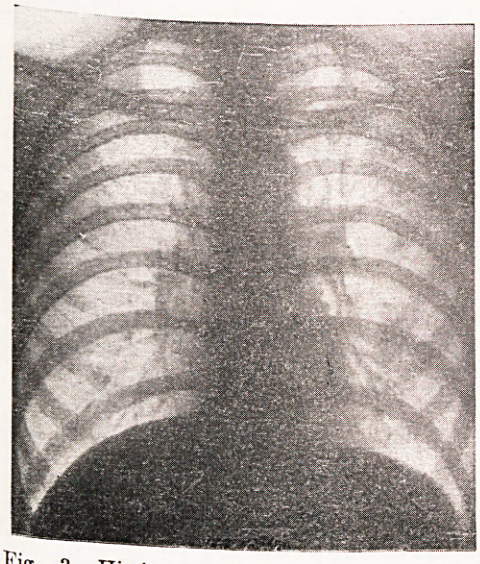

Fig. 3.—Hindu male, aged 20 years. Not suggestive of tuberculosis; showing marked eosinophilia.

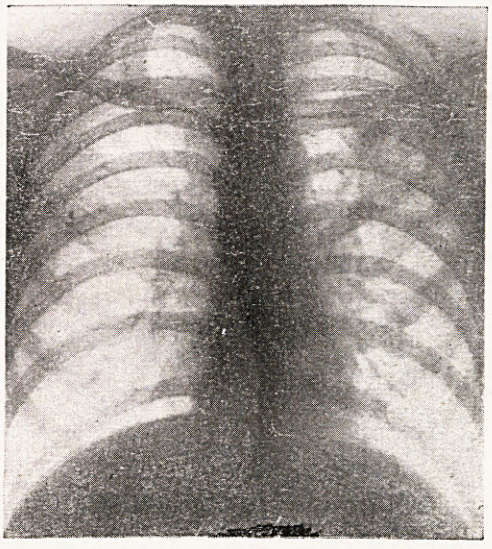

Fig. 4.—Same patient as in figure 3 after treatment with acetylarsan. Diffuse loss of translucency below the left clavicle with a cavity, the mottling otherwise being less pronounced than in figure 3.