

## PULMONARY EOSINOPHILIA

BY

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Eosinophilia in the blood is an incidental finding in certain well-defined pulmonary conditions such as the resolving stage of pneumonia, hydatid disease of the lung, Hodgkin's disease, and sarcoidosis (Longcope, 1941). This paper is concerned with a less well defined group of diseases in which, at one time or another, infiltrations are observed radiologically and are accompanied by a blood eosinophilia. To this group the term "Löffler's syndrome" has often mistakenly been applied. As Löffler himself has pointed out, the syndrome described by him includes only a section of the group of diseases in which there are pulmonary infiltrations accompanied by blood eosinophilia. There is, in fact, no currently accepted term which will include the entire range of these disorders. On the analogy of "tropical eosinophilia," a name now widely accepted, we suggest using "pulmonary eosinophilia" to describe the whole group. Pulmonary eosinophilia is defined as a condition in which pulmonary infiltration on the radiograph is accompanied by blood eosinophilia, but in which any of the four diseases listed above can be excluded. This definition is not in itself absolute. Certain patients have eosinophilia in some of their attacks, but not in others which are in every other way identical. Again, cases of tropical eosinophilia, which should be included in the group, may or may not have pulmonary infiltrations. These exceptions to the definition are pointed out not to invalidate the general term "pulmonary eosinophilia," but to remind the reader that it is merely a convenient heading under which to group together patients whose illnesses have certain characteristics in common. Like most other names for diseases or syndromes, "pulmonary eosinophilia" has no absolute value in a platonic sense.

The following account is based on a personal experience of 16 cases and a review of some 450 cases reported in the literature.

### CLASSIFICATION OF CASES OF PULMONARY EOSINOPHILIA

The definition of pulmonary eosinophilia as "pulmonary infiltration with blood eosinophilia" covers a very wide range of diseases, varying from the mild and transient changes in true Löffler's syndrome to the severe and often fatal manifestations of polyarteritis nodosa with lung involvement. We think that both clinically and pathologically all these cases form a continuum. It is convenient to subdivide the continuum into certain subgroups, but it should be emphasized that these fade into one another. The following classification is suggested: (1) simple

pulmonary eosinophilia or Löffler's syndrome, transient infiltrations ; (2) prolonged pulmonary eosinophilia, prolonged or recurrent infiltrations without asthma ; (3) pulmonary eosinophilia with asthma, infiltrations with asthma ; (4) tropical pulmonary eosinophilia, usually with asthmatic symptoms ; (5) polyarteritis nodosa.

Tropical eosinophilia is a particularly well defined group and its relationship to the rest of the continuum is at present uncertain.

There are several reasons for grouping the cases together. On clinical grounds they can be placed in a series varying from the mildest to the most severe. All have in common pulmonary infiltration on the radiograph. The term "infiltration" is, perhaps fortunately, vague ; it serves to exclude such conditions as tumours, or hydatid cysts in which the abnormal shadows are well defined. The cases also have in common a blood eosinophilia. We have arbitrarily taken a level of 6% of the total white blood cells, or above, as indicating an eosinophilia. Absolute counts would be more satisfactory, but in many of the reported cases only the percentage is given.

The characteristics of the individual groups will now be considered.

#### SIMPLE PULMONARY EOSINOPHILIA (LÖFFLER'S SYNDROME)

**HISTORY.**—Löffler (1932), of Zürich, first drew attention in 1932 to the syndrome which bears his name. He described four cases with slight or no symptoms in which transient pulmonary infiltrations were detected in the radiograph. All had normal total white cell counts ; in two the differential count showed an eosinophilia of 9 and 22% respectively, though in the other two the proportion of eosinophils was only 3.5 and 5%. A fifth had no blood count done. By 1936 Löffler (1936) had collected 51 cases and the syndrome was well established. In 1943 Maier (1943) was able to publish 100 cases detected in Löffler's clinic. In addition there are at least 112 other cases reported in the literature\* which we are satisfied conform to the criteria laid down by Löffler.

**GEOGRAPHICAL DISTRIBUTION.**—Cases have been reported from Switzerland, Germany, France, Scandinavia, North America, South Africa, and China. As far as we know, none has been described in England, though we have encountered one example which is described later. There are others published under the title of Löffler's syndrome, which we think ought more properly to be classified under different headings.

**CLINICAL FINDINGS.**—In Löffler's syndrome, as defined by the original author (1936, 1945), the symptoms are mild or even absent altogether, and abnormal physical signs in the chest are only detected with difficulty, if at all. Abnormal shadows in the lung fields are always shown on the radiograph, but these are by definition transient, disappearing in a matter of six to 12 days. An eosinophilia in the blood is essential to the diagnosis. The proportion in Löffler's cases varied

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\* Wild and Loertscher (1934); Engel (1935); Steiger (1937); Müller (1938a); Douady and Cohen (1938); Leitner (1938, 1941); Lavier, Bariéty, and Caroli (1939); Delbecq, Garnier, and Depasse (1939); Benda and Weinberg (1940); Vogel and Minning (1942); Contratto (1943); Glenn (1943); Alwall (1943); Sommer (1943); Ameuille and Marmier (1943); Baumann (1944); Leutenegger (1944); Spühler and Kartagener (1944); Randall (1945); Wright and Gold (1945, 1946); Peirce, Crutchlow, Henderson, and McKay (1945); Bourquin (1946); Grayce (1946); Dörig (1946); Alpher (1947); Meyer (1937); Slowey (1944); Ham and Zimdahl (1948).

from 3.5 to 60%. The total white cell count is usually in the upper range of normal. The eosinophilia is also transient, reaching a peak three to four days after the peak of the radiographic changes and disappearing usually in 10 to 15 days.

Reviewing the reported cases it appears that, when symptoms are present, cough is the commonest, though it is often absent, especially if the cases are only detected on routine fluoroscopy. Only five out of 28 cases diagnosed by Spühler and Kartagener (1944) on routine screening complained of cough. The cough is usually slight, but may be severe. There is often no sputum; when present it may be lemon-yellow and may occasionally be blood-stained (Löffler, 1936; Douady and Cohen, 1938). It often contains eosinophils. Other symptoms which have been described include malaise, headache, upper respiratory catarrh, hay fever, night sweats, substernal or unilateral chest pain, angioneurotic oedema, cheirpomphylyx, "creeping skin eruption" (associated with infestation by *Ankylostomum braziliense*) and jaundice due to *Distomum hepaticum* (Lavier, Bariéty, and Caroli, 1939). We have not seen a case described in which there were asthmatic symptoms, though tightness in the chest (Vogel and Minning, 1942; Spühler and Kartagener, 1944) is occasionally recorded.

There is often no fever; when present, it is not usually over 100° F., and settles to normal in a few days, though temperatures of up to 104° F. have been recorded (Peirce, Crutchlow, Henderson, and McKay, 1945). There are often no abnormal physical signs in the chest, but there may be slight impairment of percussion note, diminished breath sounds, or a few crepitations over some areas of the lungs.

**RADIOGRAPHIC CHANGES.**—The radiographic shadows are usually fan-shaped and fairly homogeneous, but with indefinite borders. These may be unilateral or bilateral and may disappear in one part to appear in another. The shadows may be small or may occupy most of the lung field. Occasionally they are nodular (Ameuille and Marmier, 1943) or rounded (Leitner, 1943). According to Löffler the shadows usually disappear in six to 12 days; we have only classified as true Löffler syndrome those cases in which the radiograph became clear within a month.

**BLOOD CHANGES.**—Total white blood cell counts vary from 4,200 per c.mm. with 12% eosinophils (Bourquin, 1946) to 22,800 with 26% (Contratto, 1943). We have not regarded those with less than 6% eosinophils as cases of Löffler's syndrome; the proportion has varied from this figure to 70% of a total white cell count of 12,900 (Lavier and others, 1939). Commonly the proportion of eosinophils is under 20% and the total count is in the upper range of normal.

**AETIOLOGY.**—Aetiologically a number of factors have been associated with Löffler's syndrome. It seems clear that infestation with *Ascaris lumbricoides* is by far the commonest, the prevalence of this condition in Switzerland being responsible for the large number of cases seen at Löffler's clinic. *Ascaris* infestation was proved in 23 out of 100 of Löffler's and Maier's cases (1944). Many other cases with *ascaris* infestation have been reported (Wild and Loertscher, 1934; Müller, 1938a; Leitner, 1941; Sommer, 1943; Baumann, 1944; Spühler and Kartagener, 1944). Skin tests with *ascaris* extracts were often positive (Sommer, 1943; Spühler and Kartagener, 1944), though they may also be positive in a proportion of controls

(Zweifel, 1944). Many years ago Koino (1922) produced a pneumonia in himself and his brother by swallowing a large number of ascaris eggs, and the life-cycle of ascaris is known to involve a pulmonary migration (Müller, 1938a and b). Löffler has induced the condition in guinea-pigs by infecting them with ascaris (Löffler, Essellier, and Macedo, 1948). Sprent (1949) has sensitized mice to various ascaris extracts by parenteral injection, and has produced striking pulmonary changes, including an infiltration with eosinophils. This suggests that Löffler's syndrome might sometimes be produced by sensitization even if there is no pulmonary migration. Finally Vogel and Minning (1942) reproduced the complete syndrome in five out of six volunteers by feeding them with six to 45 ascaris eggs. Müller (1938a) also reproduced the condition in a volunteer by feeding him earth containing ascaris eggs. Pulmonary migration, and hence the manifestations of Löffler's syndrome, occurs usually within two weeks of infection. The worms become adult in two months and then eggs can be found in the stools. Consequently, in many cases the opportunity for making a diagnosis of ascariasis may not arise until some weeks after all manifestations of Löffler's syndrome have disappeared, by which time the patient may no longer be under observation.

Though ascariasis seems to be much the commonest associated factor many others have been incriminated. These include other worms, such as *Ankylostomum braziliense* (Wright and Gold, 1945, 1946), *Trichuris trichiura* (Grayce, 1946), *Taenia saginata* (Benda and Weinberg, 1940), *Distomum hepaticum* (Lavier and others, 1939), and hydatid of the liver (Dörig, 1946). Among the miscellaneous allergens blamed are pollens, such as that of the privet, *Ligustrum vulgare* (Engel, 1935), and of lily of the valley, *Convallaria majalis* (Meyer, 1937), beeswax (Falk and Newcomer, 1949), pneumococci (Alwall, 1943), and sulphonamides (Contratto, 1943). Certain cases have been doubtfully attributed to the presence of epidermophytosis (Glenn, 1943), and amoebiasis (Randall, 1945). Leitner (1938, 1941) considers some cases as being due to hypersensitivity to tuberculin and has reviewed the association of blood eosinophilia with tuberculosis. That Löffler's syndrome itself is ever due to tuberculosis seems very doubtful.

#### PROLONGED PULMONARY EOSINOPHILIA

There are a number of cases reported which differ from Löffler's syndrome mainly in the longer duration of the illness and of the radiographic shadows. For this group we suggest the term "prolonged pulmonary eosinophilia." We include in it those in which abnormal radiographic shadows persist for over a month. This difference is, of course, arbitrary; in some cases of Löffler's syndrome the radiograph does not become clear for three weeks or more, while "prolonged infiltrations" may disappear within six weeks.

In the literature we have found accounts of 17 cases which may be classified as "prolonged pulmonary eosinophilia."\* The ages of the patients ranged from 2 to

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\* Ham and Zimdahl (1948); Ellis and McKinlay (1941); Willett and Oppenheim (1946); Berk, Woodruff, and Frediani (1943); Eichwald and Singletary (1946); Léon-Kindberg, Adida, and Rosenthal (1940); Kartagener (1942); Elsom and Ingelfinger (1942); Elkeles and Butler (1946); Brulé, Gilbrin, and Viguié (1943); Perlingiero and György (1947); Zuelzer and Apt (1949); Rifkin and Eberhard (1946); Harkavy (1943).



58 years. A variant of the syndrome described by Botsztejn (1941) affects very young infants and will be considered separately. There is no significant difference in incidence between the sexes. Cases have been reported from North America, Switzerland, France, England, and the South Pacific.

**CLINICAL FINDINGS.**—There is considerable variation in severity. Nine of the 17 reported cases had at some time a fever of 100° F. or over, and four had temperatures of 103° F. or over; but often the patient was much less ill than the temperature chart would lead one to suspect. The fever frequently lasts for a month or more; in one it continued irregularly for six months. Three cases had no cough; in most of the others it was non-productive. In three of the cases with a productive cough the sputum contained eosinophils. None had asthmatic symptoms before or during the illness.

**RADIOGRAPHIC CHANGES.**—The radiographic shadows differ very considerably. Probably their appearance depends partly on the stage of the disease at which the film is taken. In the reported cases the changes varied from indefinite localized mottling to a relatively homogeneous shadow occupying most of the lung field. The edges of the shadow were often indefinite; as lateral films were not taken in most instances, it is difficult to say how far the shadows corresponded to lung segments. The changes were almost always more pronounced in the upper than in the lower zones and they were bilateral at some stage in the majority. In most instances successive shadows were observed; one infiltration would resolve to be replaced by others on the same or the opposite side. In only one case is it clear that the same shadow persisted throughout (Kartagener, 1942). Elkeles and Butler's case (1946) was thought to have a cavity in the centre of an infiltration at the right apex; cavity and infiltration disappeared in about six weeks.

**BLOOD COUNTS.**—The maximum degree of eosinophilia in each case tended to be higher than in Löffler's syndrome. It varied from 10% of a total white count of 10,800 to 72% of a total count of 117,000. Seven out of 17 cases had total counts of over 20,000, and all except one had an eosinophil percentage of 20 or over.

**PROGNOSIS.**—The illness usually lasts two to six months, though some recovered in six weeks. One patient (Kartagener, 1942) still had a cough 14 months after the onset, and there were persistent mottled shadows in the right upper zone with a blood eosinophilia of 20% of 7,000 white cells; she had never been febrile, and continued to work as a housewife throughout her illness. Recovery is usually complete. Occasionally a dry cough persists and sometimes the blood eosinophilia continues long after all other manifestations have disappeared. One case had another attack after five months free from symptoms (Brulé, Gilbrin, and Viguié, 1943), and a second (Ham and Zimdahl, 1948) relapsed after 18 months, though the infiltration was not on this occasion accompanied by blood eosinophilia.

**INVOLVEMENT OF OTHER ORGANS.**—In three cases there were manifestations in organs other than the lungs. One had giant urticaria (Elkeles and Butler, 1946), a second (Perlingiero and György, 1947) had a focal necrosis of the liver at biopsy, and the third (Harkavy, 1943) had sinusitis, bilateral eosinophilic pleural effusions, and local necrosis of the skin of the thigh.

**AETIOLOGY.**—In seven of the 17 cases there was a personal or family history suggestive of an allergic diathesis. In nine cases probable aetiological factors were found. In two skin tests were positive to various allergens (Elkeles and Butler, 1946; Harkavy, 1943). In one the disease seemed to be due to hypersensitivity to sulphanilamide (Ellis and McKinlay, 1941). In two cases significant agglutinin titres for *Brucella abortus* were found (Elsom and Ingelfinger, 1942). Two occurred with coccidioidomycosis infection (Willett and Oppenheim, 1946). Another recovered after vomiting an ascaris worm, and skin tests with ascaris extracts were strongly positive (Perlingiero and György, 1947). In one case larvae of *Strongyloides stercoralis* (Berk, Woodruff, and Frediani, 1943) were consistently found in the stools, and it seems possible that "pneumonitis" and eosinophilia may often occur in strongyloides infestation (Hinman, 1938). In one case in the South Pacific (Rifkin and Eberhard, 1946) microfilariae were found in the sputum. In only four out of 17 cases was there no evidence either of an aetiological factor or of an allergic diathesis.

**PROLONGED PULMONARY INFILTRATIONS IN INFANTS.**—A series of five cases of a peculiar pneumonia in infants, described by Botsztejn (1941) from Zürich, is best considered separately. The infants were aged 2 weeks to 2 months and several had been born prematurely. The symptoms suggested whooping-cough, and there were physical signs of bronchitis. The radiographs showed bilateral perihilar bronchopneumonic mottling, and in several there was pleural involvement. In one case the radiograph suggested collapse and consolidation of the left upper lobe and in another of the middle lobe. In all there was a leucocytosis in the acute stage, varying from 15,000 to 22,000, with an eosinophilia of 9 to 30%. The symptoms usually lasted several weeks and the radiographic changes one to four months. In several cases other members of the family had recently had an "influenza-like" illness. Whooping-cough was ruled out because of the unusual blood count, the absence of exposure, and the fact that at least one case developed pertussis later. The von Pirquet test was negative in the two patients on whom it was done. The cases did not occur as an epidemic, but were seen in the course of several years.

### TROPICAL EOSINOPHILIA

We do not propose to discuss at length the syndrome of tropical eosinophilia or "tropical pulmonary eosinophilia" as Ball (1950) has more logically called it, which is now comparatively well known. Attention was first drawn to it through the work of Frimodt-Möller and Barton (1940) and of Weingarten (1943) in India. Further reviews and large numbers of cases have since been published.\* Cases have been reported from most tropical countries. In this syndrome there is sometimes an initial stage of malaise, fever, coryza, and dry cough, lasting from one week to a month. During this phase the spleen may be palpable. The bronchitic aspect then becomes the most prominent feature and this may continue for months or years. It is followed by an asthmatic phase, in which there is marked wheezing

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\* Weingarten (1943); Parsons-Smith (1944); Ritchie (1944); Treu (1944); Apley and Grant (1945); Viswanathan (1945); Patel (1945); Hodes and Wood (1945); Van der Sar (1946); Hall (1946); Irwin (1946); Hunter (1946); Stephan (1946); Fond and Ravenna (1948); Soysa (1949); Ball (1950).

or sometimes clear-cut asthmatic attacks. This stage may also last months or years, though at any time the condition may resolve spontaneously. In perhaps one half of these cases, the radiograph, if taken between one and six months after the onset, will show a diffuse mottling throughout both lung fields, though sometimes the lesions are more localized. There may be hilar glandular enlargement, especially in children (Ball, 1950). There is always a gross blood eosinophilia. The total white count is almost always over 15,000, often 50,000 or more, and the eosinophils vary from 20 to 90%. Perhaps the most dramatic feature of the syndrome is the response to organic arsenic by mouth or intravenously; this results in clinical cure in the majority, often within a few days. Adrenocorticotrophic hormone has been given to a case with some lowering of the eosinophils, but no effect on the radiograph (Rose, 1950).

The cause of tropical eosinophilia is not yet established. There is little suggestion that it occurs in individuals unusually susceptible to allergic disorders. There is now a good deal of evidence to incriminate a mite infestation of the respiratory tract (Van der Sar, 1946; Ball, 1950; Carter, Wedd, and D'Abrera, 1944; Soysa and Jayawardena, 1945; Carter and D'Abrera, 1946). The mites belong to various genera; *Tarsonemus*, *Tyroglyphus*, *Glyciphagus*, and *Carpoglyphus* have been found in the sputum of cases. Control studies by Soysa (1949) in Ceylon have failed to demonstrate mites in the sputum of patients with other respiratory conditions. At best mites are only detected in some 60% of cases, and we have found it worth while submitting sputum specimens to a skilled entomologist. It has been suggested that filariasis may be responsible (Irwin, 1946; Van der Sar and Hartz, 1945), but the evidence for this is at present tenuous.

#### PULMONARY EOSINOPHILIA WITH ASTHMA

Apart from tropical eosinophilia a large number of cases have been reported in which pulmonary infiltrations and eosinophilia have been associated with asthmatic symptoms.\* In most cases the occurrence of pulmonary infiltrations was only an incident in chronic or recurrent bronchial asthma, but some had asthmatic symptoms only while the pulmonary infiltrations were present. In a few, though there was a history of asthma, no asthmatic symptoms occurred during the period when the infiltrations were observed (Alwall, 1943; Hennell and Sussman, 1945; Freund and Samuelson, 1940; Baer, 1941; Woolf and Gould, 1949). In one case asthma developed for the first time three months after the lung infiltrations had cleared (Peabody, 1944), and in another for the first time in the last two years of a seven-year period during which there had been recurrent pulmonary infiltrations (Hennell and Sussman, 1945).

It is not to be denied that patients with chronic asthma may develop an intercurrent pneumonia, and some of these cases may have an eosinophilia associated with the original asthma. Saupe (1940) reviewed films taken of 355 cases of asthma

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\* Peirce, Crutchlow, Henderson, and McKay (1945); Alpher (1947); Gravesen (1938); Strand (1943); Saupe (1940); Bezançon, Jacquelin, Joly, and Moncharmont (1939); Hennell and Sussman (1945); Gottdiener (1945); Smith (1943); Squier (1947); Blanton (1945); Karan and Singer (1942); Pruvost and Brincourt (1946); Schulze (1940); Hansen-Pruss and Goodman (1944); Simonin and Girard (1946); Henderson and Peirce (1947); Hoff and Hicks (1942); Freund and Samuelson (1940); Baer (1941); Woolf and Gould (1949); Peabody (1944); Chafee, Ross, and Gunn (1942); Bayley, Lindberg, and Baggenstoss (1945); Harkavy (1943).

in a 10-year period. Infiltrations were observed at some time in 11.6% of these. The finding of the infiltration was usually an isolated incident and in only three cases was a definite eosinophilia recorded. In most cases the abnormal shadows were attributed to intercurrent pneumonia, though the radiographic appearance was very variable.

AGE.—Pulmonary eosinophilia with asthma has been recorded at all ages. Out of 58 cases in which the age was given, nine were 20 or under, 20 were aged 21 to 30, 11 aged 31 to 40, and 18 over 40.

SEX.—The condition is more than twice as common in women as in men.

GEOGRAPHICAL DISTRIBUTION.—There is no unexpected geographical distribution, cases having been reported widely in Europe and America.

CLINICAL FINDINGS.—During the attack most patients complained of cough, though sometimes this has been notably absent (Peirce and others, 1945). The cough is usually productive and sputum frequently abundant. It is usually mucoid, sometimes mucopurulent. It is often viscous, and occasionally, as in one of our cases, bronchial casts are expectorated. The sputum usually contains eosinophils, which are sometimes very numerous.

FEVER.—Of those cases in which it is recorded, about three-quarters ran a fever, though of course many of those in which there is no mention of fever were probably febrile. In the majority the maximum temperature was 100°–103° F. Of those in whom the duration of the fever is recorded, in about half the fever lasted for less than 10 days, but in a considerable number there were recurrent bouts of fever lasting more than a month.

RADIOGRAPHIC CHANGES.—In the radiographs of the reported cases bilateral abnormal shadows were seen about twice as often as unilateral, though they might appear first on one side only. In some cases one or more abnormal shadows were detected during the attack and no further infiltrations were recorded. In about the same number of cases the original shadow or shadows cleared only to be replaced by others, usually at intervals of days or weeks, sometimes of months, and occasionally even of years. It is difficult to generalize about the appearance of the abnormal shadows, which are usually referred to as "infiltrations." Much no doubt depends on the stage of the attack at which the first film was taken. Lateral films appear to have been seldom obtained. Not uncommonly the infiltrations are uniform as in consolidations; in a few cases there is mottling, sometimes resembling localized miliary lesions. In others, especially the more severe, they might be likened to clouds of smoke rising after an explosion in the region of the hilum and drifting up against the chest wall peripherally. Sometimes there are dense peripheral opacities with irregular margins, tailing off towards the hilum, or there may be chains of peripheral opacities resembling plaits of hair. It seems possible that had lateral films been taken many of the shadows would have been shown to have a segmental distribution. The abnormalities are a little commoner in the upper zones than in either the middle or lower. As far as we know, bronchiectasis has not previously been described in the region of the infiltrations, but saccular dilatations, sometimes of gross degree, were demonstrated in several of our patients. It seems most likely that the bronchiectasis was secondary to recurrent or prolonged consolidation.

**BLOOD COUNT.**—As in the prolonged infiltrations without asthma, the total white count is usually raised. Only five out of the 55 cases in which it was recorded had a maximal total white count of 10,000 or less, and 24 had counts of 20,000 or above. Forty-three out of 66 had eosinophil percentages of over 20, and 23 of over 50, the highest being 82 of 70,000 (Harkavy, 1943).

**INVOLVEMENT OF OTHER ORGANS.**—Among 78 cases in the literature with asthma, pulmonary infiltrations, and eosinophilia, there were 11 in which polyarteritis was proved, either at biopsy or necropsy. These 11 have been considered separately and are not included in the present group. Of the remaining 67 cases lesions were discovered in organs other than the lungs in 29. These comprised sinusitis in 21, pleural effusion in nine, purpura in six, paralyzes in five, adhesive pericarditis in four, ascites in four, polyarthritis in four, pericardial effusion in two, urticaria in two, ulcerative colitis in two, enlarged hilar glands in two, encephalitis in one, enlarged liver in one.

A number of cases, of course, had lesions in several organs. It might be argued that some of these cases had unproved polyarteritis nodosa. In nine out of 16 with lesions in organs other than the lungs, pleura, or sinuses, there was histological evidence available, in six at biopsy and in three at necropsy. None of the nine showed evidence of polyarteritis histologically, though in some (Hennell and Sussman, 1945 ; Broch, 1943 ; Harkavy, 1943) the appearances were intermediate between those of simple pulmonary eosinophilia, to be discussed later, and those of "pure" polyarteritis nodosa. Of the remaining seven cases in which there was no histological information five had apparently recovered at the time of reporting ; in the other two the fate was unknown. It is therefore reasonable to classify all these cases, in spite of the involvement of several organs, as cases of pulmonary eosinophilia with asthma, placing them towards the polyarteritis end of the continuum.

**PROGNOSIS.**—From the available data it is not easy to generalize about the prognosis. The duration of the illness is very variable. Many have had asthma for years and return to their chronic state after the acute illness, as judged by the acute symptoms, fever and infiltrations, has subsided. On these criteria the illness lasted for less than a month in a little under a third of the cases reported, for one to three months in about a third, and for more than three months in a little over a third. Many of the latter had recurrent attacks, usually over weeks or months, sometimes over years. A few cases undoubtedly became symptom-free and remained so, at any rate for a number of years (Gravesen, 1938 ; Saupe, 1940 ; Hennell and Sussman, 1945 ; Chafee, Ross, and Gunn, 1942 ; Bayley, Lindberg, and Baggenstoss, 1945 ; Harkavy, 1943). Nine died, three in an acute episode of asthma, several with cardiac failure, and one suddenly and unexpectedly after using an adrenaline spray. All except one of those who died had lesions in organs other than the lungs.

**AETIOLOGY.**—Aetiological factors have been searched for with varying enthusiasm or not at all, so that it is difficult to generalize. In a few cases a family or personal history of hypersensitivity has been recorded. In about a quarter skin tests were positive to pollens, dusts, animal products, food, or pneumococcal polysaccharides (Harkavy, 1943), but in many others no skin tests were done. Other possible factors in individual cases were ascariasis (Hansen-Pruss and Good-

man, 1944 ; Peabody, 1944), amoebiasis (Hoff and Hicks, 1942), pneumococci (Alwall, 1943 ; Harkavy, 1943), *Staphylococcus aureus* (Lumb, 1950), and adrenaline sensitivity (Gravesen, 1938 ; Pruvost and Brincourt, 1946). It should perhaps be noted here that, apart from the more cryptic cases we are discussing, pulmonary infiltrations, asthma, and eosinophilia have been recorded in filariasis (Malhotra, 1950) and schistosomiasis (Mainzer, 1950).

TREATMENT.—There is little guidance in the literature to the treatment of these cases. Where there has been an apparent cause which could be treated specifically, as in those associated with pneumococci (Alwall, 1943) and with amoebiasis (Hoff and Hicks, 1942), there seemed to be a response to the relevant specific treatment. One associated with ascariasis recovered after de-worming (Hansen-Pruss and Goodman, 1944). A case with pollen sensitivity apparently settled after desensitization (Hennell and Sussman, 1945). The antihistamine drugs were not available when most of them were reported, but one case (Pruvost and Brincourt, 1946) seemed to clear up when these drugs were used though autohaemotherapy was also given.

Two of our own cases seemed to improve under antihistamine drugs, and another remained free of attacks over a long period while taking "anthisan" prophylactically, though she relapsed when she stopped the treatment.

#### POLYARTERITIS NODOSA

We do not propose to discuss polyarteritis nodosa in detail, as a great deal has been written about it. Though lung changes are frequent at necropsy, there are only a limited number of proved cases recorded in which blood eosinophilia was associated with pulmonary infiltrations on the radiograph (Peirce and others, 1945 ; Hennell and Sussman, 1945 ; Weir, 1939 ; Miller and Daley, 1946 ; Elkeles and Glynn, 1944 ; Svanberg, 1945). About two-thirds of these had asthma. Of those with asthma some had had a long history of it, but others developed asthmatic symptoms only during their final illness.

The total white count was usually over 20,000 and the eosinophilia over 20%. The type of radiographic change was very variable. In all cases in which it was recorded changes occurred in both lungs. In the majority it was described as infiltration, but in some there was miliary mottling. Nearly all these patients died, though one (Tomenius, 1949), who had been treated with antihistamine drugs, apparently recovered, at least temporarily.

#### EOSINOPHILIC PLEURAL EFFUSIONS

Pleural effusions containing a high proportion of eosinophil granulocytes may occur in any of the subgroups of pulmonary eosinophilia. It seems probable that on occasion the effusion may obscure an underlying lung lesion and the case present as one of primary eosinophilic pleural effusion. Such cases should probably be included in the syndrome of pulmonary eosinophilia.

Reinikainen (1947) has reviewed the literature of eosinophilic pleural effusions and described four cases in which there was no obvious underlying lung lesion ; three of them had a blood eosinophilia. In a more recent review MacMurray, Katz, and Zimmerman (1950) have listed a large number of conditions which have been

associated with eosinophilia in the pleural fluid ; they described three cases of their own, one associated with pneumonia, one with Hodgkin's disease, and the third apparently primary. Punch and Close (1938) recorded a case in which there was purpura and pericardial effusion as well as eosinophilic pleural effusion. Occasionally tuberculous pleural effusions contain many eosinophils and are accompanied by a blood eosinophilia (Gill, 1940). Such effusions have also been described as a complication of artificial pneumothorax for tuberculosis.

In about two-thirds of the reported cases of eosinophilic pleural effusions, whatever the primary cause, the effusion has been haemorrhagic.

TABLE  
SUMMARY OF CLINICAL CHARACTERISTICS OF DIFFERENT TYPES OF PULMONARY  
EOSINOPHILIA

Pulmonary Infiltrations with Eosinophilia						
Group	Severity of Symptoms	W.B.C.s	Eosinophils (%)	Other Organs Involved	Duration of Illness	Fatal Outcome
Simple pulmonary eosinophilia ..	Slight	High normal	Usually under 20	Rarely	Under 1 month	Never
Prolonged pulmonary eosinophilia .. ..	Slight or moderate	High or very high	Usually over 20	Rarely	2-6 months or longer	Never
Pulmonary eosinophilia with asthma ..	Slight, moderate or severe	Usually high or very high	Often over 20	Sometimes	Varies. Often 3-4 months, may be years	Sometimes
Tropical eosinophilia .. ..	Moderate or severe	High or very high	Usually over 20	Never	Months or years	Never
Polyarteritis nodosa ..	Usually severe	Usually high or very high	Usually over 20	Always	Varies, usually months	Usually

### PATHOLOGY

**SIMPLE PULMONARY EOSINOPHILIA.**—In Löffler's syndrome opportunities of studying the pathological lesions are naturally rare, since the condition is by definition not fatal. Von Meyenburg (1942) discovered in the lungs of three young soldiers dying from trauma, and of one dying from tetanus, changes which he considered to be those of Löffler's syndrome. The lesions in the lungs consisted of irregular bronchopneumonic foci which microscopically were small areas of alveolar exudate with many eosinophils. Foreign body giant cells were present in three cases ; in one there was an eosinophil infiltration of the interstitial tissue, and in some places early organization was seen. Little evidence of vascular damage was present, though in two cases there were perivascular collections of leucocytes and small thromboses. In two cases ascaris worms were found in the intestines, and in one an eosinophil focus was found in the liver.

**PROLONGED PULMONARY EOSINOPHILIA.**—No fatal case of prolonged pulmonary eosinophilia has been described but biopsies were taken in two cases. In one of Harkavy's (1943) cases biopsy of a necrotic area of skin in Scarpa's triangle showed acute diffuse inflammation with infiltration by eosinophil cells. In Perlingiero and György's case (1947) a biopsy of the liver in the acute stage showed focal necrosis with giant cells and infiltration by eosinophil and neutrophil cells. A further biopsy five months later was normal.

**TROPICAL EOSINOPHILIA.**—Viswanathan (1947) has described the post-mortem findings in a patient with tropical eosinophilia who died from arsenical encephalopathy. His description of alveoli full of macrophages and eosinophils, large multinuclear giant cells, interstitial fibroblastic proliferation, and marked congestion of interalveolar capillaries bears close resemblance to the cases already described. The lesion occurred mainly near the terminal bronchioles, but no lesions of the bronchi themselves are mentioned. The haemorrhages and engorgement of interalveolar capillaries were attributed to the arsenical intoxication.

**PULMONARY EOSINOPHILIA WITH ASTHMA.**—There have been a number of necropsies reported in patients dying from pulmonary eosinophilia with asthma. Broch (1943) described the findings in a young woman who, having had asthma for only a year, died suddenly after using an adrenaline spray for the first time. The blood had shown a 70% eosinophilia. A radiograph of the chest before death revealed a small area of consolidation in the second right interspace, and histologically the alveoli in this area were stuffed with lymphocytes, plasma cells, and eosinophils. The thickened interstitial tissue also contained eosinophils and the capillaries were distended. Some of the bronchi were intensely infiltrated with neutrophils and eosinophils. Chafee and others (1942) also described the post-mortem findings in a young man who, having had asthma for only three months, died in status asthmaticus after an injection of morphine. He had had an eosinophilia of 14%. The chest radiograph had shown an irregular mottling throughout both lungs and this was found to be due to scattered areas of consolidation. The bronchial mucous glands were hypertrophic and some of the lumina were filled with an exudate containing numerous eosinophils. The alveoli were full of inflammatory exudate, eosinophils, and fibrin, while the interstitial tissue showed early organization and the branches of the smaller blood vessels were thrombosed. Similar areas of degeneration with massive eosinophilic infiltration were also found in the heart. Buckles and Lawless (1950) have described an interesting case of a man aged 59 who had had five months' cough, wheeziness, and loss of weight, with a persistent radiographic shadow at the right apex. His blood showed a 43% eosinophilia and there were eosinophils in his sputum. As it was impossible to exclude carcinoma of the bronchus a pneumonectomy was performed and a firm, yellow mass was found in the right upper lobe. Microscopically this was found to consist of fibrosis, massively infiltrated with eosinophils. There were also granulomatous areas, endothelial cell proliferation with giant cells, arteriolitis, and periarteritis. The patient made a good recovery and two months later the eosinophilia had disappeared.

The next type of case in order of severity is the established asthmatic with a history of perhaps several years of recurrent pulmonary infiltrations associated with



eosinophilia, who dies eventually either in status asthmaticus or in congestive cardiac failure. Here we would expect to find more chronic changes, and this is borne out by such a case as that described by Bayley and others (1945). Their patient had had asthma for seven years with recurrent infiltrations and eosinophilia. At post-mortem examination there were numerous nodules of various sizes throughout the lungs. Microscopically these were areas of organized pneumonia containing many eosinophils, much fibrous tissue, and granulomata similar to those seen in rheumatic fever. The nodules of the bronchioli were infiltrated with eosinophil leucocytes and plasma cells. The blood vessels showed a severe inflammatory process with actual necrosis in places. Harkavy (1943) also described 15 cases of asthma associated with recurrent pulmonary infiltration and eosinophilia; four of his patients died and he found the pulmonary infiltrations to be areas of congestion and oedema with thickened interalveolar septa infiltrated by eosinophils, polymorphs, and lymphocytes. The lesions in the blood vessels varied from a simple intimal thickening to acute necrotizing arteritis; two of the cases were regarded as polyarteritis nodosa. Similar changes were seen in the vessels of the pleura, pericardium, heart, liver, kidneys, uterus, and intestines, and in a skin nodule in one patient.

**POLYARTERITIS NODOSA.**—Bergstrand (1946) described similar pathological findings to those of Harkavy in the lungs, heart, and other organs of four asthmatics who had had transient pulmonary infiltrations and eosinophilia. The lesions of polyarteritis nodosa were found in all four cases. There was a good deal of fibrosis, and it seems likely that fibrosis can occur also in the late stages of pulmonary eosinophilia with asthma.

Smith (1948) described the findings in a woman of 48 years, who developed recurrent attacks of infective asthma and haemoptyses and died after six months in congestive cardiac failure. Radiographic examination had shown a mottling throughout the lungs which was seen at necropsy to be due to numerous small, brownish-yellow nodules. Microscopically the nodules were focal necrotic granulomatous areas containing eosinophils and often giant cells. The submucosa of the bronchi was stuffed with eosinophil leucocytes and plasma cells. All stages of polyarteritis nodosa were seen in the vessels of the lungs and also in those of the heart, spleen, and kidneys. Lumb (1950) has described a somewhat similar case.

These findings indicate that histologically the lesions in all cases of pulmonary eosinophilia are basically similar. As with the clinical manifestations there is a trend of increasing severity from the mainly alveolar infiltrations, with residual necrotic foci and giant cells, of simple pulmonary eosinophilia or Löffler's syndrome to the widespread damage and severe necrotic arteriolar foci found in polyarteritis nodosa. Where there are asthmatic symptoms the lesions appear to be closely related to the bronchi, as in tropical eosinophilia, or actually to involve the bronchial wall, as in pulmonary eosinophilia with asthma.

## DISCUSSION

It is clear that the cases included in the syndrome of pulmonary eosinophilia have certain factors in common besides eosinophilia and pulmonary infiltrations. We have shown that the cases can be put in a series comprising all grades of severity, from the mild, transient, and often symptomless infiltrations of Löffler's

syndrome to the severe, prolonged, and usually fatal manifestations of polyarteritis nodosa. We have also shown that the pathological findings in the different types of pulmonary eosinophilia suggest that they are different grades of the same fundamental process. The diversity of the causative agents which have been identified, the eosinophilia, and frequently the family or personal history of allergic illness strongly suggest that pulmonary eosinophilia is a manifestation of hypersensitivity. The occurrence of asthma and urticaria in a number of cases is also in favour of this view.

There is a certain amount of experimental evidence bearing on the problem. Fried (1933) produced "allergic lobar pneumonia" by intratracheal injections of horse serum in sensitized rabbits. Herbut and Kinsey (1946) reproduced the radiographic changes of Löffler's syndrome in rabbits by similar methods. Rich's work (Rich, 1942; Rich and Gregory, 1943a and b) has conclusively shown that polyarteritis nodosa is a hypersensitive reaction, and many of his experimental animals had lung lesions.

There are certain objections. In many cases, especially those of Löffler's syndrome and tropical eosinophilia, there is no family or personal history to suggest a tendency to hypersensitive reactions. Nevertheless it may be that certain allergens are so powerful that they are able to induce hypersensitive reactions even in those with no intrinsic tendency to react in this way. Sprent (1949) has shown that various extracts of ascaris worms are very powerful allergens and this may account for the lower incidence of a family or personal history of allergy in cases of Löffler's syndrome. If mites are indeed an important cause of tropical eosinophilia it is possible that they may prove to be particularly powerful allergens.

All the conditions we have been mentioning are probably "diseases of adaptation." Adrenocorticotrophic hormone (A.C.T.H.) has been used successfully in the treatment of asthma (Rose, 1950) and a case of "Löffler's syndrome" is said to have responded well; details of the case suggest that it should be classified as pulmonary eosinophilia with asthma. In five other cases of "Löffler's syndrome" the radiograph is said to have cleared under treatment with A.C.T.H. within 24 to 48 hours, but three of them relapsed later. Insufficient details are given to indicate into which clinical group these cases should be included.

### CONCLUSIONS

We suggest, as others, notably Harkavy, have indicated before, that the syndrome of pulmonary eosinophilia represents a peculiar reaction of the body to various stimuli. This reaction can be regarded as one of hypersensitivity, though some of the allergens are probably capable of producing a reaction in most people. When the hypersensitive reaction is brief and involves only the alveoli the manifestation is a "simple pulmonary eosinophilia" as described by Löffler; when the reaction is more prolonged it may be called "prolonged pulmonary eosinophilia." When the bronchi are also involved the condition becomes "pulmonary eosinophilia with asthma" or, possibly when the precipitating factor is a bronchial infestation with mites, "tropical eosinophilia." If, in addition, there are gross lesions of the blood vessels there will probably be lesions of other organs and the condition may go on to the full picture of polyarteritis nodosa.

Thus both clinically and pathologically there is a continuum from the simple and transient abnormalities of Löffler's syndrome to the severe and often fatal manifestations of polyarteritis nodosa. To certain parts of this continuum, previously nameless, we have given arbitrary names. We would emphasize that we are not trying to fossilize these conditions into rigidly separate categories but are merely proposing convenient labels as a necessary preliminary to the further discussion and investigation of an obscure group of diseases.

### CASE REPORTS

The following patients were all under the personal care of one or other of the authors and may perhaps be taken as representative of pulmonary eosinophilia as seen in London hospitals.

#### SIMPLE PULMONARY EOSINOPHILIA

*Case 1.*—An English doctor, a man aged 50, had a history of winter cough following colds for a few years.

On September 4, 1950, he developed an increasing cough, lemon-yellow sputum, wheeze, feverishness. Up to eight days before he had been staying on a farm with exposure to the usual dairy products. He was admitted to Hammersmith Hospital on September 7. His temperature was 99° F. for three days, there were rales at the left base, and radiographs showed a patch of consolidation in the posterior segment of the left lower lobe. His sputum was of a striking lemon-yellow and contained 40% eosinophils with no pathogenic bacteria. He was treated initially with penicillin. W.B.C. counts on the third day of illness showed a total of 7,600 per c.mm., with 380 (5%) eosinophils; on the seventh day the eosinophils were 720 (12%), on the sixteenth day 780 (13%), and on the twenty-fourth day 120 (2%). The symptoms, signs, and radiographic changes resolved within 14 days. Stool examinations for ascaris ova, continued over four months, were negative.

The relatively slight general symptoms, low pyrexia, striking lemon-yellow sputum containing eosinophils, transient pulmonary shadow, and mild transient eosinophilia are all typical of Löffler's syndrome. Some rales persisted at the opposite (right) base during the following ten months. These were probably associated with an area of local bronchiectasis which was responsible for his winter cough.

#### PROLONGED PULMONARY EOSINOPHILIA

*Case 2.*—An Indian schoolboy, aged 9, in 1942 (aged 6 months) had an unexplained fever for five days while in a malarial area; the fever responded to quinine and sulphonamides. In 1944 (aged 2) measles was followed by cough and fever which lasted three weeks. Afterwards there was a little cough off and on, and every few months attacks of fever with some increase in cough, but no abnormal physical signs in the chest. No blood counts, blood slides, or chest radiographs were taken, and the fever always responded to quinine and sulphonamides. His father had once had urticaria and a grandfather had had dermatitis.

In November, 1950, he arrived in England in good health. On March 22, 1951, he had a sudden recurrence of cough, followed by a left pleuritic pain a few days later. Physical examination was negative and there was no fever. Radiographs showed consolidation of the anterior basal segment of the left lower lobe (Figs. 1 and 2). A month later symptoms had subsided, but radiographs showed a slight extension of the lesion.

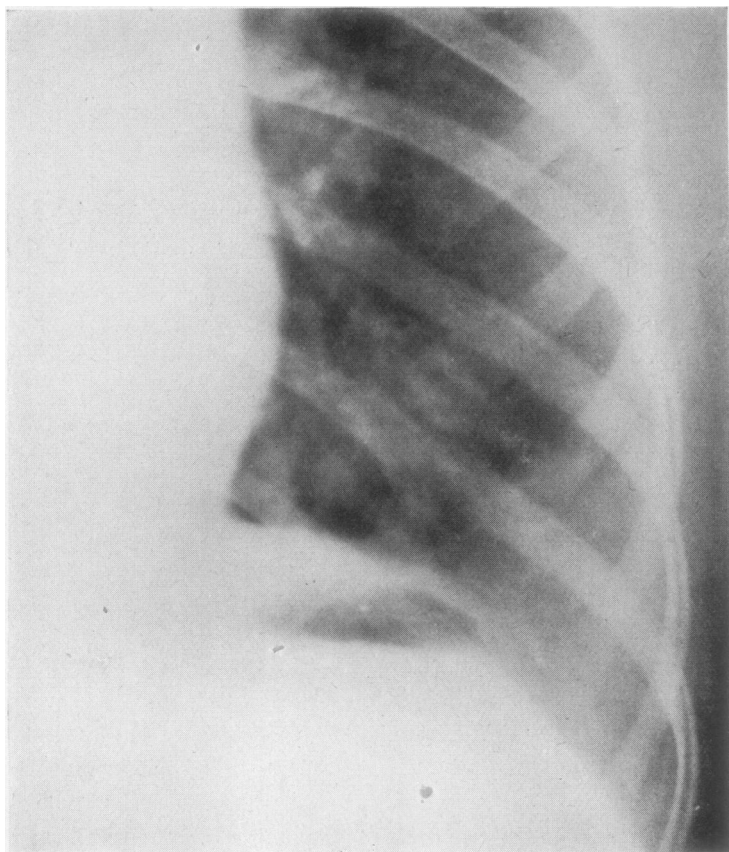


FIG. 1.—Segmental consolidation at the left base (Case 2). Dextrocardia.

FIG. 1

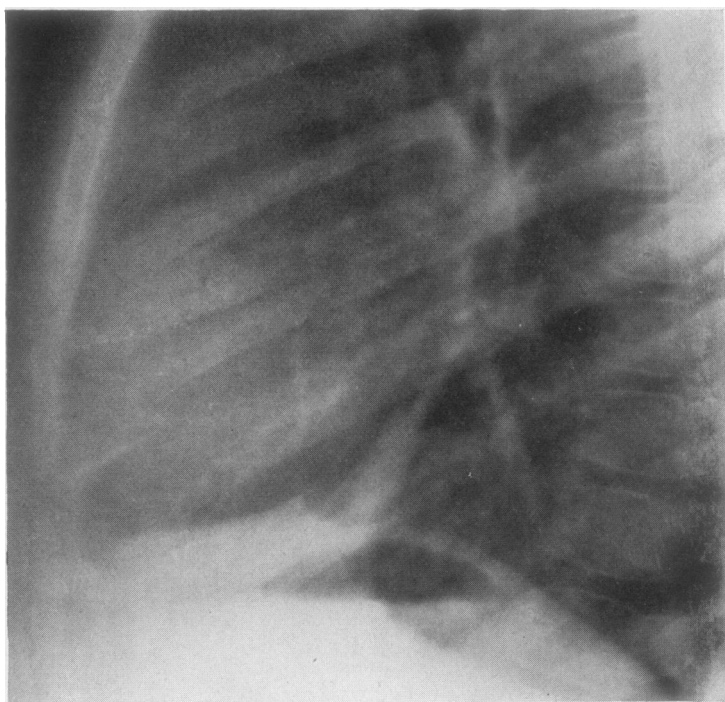


FIG. 2.—Lateral view of Fig. 1.

FIG. 2

He was admitted to Hammersmith Hospital, where the following investigations were carried out. A white cell count gave 16,000 per c.mm., eosinophils 4,320 (27%). In the sputum (trace only obtainable) were seen a few eosinophils, mixed flora, but no tubercle bacilli. In the stools, only trichomonads were found. There were no parasites in the blood (including midnight specimen). There was no eosinophilia in the father's blood film. The boy was Mantoux positive (1 in 10,000); Casoni negative; skin tests were negative to standard allergens.

Under observation the lung lesion slowly cleared, and a film on June 27, 1951, was virtually clear. Blood eosinophils also slowly declined to a white cell count of 6,000, with 350 (5%) of eosinophils on this change.

A case of prolonged pulmonary eosinophilia arising in England in an Indian boy. A local infiltration in the lung was accompanied by an eosinophilia of 27%, but there were minimal symptoms. The infiltration and eosinophilia resolved slowly over three months. There was no evidence that the previous febrile attacks in India had been of the same nature.

#### PULMONARY EOSINOPHILIA WITH ASTHMA

*Case 3.*—A man aged 36 had no family history of allergy or tuberculosis. In childhood he had "hay-fever" with certain odours such as fried fish, gas, or pollens. In 1925, at 10 years of age, he developed a cough and loss of weight, was notified as a case of tuberculosis, and attended a tuberculosis dispensary till he was 16 years. *M. tuberculosis* was never found.

In 1939, aged 24, he joined the Army, but in 1940 developed recurrent asthmatic bronchitis. Radiological examination showed opacities in the right upper and both lower zones, and he was invalided from the Service with a diagnosis of pulmonary tuberculosis (Figs. 3 and 4). He was in a sanatorium for two years with slight cough, haemoptysis, and dyspnoea with an opacity below the left clavicle. Sputum was repeatedly negative. He was discharged in April, 1942.

In July, 1943, he was admitted to another sanatorium with a lesion at the right apex: sputum and gastric lavage were negative on culture. He then continued under the supervision of a chest clinic with recurrent asthmatic bronchitis in the winter months and transient radiological opacities in different areas of both lungs (Figs. 5, 6, and 7).

In November, 1947, he was admitted to the Brompton Hospital with chronic infective asthma. Skin tests were negative: the sputum contained a mixed flora. There was a leucocytosis varying between 23,000 and 8,000 per c.mm., with 16 to 17% of eosinophils. A course of "novarsenobillon" (2.1 g.) was given without appreciable benefit.

Bronchograms in February, 1948, showed patchy fusosaccular bronchiectasis in various parts of all lobes on both sides (Figs. 8 and 9).

He continues to have recurrent bouts of infective asthma with transient pulmonary opacities. The leucocytosis varies between 18,000 and 14,000 per c.mm., with eosinophils between 10% and 5%.

An allergic individual started to have infective asthma at the age of 24, at which time he was thought to be suffering from pulmonary tuberculosis. Asthmatic bronchitis and transient infiltrations persisted since, the correct diagnosis being made when he was aged 32. Fusosaccular bronchiectasis is now present.

*Case 4.*—A journalist aged 23 had had mild eczema as a baby. Hay fever and asthma started at the age of 3 and have persisted intermittently since, being never more than moderately severe. In March, 1947, he was confined to bed for a month with right pleuritic pain and bronchitis, a fair response being obtained from penicillin. He con-

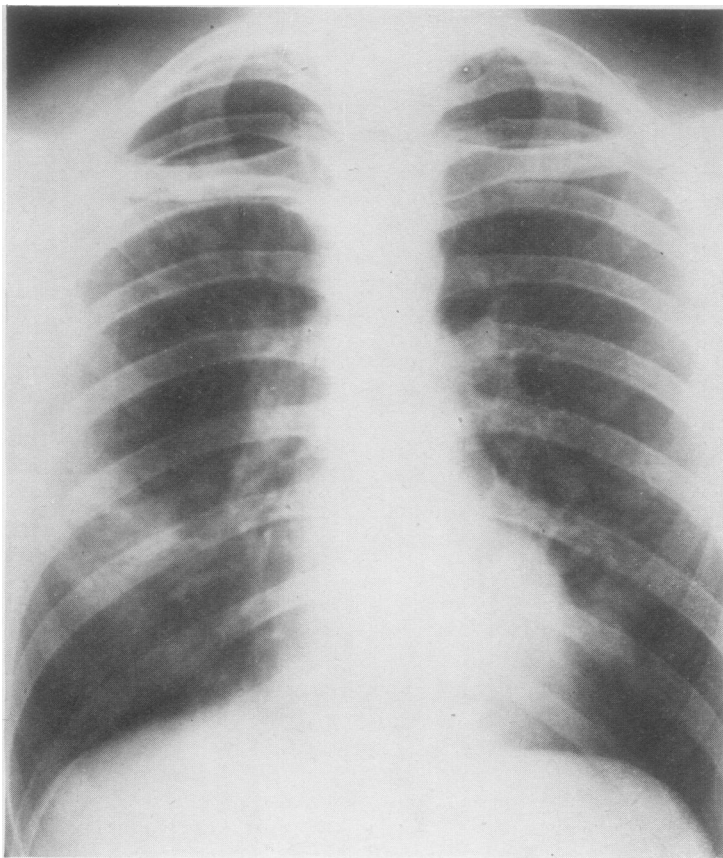


FIG. 3

FIG. 3.—November, 1940:  
opacity right upper  
zone and both lower  
zones (Case 3).

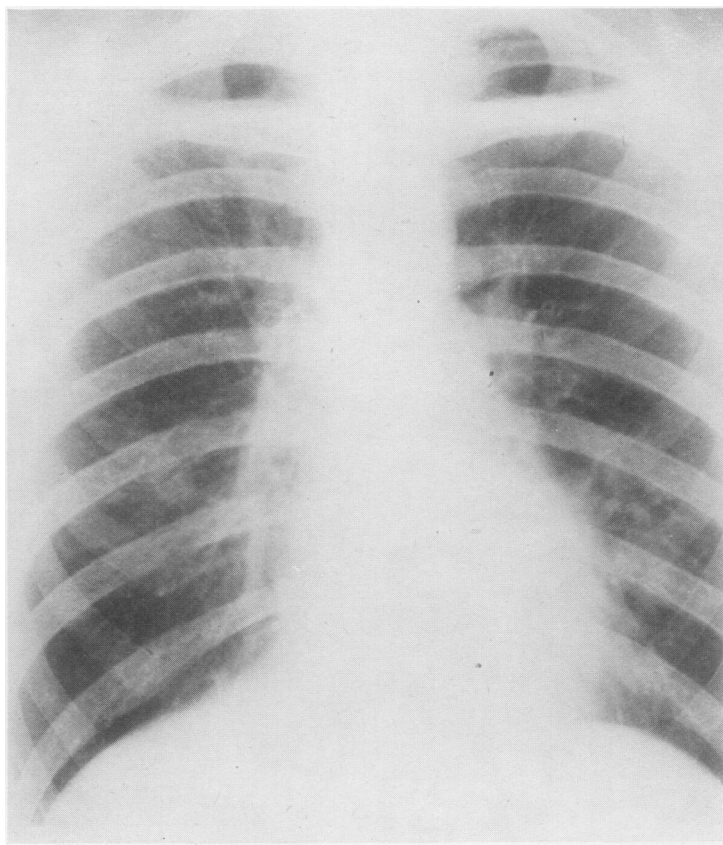


FIG. 4.—December, 1940  
(five weeks later): con-  
siderable clearing of  
lesions on the right,  
but further extension  
in left lower zone  
(Case 3).

FIG. 4

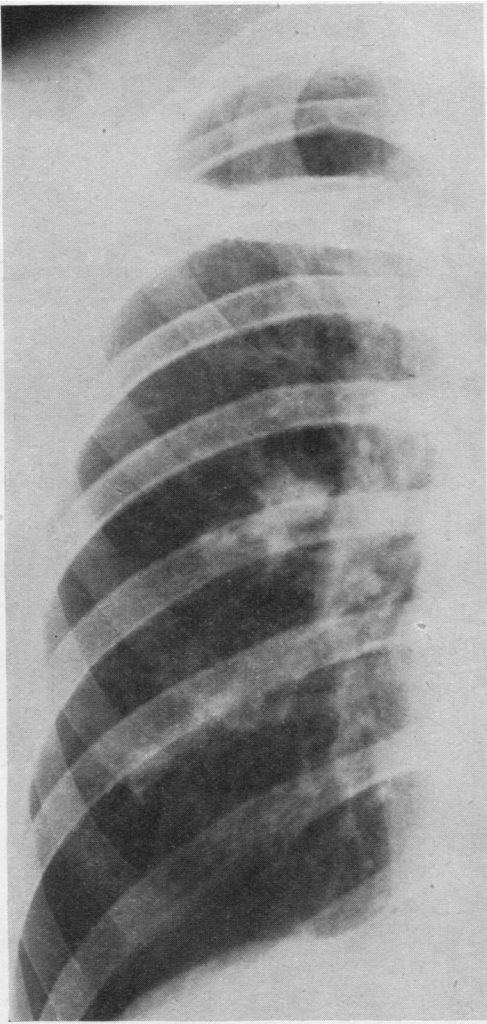


FIG. 5

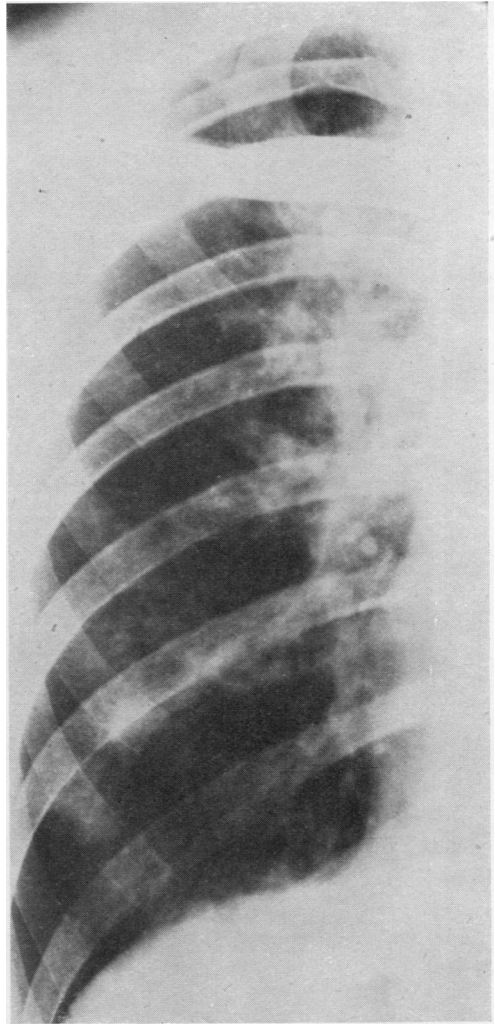


FIG. 6

FIG. 5.—July, 1947 (seven years later): streaky infiltration in right upper zone with patchy consolidation in right mid and lower zone (Case 3).

FIG. 6.—August, 1947: extension of infiltration in the right upper zone (Case 3).

FIG. 7.—September, 1947: considerable clearing of infiltration (Case 3).

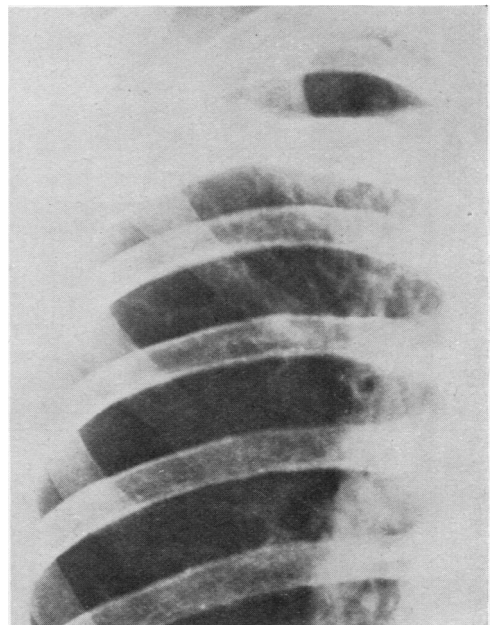


FIG. 7



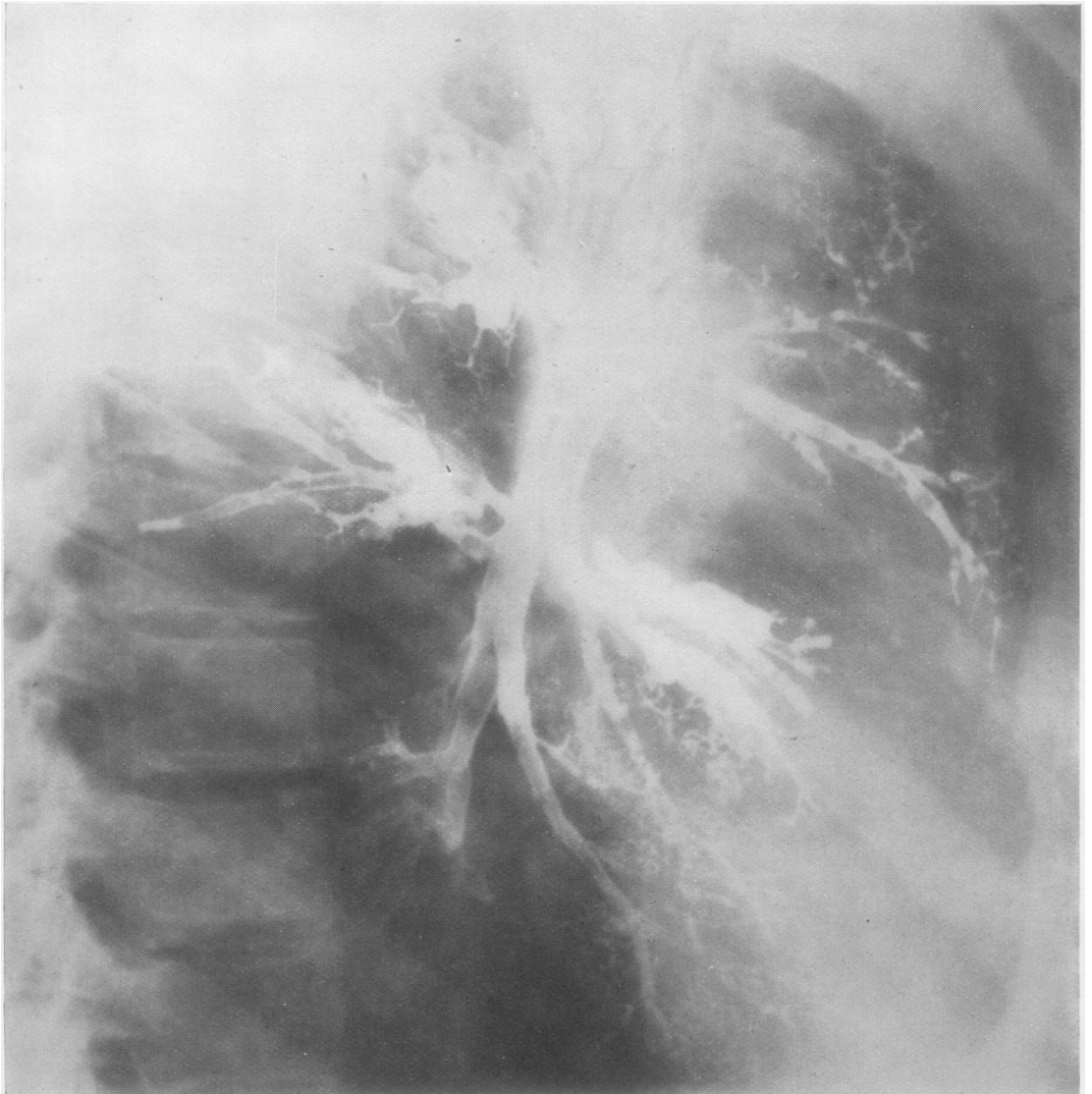


FIG. 8.—January, 1948: right bronchogram showing fusosacculary bronchiectasis of apical and posterior segment of right upper lobe, right middle lobe, and apical segment of right lower lobe (Case 3).

tinued to feel unwell, and in May, 1947, his first radiograph showed scattered mottling in the upper half of the right lung. During a month's observation in St. Bartholomew's Hospital, London, he ran an evening fever in the region of 99° F. A single blood count showed a normal total and differential white cell count, and no tubercle bacilli were found on direct smear on 12 occasions. The radiological appearances changed little in this time (Fig. 10). A mistaken diagnosis of pulmonary tuberculosis was made and a right artificial pneumothorax induced. The infiltration almost disappeared in three



months, to be followed by a massive consolidation in the right lower lobe. In December, 1947, a fresh pneumonic patch developed in the left mid zone, which was treated with penicillin and resolved in three weeks. During 1948 he felt well and his pneumothorax was maintained for residual infiltration in the right lung. In April, 1949, he suddenly became ill with a fever of 104° F. A radiograph showed a fresh consolidation in the left upper zone (Fig. 11) and a blood count of 15,000 white cells, of which 3,600 (24%) were eosinophils. The nature of his disease was then realized and the right pneumothorax abandoned. He recovered in two months and his blood count returned to normal.

He is still under observation and was seen in February, 1951. Throughout this time the right lung has shown a variety of consolidations, occupying on an average about a quarter of its substance; the left lung has shown patchy infiltrations from time to time.

Bronchograms in 1949 showed the characteristic cystic bronchiectasis at some of the sites of his former consolidations (Fig. 12).

An allergic subject had a series of consolidations in both lungs, some of which were accompanied by eosinophilia, over a period of four years. A mistaken diagnosis of tuberculosis was made at the beginning and an artificial pneumothorax maintained for almost two years.

*Case 5.*—A secretary, aged 34, had no previous history of respiratory or allergic disease. In May, 1948, she noticed a wheeze in her chest on moderately strenuous exercise. This persisted, but did not in any way interfere with her

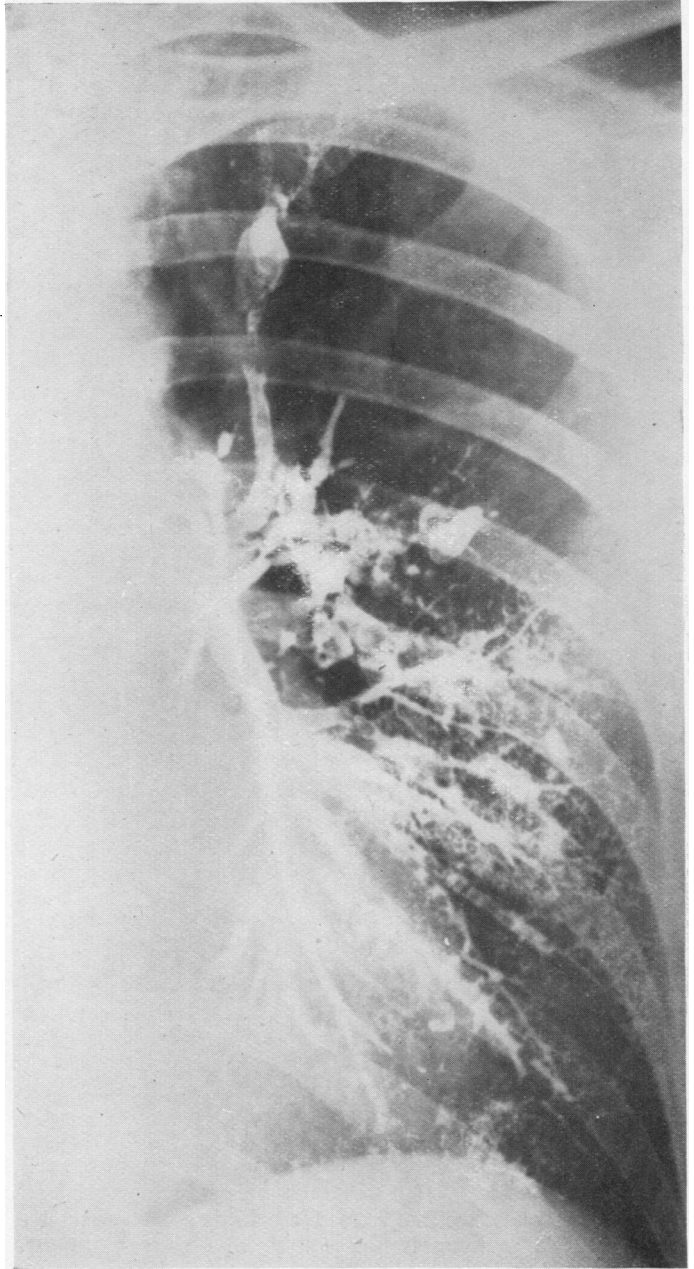


FIG. 9.—January, 1948: left bronchogram showing fusosaccular bronchiectasis in left upper lobe and some segments of left lower lobe (Case 3).

daily routine. In November, 1948, she developed a cold in the head which was quickly followed by bronchitis and a fever of 100° F. She was admitted to St. Bartholomew's Hospital, London, a fortnight later; her general nutrition was good and she was not in any way distressed. Her temperature was 101° F., and she had a wheeze in both lungs during the latter part of expiration. A radiograph of the chest showed scattered infiltration in both upper zones and a blood count 10,000 W.B.C.s per c.mm., of which 3,200 (32%)

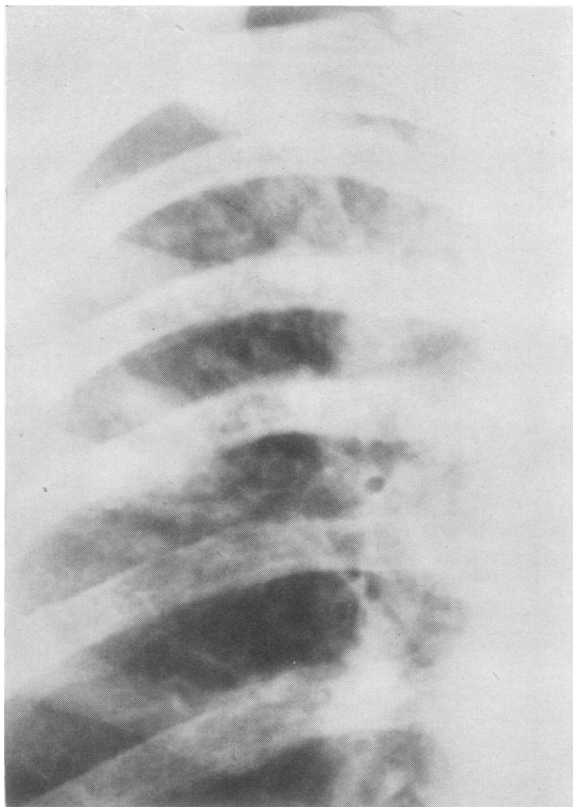


FIG. 10.—July, 1947: patchy infiltration of right upper and middle zones, the rest of the lung fields being clear at that time (Case 4). The infiltration remained virtually unchanged for six weeks and was mistakenly diagnosed as pulmonary tuberculosis.

were eosinophils. She remained in excellent health throughout her two and a half months in hospital, and her temperature gradually returned to normal over a period of nine weeks; the white blood count varied from 7,000 to 13,000 per c.mm. and the eosinophils returned to normal at the end of 10 weeks. A radiograph of the chest taken a week after admission was virtually clear, but a film taken a week later showed even more infiltration in the upper zones than formerly and lines of infiltration down the outer parts of the film, resembling plaits of hair (Fig. 13). These infiltrations slowly resolved in the next eight weeks.

She was followed up until January, 1951, and four more films were taken, all of which were clear. She remains at work and in good health, with some wheeziness on strenuous exercise.

This woman developed a wheeze at the age of 34 which persisted during two and a half years' observation. She had an episode of pulmonary infiltrations with eosinophilia which lasted for three months and has not recurred.

*Case 6.*—An electrical engineer, a man aged 26, since the age of 5 had had wheezy attacks, worse in late summer, lasting two to three weeks and averaging one to two a year. In 1942 (aged 18) he had an attack diagnosed as bronchopneumonia in which a radiograph was said to have shown "lungs filled with deposits (especially the right base), probably fibrous in nature; apices nearly clear." He was free of attacks for three years when he was in the Middle East during the war. Since the summer of 1949 he was easily tired, with intermittent wheeze and cough with white sputum. A radiograph in October, 1950, showed small infiltrations underlying the right and left clavicles which

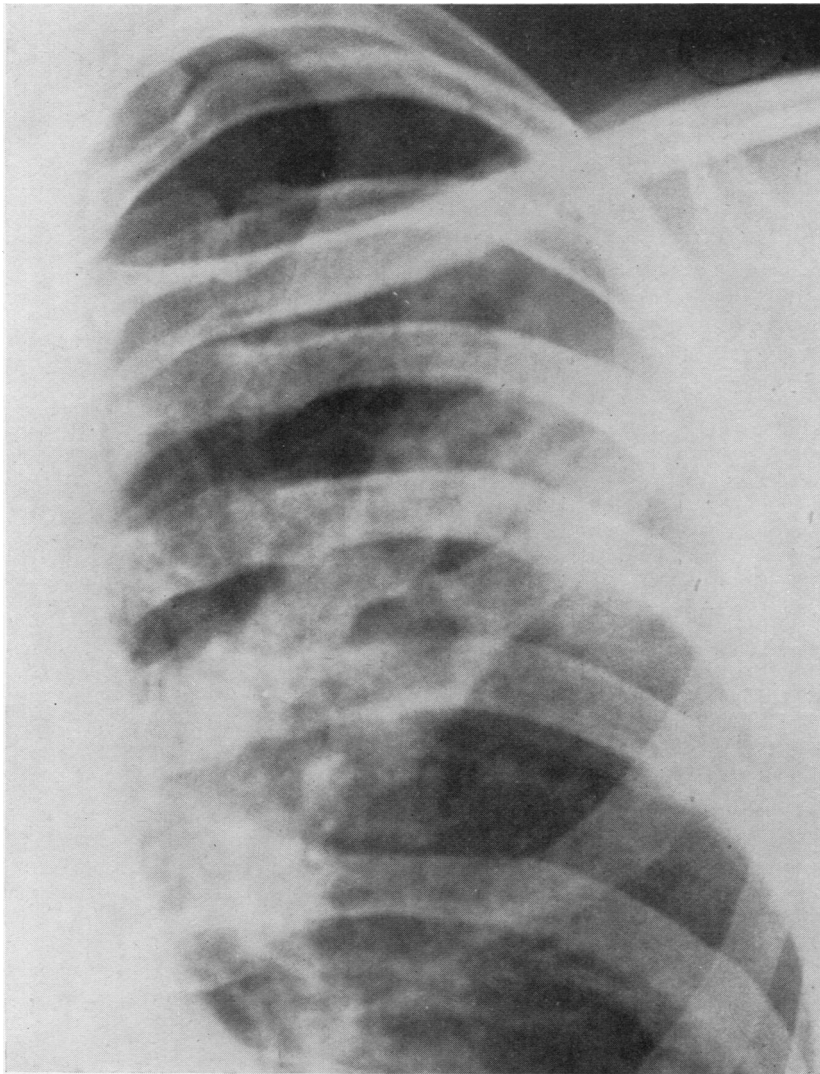


FIG. 11.—March, 1949: acute infiltration and cavitation in left upper and middle zones during a period of high fever and eosinophilia (Case 4).

remain unchanged. W.B.C. counts had shown repeatedly totals of about 20,000 with about 2,000 (10%) eosinophils. There was no family or other personal history of disorders of hypersensitivity.

He was admitted to Hammersmith Hospital, London, in January, 1951. He had no fever or significant physical signs. Radiographs confirmed the previous findings. A white cell count gave 9,000 per c.mm., eosinophils 1,080 (12%). Sputum showed no eosinophils, mixed organisms, and no tubercle bacilli. A bronchogram revealed slight distortion of the bronchi in the posterior segment of the right upper lobe and apex of the left lower lobe in areas corresponding to the infiltrations.

Skin tests gave no reaction to standard allergens except rabbit. (He had been wheezy after eating rabbit.) Intradermal reactions with bacteria from his sputum were the same as for a control patient. Blood eosinophils showed a drop of 64% after 100 mg. ephedrine and of 40% after 25 mg. A.C.T.H. Since discharge he has taken "phenegan"

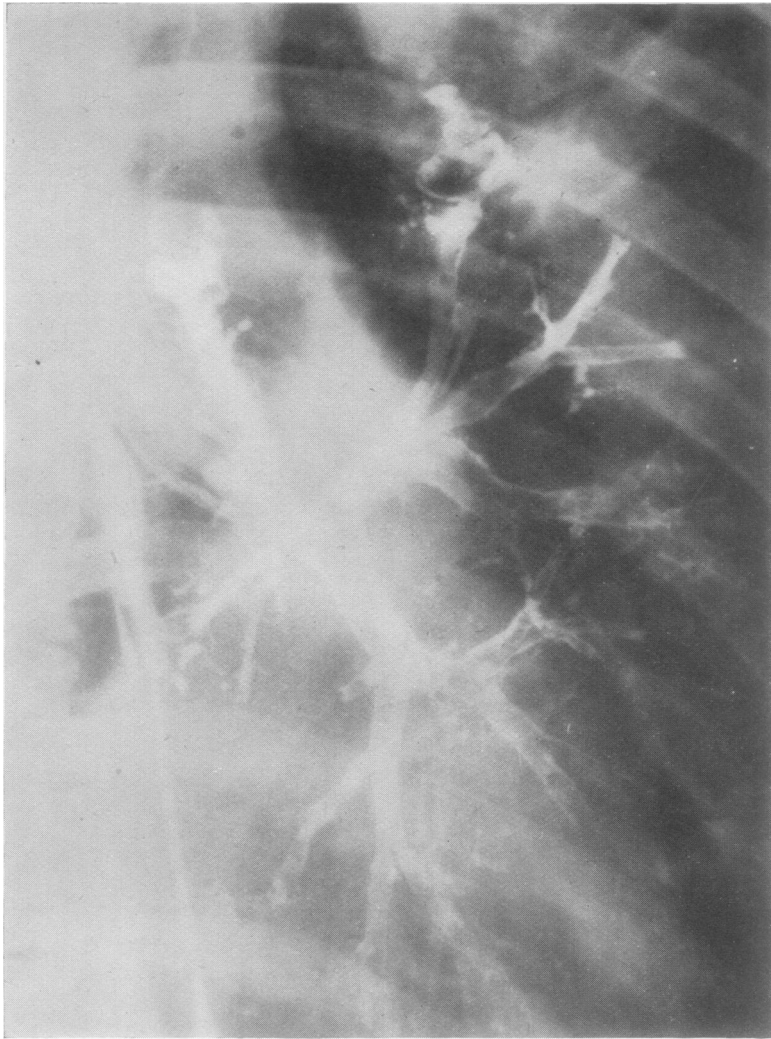


FIG. 12.—August, 1949: bronchogram of left lung showing patchy bronchiectasis in upper lobe and apical segment of the lower lobe (Case 4).

(50 mg.) at 10 p.m. and "anthisan" (50 mg.) at 4 p.m. daily, and had no further symptoms up to June, 1951.

A patient with pulmonary eosinophilia with asthma, mild in type, has remained symptom-free under treatment with antihistamine drugs, but is still under observation. There was distortion of the bronchi in the affected areas, but no definite bronchiectasis.

*Case 7.*—An English school-teacher, a woman aged 48, had had no previous chest trouble. In the winter of 1945–6 she had an intermittent cough, sputum, and mild fever. Between January and June, 1947, she had about six bouts of fever, cough, sputum, and diffuse chest pain. She was well between attacks except for increasing shortness of breath and wheeziness. Radiographs between March and June, 1947, showed transient, patchy areas of consolidation in various parts of the upper zones of both lung fields. In May, 1947, there were 17,800 W.B.C.s per c.mm., eosinophils 1,780 (10%).

She was admitted to Hammersmith Hospital, London, in June, 1947, where the wheezy, asthmatic breathing and eosinophilia were confirmed; there was no fever. Her sputum was coughed up in tough casts, sometimes branched, which were stuffed with eosinophils; there was a mixed flora, and yeasts which could not be cultured. No tubercle bacilli or mites were isolated. The sternal marrow showed 22% eosinophils. Skin tests were negative to standard allergens; reactions to bacteria from sputum were less than in a control subject. No parasites were found in the stools. She gradually improved in hospital and the chest became clear, with no further infiltrations in two months. Little effect was obtained from organic arsenic intravenously, but slight improvement followed the use of "benadryl." Eosinophils remained at about 2,000 per c.mm.

She subsequently felt better, but had another attack with fever and infiltration in December, 1947, four attacks in 1948, and two in February and March, 1949. The attacks were usually relieved by coughing up casts and were cut short by taking ammonium chloride in large doses to encourage expectoration. Eosinophils remained at 2,000 per c.mm. A bronchogram in April, 1948, showed marked bronchial dilatation in the posterior segment of the right upper lobe and middle lobe with a few scattered abnormal bronchi in the right lower lobe. On the left there was dilatation in the posterior and anterior segments of the upper lobe and one abnormal area in the lower lobe.

In March, 1949, she began taking "anthisan" (100 mg. thrice daily) prophylactically. In November, 1949, she had an attack of a different nature, without tightness in the chest, which was probably acute bronchitis. No radiograph was taken in the acute stage, but just afterwards the W.B.C.s numbered 30,000 per c.mm., with eosinophils 600 (2%). She was then much improved until September, 1950, when she had a haematemesis; the anthisan was stopped. From October, 1950, to June, 1951, she was confined to her house with almost continuous attacks of asthma, fever, and cough. She has now resumed prophylactic anthisan.

A patient is described with pulmonary eosinophilia with asthma, whose symptoms began at the age of 48 and who had recurrent attacks for four years, except during the 18 months in which she was taking an antihistamine drug prophylactically.

*Case 8.*—A girl of 17 years of age was referred by Dr. J. H. Dadds. There was no family history of allergy. At about 13 years of age she developed erythema multiforme.

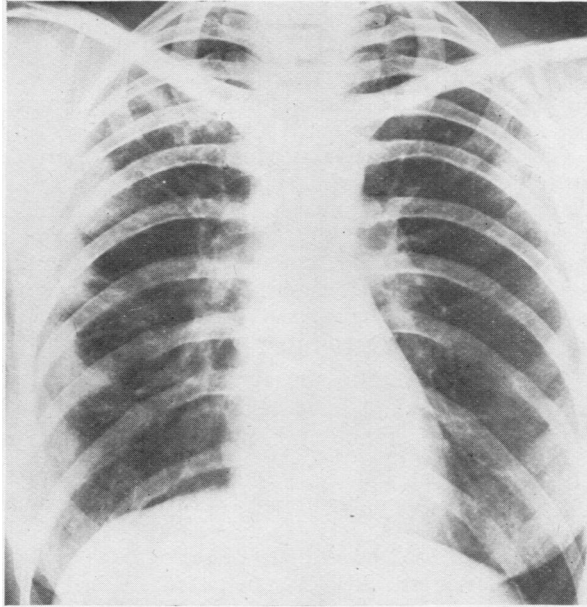


FIG. 13.—Patchy infiltration in the right upper zone with peripheral shadows in both lungs resembling plaits of hair (Case 5).

At 14 she developed sudden asthma without obvious infection, and this was followed by recurrent attacks of severe infective asthma with persistent wheezing, cough, and purulent sputum. She had slowly gone downhill during three years' observation.

White blood cell counts have varied between 16,000 and 24,000 per c.mm., with eosinophilia between 6 and 14%. Skin tests were negative and intestinal parasites have not been found. Skiagraphs showed transient pulmonary opacities in various parts of the lung fields for three years. Bronchograms showed patchy fusosaccular bronchiectasis in different segments.

Asthma developed at the age of 14 and was quickly followed by pulmonary eosinophilia; these have persisted during three years' observation.

*Case 9.*—A man of 39 years had no family history of allergy. In 1943 (aged 32), when in the Dutch West Indies, he developed dyspnoea with purulent sputum, followed by recurrent attacks of asthmatic bronchitis. Symptoms cleared on leaving the island, and he was in good health for six months, but on returning to England he developed chronic asthma which has persisted since. In 1945 he had a left spontaneous pneumothorax associated with infective asthma. There were no nasal symptoms. The asthma failed to respond to every form of treatment, and he had a sulphonamide toxic reaction with fever in 1949. In January, 1949, pulmonary infiltrations were first noted and have recurred at intervals since. His condition has been more or less stationary for five years.

His white blood cell counts have varied between 7,000 and 14,000 per c.mm., with eosinophilia between 5 and 11%. No intestinal parasites or mites have been found, and skin tests were negative. Bronchograms show minimal fusosaccular bronchiectasis in the right apical segment.

Asthma started at the age of 32. Pulmonary infiltrations were first observed six years later and have persisted during two years' observation. There was a spontaneous pneumothorax, and recent bronchograms showed a little fusosaccular bronchiectasis.

*Case 10.*—A housewife aged 45 had no previous history of respiratory or allergic disease.

In June, 1946, she started to have a cough and sputum, and in August, 1946, a mild wheeze developed. In November, 1946, she had pneumonia of the left lower lobe which resolved radiologically in a month. During the next year the wheeze persisted, and she lost 2 st. in weight. In November, 1947, two large masses of consolidation appeared in the left lung, occupying about three-quarters of the lung between them. Although the constitutional upset was slight, she ran an intermittent fever of up to 102° F. and her total white blood count was 11,350 per c.mm., of which 3,178 (28%) were eosinophils. The consolidations gradually resolved in a month, during the third week of which the left upper lobe became consolidated, to resolve in a month. Towards the end of January, 1948, after two months in hospital, she felt well apart from the wheeze and she was afebrile; her white blood count was 13,500 per c.mm., with 15% eosinophils.

A follow-up by correspondence in June, 1949, revealed that two further consolidations had occurred and the wheeze persisted.

Massive consolidation with eosinophilia started a few months after the onset of mild asthma and has recurred for two and a half years.~

#### PULMONARY EOSINOPHILIA WITH ASTHMA AND FEATURES OF POLYARTERITIS NODOSA

*Case 11.*—A woman aged 31 years. Her grandfather and two paternal uncles had asthma. She had frequent bronchitis in childhood, and at the age of 15 was in bed for five months with cough and loss of weight. Investigations in a sanatorium were

negative for tuberculosis. At 16 years she began to have asthma with the attacks of bronchitis.

She joined the W.A.A.F. in 1941, aged 20 years, and remained well until October, 1942, when she developed asthmatic bronchitis with blood-stained sputum which persisted off and on for three months. In December, 1942, she was in an R.A.F. hospital and had a course of sulphonamides with some improvement. In February, 1943, she developed a left pleural effusion containing 93% of eosinophils.

In March, 1943, she was admitted to the Brompton Hospital, London, with a bilateral hydrothorax and signs of infective asthma. There was irregular pyrexia up to 101° F. with pulse rate up to 130. The spleen was palpable. Radiographs showed large bilateral effusions with soft opacities in both upper zones (Fig. 14). There was a leucocytosis up to 22,000 per c.mm. and an eosinophilia varying between 12 and 44%. Investigations for tuberculosis, intestinal parasites, and hydatid disease were repeatedly negative. Fluid containing predominantly eosinophilic cells was aspirated repeatedly until August, 1943, when both pleurae were dry and the patient was symptomless, with a normal blood count. Serial radiographs showed clearing of the apical opacities, but at the end of August fresh lesions were noted in both upper zones without clinical symptoms (Figs. 15, 16, 17, and 18).

In October, 1943, painless nodules developed in the left forearm and palm. Biopsy showed a granuloma with multiple yellow foci in the muscles. Microscopically these consisted of epithelioid cells surrounding a necrotic centre of degenerate collagen material. There was no evidence of polyarteritis nodosa. Subsequently painful nodules resembling whitlows appeared on the fingers. She was discharged from hospital in March, 1944, with a normal radiograph of the chest and a leucocytosis of 19,600 per c.mm., with 4% of eosinophils (760 per c.mm.).

She remained well and at work during the next year, apart from occasional attacks of mild asthma and bouts of diarrhoea and vomiting every six to eight weeks; she married in June, 1945.

In September, 1946, asthmatic bronchitis recurred and she was readmitted to the Brompton Hospital in October, 1946, when the asthma had cleared but the radiograph showed an opacity in the right lower lobe suggestive of recent "pneumonia." Skin tests and other investigations were negative save for a leucocytosis of 14,500 per c.mm., with 38% of eosinophils (5,510 per c.mm.). She was found to have an ectopic gestation and a laparotomy was performed in December, 1946. She developed bronchopneumonia with pulmonary oedema and was desperately ill, but slowly recovered. Radiologically there was extensive opacity in the lower halves of the chest on both sides, but aspiration failed to reveal fluid (Fig. 19).

In March, 1947, there was a fresh crop of painless nodules in the pectoral muscles and left thumb, and biopsy showed a similar picture to the previous lesions. She was discharged to her home in April in fair health but continued to get recurrent nodules in the legs, buttocks, and forearms. In August, 1947, she had severe pain in the left forearm, with hyperaesthesia over the left hemi-trunk above the waist, necessitating morphine and analgesics for some weeks, and later there was anaesthesia of the left thumb, index, and middle fingers. After October the nodules ceased to appear, and apart from occasional wheezing she was in fair health. In June, 1948, she was well, with a leucocytosis of 12,000 per c.mm. containing 7% of eosinophils (840 per c.mm.) (Fig. 20). Bronchograms showed no evidence of bronchiectasis.

In November, 1948, she had severe left-sided migraine for three months, worse at menstruation. In May, 1949, she developed swelling below the right orbit, for which a normal canine was extracted and later swelling of the right upper eyelid for a few days.



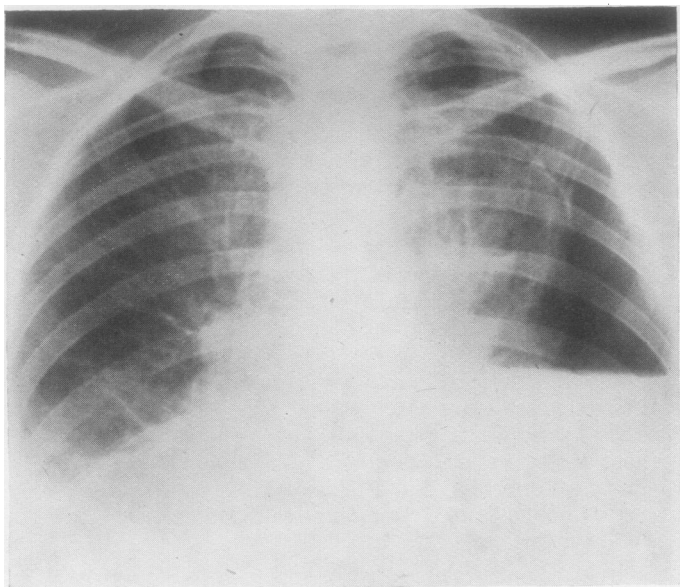


FIG. 14.—March, 1943: left hydro-pneumothorax and right pleural effusion with opacities in both upper zones (Case 11).

FIG. 15.—August, 1943: partial resolution of effusion and clearing of the upper zones (Case 11).

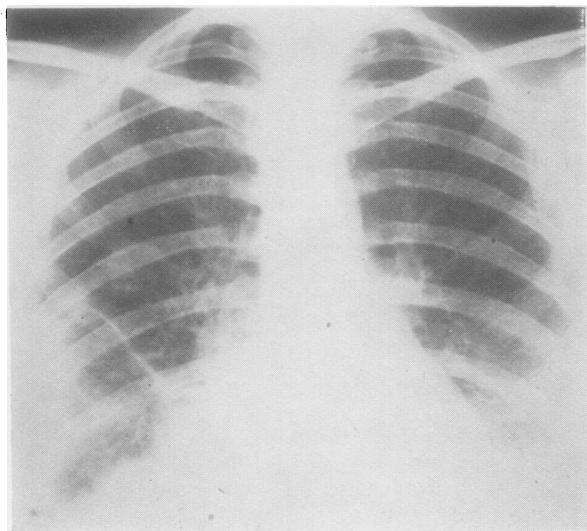


FIG. 15

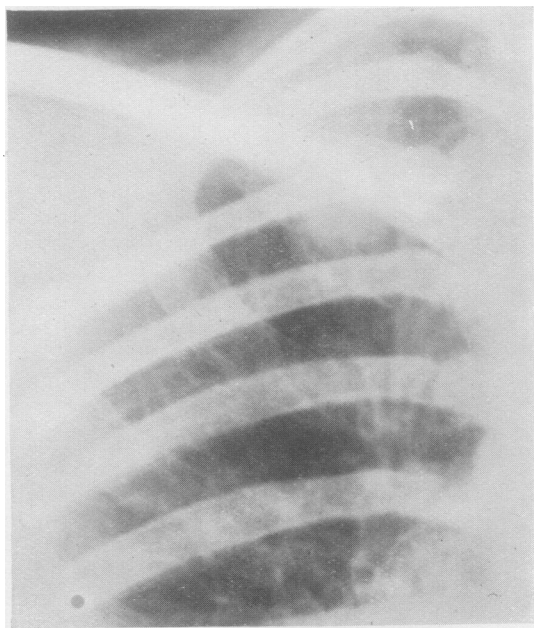


FIG. 16.—August, 1943 (three weeks later): fresh opacity in the right upper zone (Case 11).



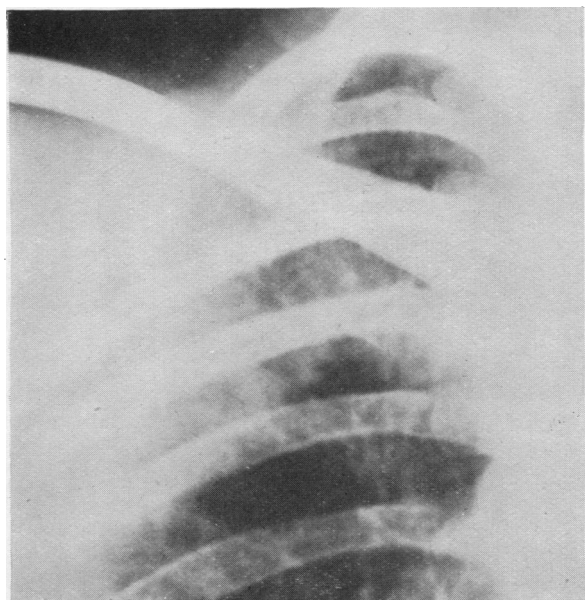


FIG. 17.—September, 1943: the opacity in the upper zone has migrated downwards (Case 11).

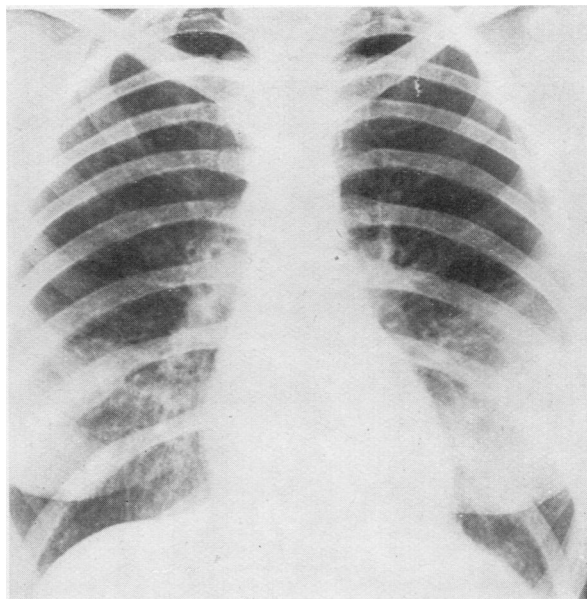


FIG. 18.—November, 1943: the opacity has resolved. The bases have become clearer (Case 11).

In August menorrhagia occurred for two months. In November there was a leucocytosis of 15,000 per c.mm., with 3% of eosinophils.

She remained well during the next 12 months with a normal radiograph of the chest and a normal blood count. There had never been evidence of renal damage nor of hypertension.

In January, 1951, she had a febrile illness for six weeks without chest symptoms; radiography showed encysted effusion at the right base, clearing in three weeks. In June, 1951, the radiograph of the chest was normal, but the patient was being treated for vaginismus. In July, 1951, she had relapsed, with pyrexia and further nodules, and in January, 1952, was admitted to hospital with cardiac failure and bilateral "pneumonia."

This case has many features associated with polyarteritis nodosa, but on careful examination of serial sections of at least five biopsies of nodules and of normal tissues there has been no microscopic evidence of arterial disease.

*Case 12.*—A woman, aged 45 years, was referred by Dr. J. H. Dadds. She had no family history of allergy. In August, 1944 (aged 39 years), when four months pregnant, she had "bronchitis" lasting three months. In February, 1945, soon after her third confinement, she developed a febrile respiratory infection with purulent sputum and asthma, and since that time has had recurrent attacks of asthmatic bronchitis, the longest period of freedom being about a month, and has steadily gone downhill. In February, 1949, she developed severe anorexia with recurrent vomiting and marked loss of weight; in July she was admitted to hospital with oedema and later developed ascites, enlarged liver with right-sided hydrothorax. The leucocyte count varied between 7,000 and 24,000 per c.mm., with up to 77% of eosinophils. During the next year she had persistent bronchospasm with 5 to 8 oz. of purulent sputum and recurrent bouts of pleural pain and fever. She had amenorrhoea for 13 months.

In November, 1950, she was admitted to the Brompton Hospital, London, with signs of asthmatic bronchitis but without cardiac failure. She developed purpura of the legs with weakness and paraesthesia of the left foot. She slowly improved with various

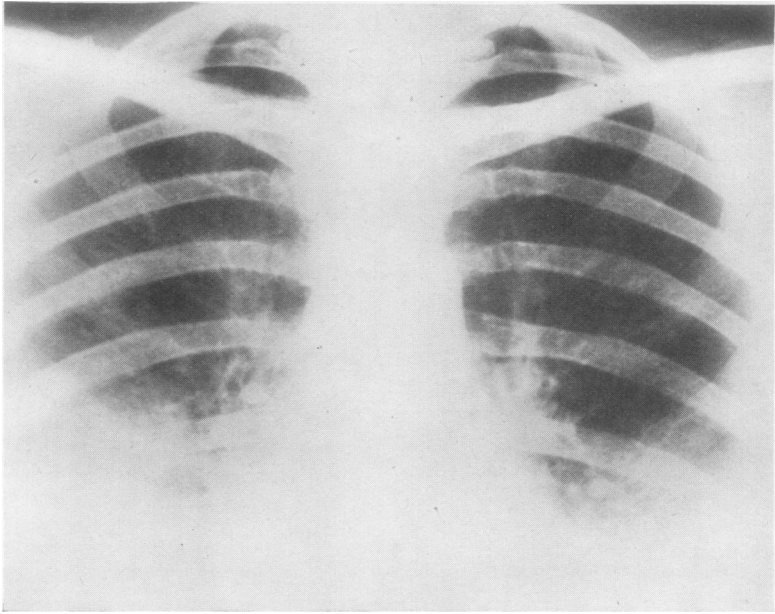


FIG. 19.—February, 1947: gross opacities at the bases (Case 11). Aspiration failed to reveal fluid.

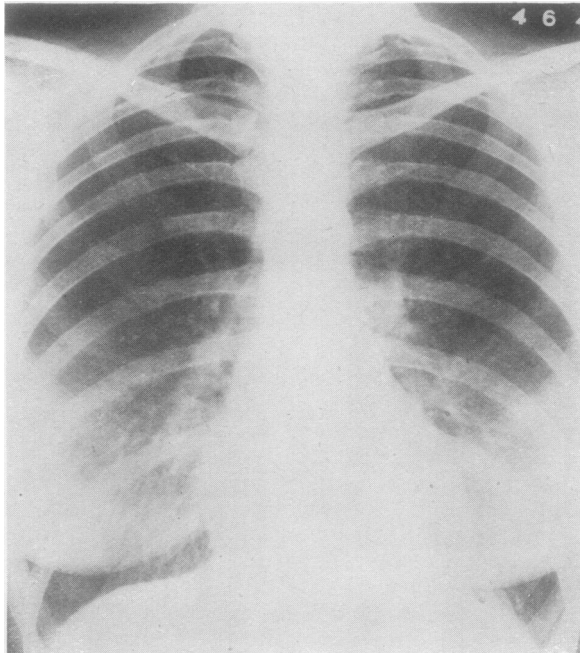


FIG. 20.—June, 1948: lung fields clear (Case 11).

antibiotics, organic arsenic, and breathing exercises, and was discharged in March, 1951, to a convalescent home.

Radiographs of the chest in July, 1949, showed small bilateral pleural effusions with an opacity in the right lower zone. In September, 1949, there was considerable cardiac enlargement in addition. In March, 1950, scattered opacities appeared in both lungs and slowly resolved by the following November, by which time her radiograph was normal, save for some thickening of the lesser fissure. Bronchograms were normal. Skin tests were strongly positive to egg, wheat, and pollens. Biopsy of muscle and lymph node was negative, no arterial lesions being found. An electrocardiogram suggested cor pulmonale.

A woman is described without an allergic diathesis who developed infective asthma at 39 years of age with recurrent attacks and a downhill course over six years of observation. There was an episode of anorexia followed by cardiac failure and hydrothorax when there was a high eosinophilia. The cardiac dilatation regressed. Pulmonary infiltrations were slight and bronchiectasis was absent. Polyarteritis was not found in biopsy of muscle and lymph node.

*Case 13.*—A woman aged 45 years. Her mother had migraine; there is no other allergic condition in the family. She had no respiratory disease except "rhinitis" for the previous 15 years, until June, 1944, when she developed bronchitis when sleeping in an air-raid shelter, followed shortly by attacks of infective asthma. In November, 1944, she developed "pneumonia," with blood-stained sputum up to 15 oz. daily, with pyrexia to 103° F. which did not respond to sulphonamides. Asthma persisted, and, in January, 1945, she was admitted to hospital with consolidation of the left lower lobe and half an ounce of brown, purulent sputum containing many eosinophils. The asthma cleared in three weeks and the patient started to lead an active life, but in March, 1945, she developed signs of progressive cardiac failure and dilatation of the heart with nephritis and hypertension. She finally died in July, 1945, in another hospital with anasarca and uraemia; no post-mortem examination was done.

The results of investigations included leucocytosis between 30,000 and 60,000 per c.mm., with an eosinophilia between 50 and 84% during her three months in hospital, after which the blood count became normal. Tests for intestinal parasites, hydatid disease, and polyarteritis nodosa were negative. Bronchoscopy showed thickened, oedematous mucosa with much bronchospasm and masses of very sticky mucus containing Charcot-Leyden crystals and eosinophils with scanty organisms. Skin tests were negative. Radiologically there were extensive opacities in both lower and mid zones which cleared in a few weeks, but fresh opacities recurred when the patient was symptomless.

After 15 years of "rhinitis" this patient developed infective asthma with pulmonary consolidations, a large amount of purulent sputum, a leucocytosis up to 60,000 per c.mm. and a high eosinophilia. She later developed myocardial involvement and progressive nephritis and died within 13 months of the onset. The clinical picture has some features of polyarteritis nodosa, but muscle biopsy was negative. A necropsy was not done.

#### TROPICAL PULMONARY EOSINOPHILIA

*Case 14.*—An Anglo-Indian electrical engineer, aged 31, was born in Madras, where he lived until he came to England in March, 1948. He was frequently in dusty factories and stores. He had often had urticaria and his mother had asthma.

Since 1942 he had had attacks of asthma, cough, and whitish sputum every few months, one of which started in January, 1949, and continued until he was admitted to

Hammersmith Hospital, London, in May, 1949. He was then afebrile and there were widespread rhonchi in both lungs: the tip of the spleen was palpable (he had had frequent malaria). A maximal white blood cell count showed 46,000 per c.mm., with eosinophils 34,500 (75%). A chest radiograph was normal. The sternal marrow contained a high proportion of developing eosinophils. Two different 24-hour specimens of sputum were examined by Dr. M. E. Solomon, of the Pest Control Laboratory, and found to contain certain mites, *Tyroglyphus farinae*. Intradermal tests with a ground-up suspension of this mite gave a much more marked reaction than with a control subject, but later controls on other subjects gave some reactions comparable to the patient's.

Treatment with anthisan for five days was ineffective. With "carbazon" by mouth there was exacerbation of symptoms for the first two days, but then symptoms and physical signs cleared dramatically. A blood film five weeks after admission showed W.B.C.s 12,000 per c.mm., eosinophils 1,320 (11%), at which time he was free from symptoms.

A typical case of tropical pulmonary eosinophilia, in which mites were found in the sputum by a trained expert, is described. There was an excellent response to organic arsenic by mouth.

*Case 15.*—A Tamil clerk, aged 38, was born in Colombo and worked there. He was not exposed in warehouse or stores. His father had "asthma" and his mother "bronchitis." Between 1929 and 1932 he had a persistent cough with periodic asthmatic bouts and dyspnoea. His symptoms recurred between 1942 and 1944, but he was otherwise well until he arrived in England in 1947. In August, 1947, he developed increasing cough, sputum, breathlessness, and wheeze, with a fever of up to 100° F.

On admission to Hammersmith Hospital, London, he was found to be very wheezy and distressed. The spleen and liver were not palpable. Radiographs showed a miliary mottling in both lung fields. The W.B.C.s were 47,000 per c.mm., with eosinophils 37,600 (80%) and eosinophil myelocytes 3,290 (7%). The sternal marrow showed a gross predominance of adult eosinophils. There were numerous eosinophils in the sputum with a mixed flora, but no mites (routine laboratory examination by Carter's method). No parasites were found in the stools and the urine was clear.

Skin tests gave no significant reaction to standard allergens. An intradermal injection of white cells from his own blood and of histamine showed reactions of the same order as in a control subject.

Treatment with benadryl had no effect. After four intravenous injections of organic arsenic, symptoms, signs, and radiographic changes cleared dramatically in a week. The eosinophil count returned to normal in two months. He was last seen in April, 1948, and had remained well.

A typical case of tropical pulmonary eosinophilia cured by organic arsenic is reported.

#### EOSINOPHIL PLEURAL EFFUSION

*Case 16.*—A man, an English factory worker, aged 41, in 1927 was ill for three weeks with right-sided pleurisy. In 1942, while serving in the Middle East, he had an attack of fever, cough, and pain in the right chest which lasted two days and a similar attack three months later. Radiographs of the chest showed no significant abnormality.

In February, 1947, he developed "influenza," with fever, headache, and joint pains, which lasted a few days. A month later he had an ache in the right chest, slight pyrexia, and cough which responded to treatment with sulphonamides. In April, 1947, pleuritic pain developed on both sides, with malaise, headache, and aches in the limbs. On admission to Hammersmith Hospital, London, in May, 1947, he was afebrile and there were

signs of a small right pleural effusion. The pleural fluid was yellow, turbid, sterile and contained no tubercle bacilli (cultured in guinea-pig); R.B.C.s 900 per c.mm., W.B.C.s 3,600, eosinophils 3,276 (91%); proteins 4.4 g.%. A blood count showed W.B.C.s 11,000 per c.mm., with eosinophils 1,430 (13%). His sputum contained some degenerate eosinophils, mixed flora, but no tubercle bacilli. Radiographs revealed a small right pleural effusion with no infiltrations. The Mantoux test was positive. No parasites were found in the stools, urine, or blood. Biopsy of an axillary lymph node showed no significant abnormality. Skin tests with routine allergens, sulphonamides, dope rubber ash (with which he worked), and with flora from the sputum were negative.

Shortly after admission, a pleural rub appeared at the left base and later a trace of pleural fluid was seen transiently at radioscopy. Twice weekly radioscopy showed no lung infiltrations.

In late June, 1947, generalized enlargement of the lymph nodes and spleen was observed. There was no fever and the blood eosinophilia persisted. By July, 1947, the pleural effusion, which had consistently shown eosinophilia, had absorbed and he was allowed up. He then developed pain in the right hypochondrium and the liver rapidly increased in size to the level of the umbilicus; a peritoneal rub was heard over it. There was no fever and the blood eosinophilia was unaltered. Liver function tests were normal. The pain and general upset subsided and he was discharged in August, 1947; the liver was still palpable to the umbilicus, the spleen just palpable, and the chest clear. The B.S.R. was 46 in 200 mm. at one hour, and W.B.C.s 13,000 per c.mm., eosinophils 780 (6%).

Over the next year the liver gradually subsided, and by June, 1948, it was only just palpable and the spleen impalpable. The eosinophilia had disappeared. He was last seen in July, 1951, and has remained well.

An unusual case is reported in which there was a small right eosinophil pleural effusion and a mild blood eosinophilia. A transient, very small pleural effusion was detected on the left, and over a period of three months there was enlargement of the lymph nodes, spleen, and liver. Throughout there was mild blood eosinophilia. The whole condition resolved in a little over a year.

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