OCULAR MANIFESTATIONS IN LÖFFLER'S SYNDROME.*†

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SINCE Löffler (1932) showed a radiograph of transient infiltration of the lungs associated with blood eosinophilia, many cases of Löffler's syndrome have been reported. The symptomatology is as follows:

The well-being of the patient is not disturbed, the blood count shows a slight leucocytosis, and there is always a more or less considerable increase in the number of eosinophils (10–60 per cent.). The shadows on the x-ray photograph of the lung vary considerably in size, but, and this is a most characteristic feature, they always disappear in a few hours or a few days.

Löffler could say little about the aetiology, but supposed that various aetiological agents were operative. An allergic response of the tissue seemed probable. He considered that one of the most important allergic noxae might be of tuberculous origin (Löffler, 1936).

After reviewing the papers that have appeared since 1932 it seems difficult to agree with Löffler and others (1952) that the clinical picture of the condition may now be considered to be clearly delineated (*fest umrissen*).

As an introduction to this difficult matter, a concise summary of our present knowledge is quoted from Reimann (1947):

Transitory lung infiltration with eosinophilia is believed to be the result of the reaction of sensitized lung tissue to an antigen. Persons suffering from asthma, allergic rhinitis, and urticaria occasionally develop the signs and symptoms of a mild inflammation of the lung. The syndrome has been observed in tuberculosis, ascariasis, trichinosis, amoebiasis, cutaneous helminthiasis, and other parasitic diseases.

The allergic character of the syndrome seemed especially evident in a description by Engel (1936) of a personal experience of the condition. His well-being was slightly disturbed. He had a mild cough, and there was some clear yellow sputum. This sputum did not contain any cells, so that, according to Engel, it had to be considered as a transudation sputum, but most investigators did find eosinophils in their cases. The shadow in Engel's x-ray picture disappeared in a few days. He was living in Shanghai and the disease was found to have an epidemic character in that city, and to occur every year about the months of May and June. He concluded that it was an allergic manifestation coinciding with the flowering-time of the bush *Lingustrum*.

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Hansen-Pruss and Goodman (1944) and other workers described asthma as occurring in the same patients who showed Löffler's syndrome, and believed asthma to be an important factor in its aetiology. But Breton (1938) reported finding Löffler's pneumonia in 5–8 per cent. of his asthmatic patients. He remarked that since Löffler's pneumonia seemed to be an allergic condition and that asthma was a very common allergic disease, the combination of the two was only to be expected. In agreement with all former authors, Breton described the shadows on the x-ray picture of the lungs as transitory; however, he observed for the first time that in some cases tiny scars might remain visible in the x-ray. This was a very important fact, since up to that time the condition was considered to be completely reversible.

Löffler's pneumonia is frequently seen in patients with intestinal parasites. The pulmonary infiltrations in tropical eosinophilia are not as fugitive as in Löffler's cases. There is always asthma and sometimes splenomegaly. The causative agent is considered to be a mite (Crofton and others, 1952). Arsenicals have a striking therapeutic effect.

In moderate climates, *Ascaris* is frequently met with in patients with transient infiltrate of the lungs, as in 23 of the 100 cases described by Maier (1943).

The eggs hatch in the duodenum or jejunum and the emergent larvae enter the intestinal wall and make their way to the lungs *via* the mesenteric lymphatics or venules, vena cava, right heart and pulmonary arteries. They break out of the pulmonary capillaries into the air sacs, migrate up the respiratory tree, crawl over the epiglottis, are swallowed and become adult worms in the lumen of the small intestine. (Faust, 1947).

Several authors believe that this migration of the *Ascaris* larvae in the respiratory organs can be an important factor causing the transitory infiltrations of the lung. This view is supported by Löffler (1952), who states that in his opinion this migration of *Ascaris* larvae is the only certain aetiological factor. According to Sprent (1949) a direct toxic influence of the *Ascaris* is very uncertain, whereas there is no doubt about the strong antigenic capacities of *Ascaris* body and fluid in causing a hypersensitive reaction.

Löffler and others (1952) describe transient infiltrations of the lung with blood eosinophilia in three patients after the intramuscular injection of oil (depocillin); 5 to 20 days after the injections cloudy shadows could be seen in the x-ray but they disappeared as soon as the injections with oil were discontinued. Besides the shadows on the x-ray a considerable blood eosinophilia developed within 10 days (rising to as high as 76 per cent.). The general health was undisturbed, though on some days there was slight fever. These authors emphasize that only one out of these three patients had an allergic condition; in the other two no sign or symptom of hypersensitivity could be detected. Consequently they consider the allergic character of the disease to be uncertain. They refer to Essellier and others (1952) who had found very small emboli in the lung 24 hrs after the subcutaneous injection of vegetable oil. In discussing these findings, they suggest that the transitory infiltrations

in these cases might be due to a tissue reaction on a micro-embolus. To support this view they argue that in resorption eosinophilia a leucocytosis is found—as in Löffler's pneumonia—whereas an allergic eosinophilia is said to be associated with leucopenia. Additional evidence for the correctness of this theory—according to Löffler and his co-authors—is seen in the absence of precipitins, without which there would be no sound basis for accepting allergy. However, precipitins are often absent in definitely allergic diseases. Moreover it is doubtful whether the precipitins may be identified with antibodies in allergic conditions. Even if one were inclined to follow Löffler's analysis of the three patients, it does not seem justifiable to extend these theories to the syndrome as a whole. More substantial criticism is required before we abandon allergy as an underlying cause. Probably these causes are manifold.

Another most potent way of elucidating a clinical problem is to study its pathology. Since Löffler's pneumonia is a harmless disease, characterized by the transiency and reversibility of its signs, it seemed unlikely that a *post-mortem* study would ever be possible. The *post-mortem* findings of Meyenburg (1942) are therefore most interesting. He held autopsies on four cases of healthy men who died in accidents. Bronchopneumonic foci, sometimes infarctoid in shape, were found in the lungs, and there was a serous exudation in the alveoli with many cells, mostly eosinophils (10–100 per cent), and some giant cells, probably derived from the alveolar epithelium. A pneumonic infiltration in the typical sense only affects the alveoli, not the interalveolar septa; it is a reversible process and consequently the clinical picture may be a transitory one. Hence these pathological findings fitted in very well with the clinical picture of Löffler's pneumonia. But two cases showed perivenous infiltration of leucocytes with thrombophlebitis, and in one case interstitial infiltration was also seen. Meyenburg thought it doubtful that such an infiltration clinically could have had a transient character; moreover, in one case a focal necrosis was seen and consequently these infiltrations could not be identified with the classical reversible pneumonic process.

It will be remembered, however, that Breton (1938) had already observed clinically that the infiltration might leave tiny scarlike shadows on the x-ray picture, and this makes us doubt whether, in all cases labeled “Löffler's pneumonia”, no traces ultimately remained. A further search in the literature with this point in mind gave interesting results.

Reeder and Goodrich (1952) described four patients with pulmonary infiltrations and eosinophilia (“P.I.E.” syndrome). In all four the disease had a prolonged course. In two cases there was a quick recovery after cortisone and ACTH, and no traces were left. A third patient showed besides pulmonary infiltration and eosinophilia, albuminuria and cylinderuria. Biopsy of the gastrocnemius muscle did not reveal periarteritis nodosa. The x-ray picture was, when last seen, normal. The fourth patient, who had

fever and pain in several muscles, showed in an excised atrophic testicle the picture of periarteritis nodosa. He died from a cerebro-vascular accident and *post-mortem* examination revealed periarteritis nodosa in several organs, but not in the lung vessels.

Crofton and others are inclined to classify cases with eosinophilia and pulmonary infiltration in different groups:

- (1) the very benign transient condition as described by Löffler;
- (2) cases with a more prolonged course;
- (3) prolonged cases with asthma;
- (4) tropical eosinophilia (possibly also belonging to this syndrome)
- (5) cases with periarteritis nodosa

In the first group the condition seems to be completely reversible, but in several cases with a prolonged course, permanent lesions, such as bronchiectasis, were found. In some patients with asthma and pulmonary eosinophilia inflammation and necrosis were found elsewhere in the body, but a definite diagnosis of periarteritis nodosa could not be made.

Harkavy (1941) described six patients with asthma, pulmonary infiltration, and considerable blood eosinophilia. Infarction in other parts of the body (liver, cutis, pleura etc.) and urticaria also occurred. The shadows on the x-ray picture of the lung were not fugitive. The lesions elsewhere were not quite typical, but strongly reminiscent of those in periarteritis nodosa.

Buckles and Lawless (1950) described a patient in whom pneumectomy was done on account of a shadow in the apex of the right lung, and a tumour was suspected. There was an eosinophilia of 43 per cent. Histological examination revealed fibrotic tissue, infiltration with eosinophils, granulomata, endothelial cell proliferation, giant cells, arteriolitis, and periarteritis.

Several cases of periarteritis nodosa with pulmonary infiltration have been described (Bergstrand, 1946; Lumb, 1950; Smith, 1948; Reeder and Goodrich, 1952; Elkeles and Clynn, 1944). The last authors refer to the experiments of Rich (1942), and Rich and Gregory (1942a,b), who demonstrated a picture identical with periarteritis nodosa by the repeated injection of serum in rabbits. They consider it to be an extreme degree of allergic reaction of the vessels.

In thirteen cases of severe asthma with eosinophilia Churg and Strauss (1951) found periarteritis nodosa in several organs. There were also extra-vascular changes in the collagenous tissue, and in the stroma of some organs: granulomata with central necrosis (of collagen fibres and eosinophil cells) surrounded by macrophages and giant cells. These "allergic granulomata", as they called them, were chiefly found near the smaller veins, leaving scarlike tissue especially around the vessels. Five of these thirteen patients showed Löffler's pneumonia.

Ehrlich and Romanoff (1951) described a patient with repeated attacks of severe asthma, resulting in cyanosis and deep coma. The patient died within 10 days. *Post-mortem* investigation revealed two tumour-like masses in the lungs with central necrosis and a brownish shell of mostly eosinophil

leucocytes. There was also involvement of all the coats of the arteries. Identical findings were met in the appendix in another patient. According to these authors:

Löffler's disease is a form of systemic allergic disease of mild character and good prognosis, in which the chief manifestations are confined to the pulmonary system. More severe forms may develop, and the extrapulmonary lesions may overshadow the pulmonary changes.

Ruzic and others (1952) described such an eosinophilic infiltrate in the wall of the stomach. Identical lesions have been described in the pleura, peritoneum, epididymis, and muscles. Since a localization in the eye has not been described up to now and moreover the ophthalmoscope enables us to follow the course of the infiltration *in vivo* it seems to be worth while to report our case in some detail.

Case Report

A female aged 37 was referred to hospital on December 7, 1950. She complained of haziness and veil before the right eye since December 4. She remembered having had the same experience some time ago, but it had then disappeared within half an hour. The behaviour of the patient was very unusual. During the examination by the ophthalmologist, she had fainted with incontinence of urine. On her arrival at the University Eye Hospital she managed with considerable difficulty to say a few words only. A diagnosis of hysteria would have been made if the right fundus had not shown a dense whitish infiltrate of considerable size. The possibility of a similar infiltration in the brain was suspected. However, after being admitted to the hospital she behaved quite normally, though she was very nervous.

Examination:

Left Eye: Visual acuity 1/3; after correction sph. -1 3/4. No abnormality.

Right Eye: emmetropic, visual acuity 1. Anterior segment: no abnormality. The vitreous showed some opacities. In the fundus, temporal and superior to the optic disc, a whitish infiltration was seen, involving the innermost layers of the retina, since the vessels were invisible for some distance in this area. The retina surrounding the infiltrate was grayish, oedematous. No haemorrhages could be traced and the vessels outside the lesion were completely normal. The aspect of the lesions is evident from Fig. 1 (overleaf).

General physical and neurological examination, no abnormality.

x ray of lungs perfectly normal on December 9, 2 days after admittance.

Blood count: erythrocyte sedimentation rate 5/15; leucocytes 11,800; diff.: basophils 0; eosinophils 46 (two being unsegmented immature forms); neutrophils: non segmented 0, segmented 16, lymphocytes 32, monocytes 6; erythrocytes 4,320,000; Hb 90 per cent. (corr. value);

Blood sugar normal values;

Cholesterol 182 mg. per cent;

Wasserman reaction negative.

Previous History.—As a child she suffered from rickets. From early youth she had always been a nervous person and easily fatigued. She had also suffered from bronchitis, but this disappeared in later years. Seventeen years ago she said she had been treated for duodenal ulcer. Furthermore, in a concentration camp in Germany during the war, she had had encephalitis of moderate severity and had been hospitalized for 3 months. Her subjective complaints at that time were diplopia and headache. Two years ago she had an endometritis. She is short of breath from time to time and wheezes, especially before she goes to bed. She is not hypersensitive to any sorts of food, plants, and dust,

FIG. 1.—December 8, 1950.

FIG. 2.—December 15, 1950.

with the exception of alcohol. If she washes with cold water the skin turns red with small itching vesicles, but as soon as she has dried herself and used some talcum powder, her skin recovers. 14 days before admission to hospital, she had taken tablets containing altogether 9 g. pyramidon for an attack of influenza.

Family History.—Her whole family had been completely annihilated in the war; her mother was said to have had the same constitution as our patient; she might sneeze continually the whole morning.

On account of this anamnesis special attention was given to a possible allergic condition, but all tests of the routine examination in the allergic department were negative. A skin test on pyramidon was also negative.

The marked eosinophilia was suggestive of the presence of intestinal parasites, but repeated examinations were negative.

Clinical Course of the Retinal Condition.—In the first days there was a marked improvement and the infiltration in the temporal upper quadrant diminished in size and intensity but on December 15 there was a sudden new infiltration in the nasal upper quadrant in the course of the nasal superior artery and vein (Fig. 2, December 15, 1950), whereas the original infiltrate was now resorbed to a considerable degree. On December 18 fresh infiltrations appeared in the retina, again mostly in the superficial layers (Fig. 3, December 24, 1950). Other infiltrates in the deeper layers now followed. The original more superficial process showed a white, dense cloudy aspect in which the vessels were discontinuous. The deeper infiltrations were more patchy and of a whitish-yellow colour.

Diagnosis.—The fugitive character of the retinal infiltrates together with the considerable blood eosinophilia called to mind the clinical picture of Löffler's transient pneumonia with marked blood eosinophilia. The x-ray picture of the lung was normal, but when it was repeated on December 20 there was a shadow in the superior and inferior lobe of the left lung. On December 22 the shadow was small and on December 28 it had completely vanished.

The condition of the lung was a most typical example of Löffler's pneumonic infiltrate, but the process in the fundus proved to be less transient in character. Nevertheless, the picture showed a vivid variability, which is evident from the further course and the fundus pictures.

Further Progress.—A whitish sheath around the nasal inferior vein was found on December 19 and this developed the character of a small retinal infiltrate. There were also some

FIG. 3.—December 24, 1950.

FIG. 4.—December 28, 1950.

tiny haemorrhages along the temporal inferior vein and artery, and oedema was marked in this region (Fig. 4, December 28, 1950).

On December 30 there was a definite regression of the infiltration in the superficial layers of the retina, whereas the process becomes more marked in the deeper layers (Figs 5 and 6, January 3 and 20, 1951).

FIG. 5.—January 3, 1951.

FIG. 6.—January 20, 1951.

Visual Fields.—A further unexpected finding was a visual field defect of the Jensen type corresponding with two lesions in the retina, one being the primary lesion. Still more unexpected was a visual field defect in the other eye, which in the whole course of the disease had shown only a tiny haemorrhage on February 8.

On January 13 vision in the right eye which had been $\frac{3}{4}$ up to that time fell to less than $\frac{1}{10}$. The region between the disc and the macula now showed a marked retinal oedema, but this was fugitive, and disappeared after some days; on January 20, vision in the right eye was $\frac{1}{2}$, and on January 27, $\frac{3}{4}$ again. During this time and in the following weeks

the fundus infiltration disappeared, with the exception of two lesions, the original one in the temporal upper quadrant and another in the nasal upper quadrant, both corresponding to visual field defects (Fig. 7).

FIG. 7.

Although the field defects were identical with those found in patients with Jensen's choroido-retinitis, the fundus picture and especially the cicatrices were unlike the findings in that disease (Fig. 8, February 13, 1951).

On February 27 the patient was discharged from the hospital. Vision in both eyes was $\frac{3}{4}$, and the visual fields still showed the same defects. The left fundus was quite normal; and in the fundus of the right eye two cicatrices remained. They had a whitish appearance, like a fibrotic scar around the vessels, especially the vein which in that region was sheathed. No pigmentary disturbances were found.

Follow-up.—Leucocytosis (12000) and eosinophilia (40 per cent.) were still present. The patient was seen repeatedly in the Out-Patient Department, and no changes were seen in the appearance of the right eye (Fig. 9, June 13, 1951). In August, 1951, there were 9,200 leucocytes and 11 per cent. eosinophils. When she was last seen one year later, in August, 1952, the blood count was normal: 8,600 leucocytes and 4 per cent. eosinophils.

FIG. 8.—February 13, 1951.

FIG. 9.—June 13, 1951.

Comment

There seems to be no doubt that the process in the fundus and the infiltrates in the lung must have had a common origin. The infiltration in the lung was very fugitive and may have had a pneumonic character, corresponding with the pathological findings described by Meyenburg (1942). The pathological appearance of the right eye, though extremely variable in extent, did not disappear as completely. No permanent lesions in other places of the body could be traced though the prolonged course of the eosinophilia points to a persistent alteration in the bone marrow.

It is tempting to consider what might be the pathological basis of the appearance of the fundus. It can be supposed that the very dense infiltration mainly of eosinophilic cells into the retina, transudation (oedema), and focal necrosis, must be held responsible for the irreversible lesion of the nerve fibre layer, and caused the defects in the visual fields. The infiltration seemed to be related rather to the veins than to the arteries. This may remind us of the allergic granulomata, found by Churg and Strauss (1951) near the smaller veins, resulting in scars around them. It is difficult to state definitely whether or not the vascular walls were involved. Only some very small haemorrhages could be detected in the whole course of the disease.

Our patient clearly demonstrates that in Löffler's syndrome a benign reversible process may be found in conjunction with more severe conditions elsewhere in the body.

As to the aetiology and pathogenesis, most authors agree upon an allergic reaction of the tissue. In our patient an antigenic noxa could not be detected. A hyperergic reaction to pyramidon can be excluded, as in such cases a marked leucopenia is always found.

The visual field defects recall Jensen's chorioretinitis. But in our patient the inflammation and the scars were restricted to the retina and differed from the typical chorioretinal scars in Jensen's disease and the pigment-epithelium was not disturbed. Moreover, the visual field defect of the left eye, with a normal fundus picture, could only be explained by a local affection of the left optic nerve.

The blood eosinophilia persisted for more than a year after the healing of the process in the retina and lung; and cannot thus be due to a resorption eosinophilia, as suggested by Löffler, but must be identical with the blood eosinophilia in allergic conditions, which is supposed to be an allergic response of the bone marrow. Habelmann (1940) found typical alteration in the leucopoietic bone marrow in allergic diseases: *e.g.* immaturity and eosinophilia. This eosinophilia did not always give a blood eosinophilia. There was some parallelism in the severity of the clinical picture and the picture of the bone marrow.

Summary

A woman aged 37 was admitted to hospital with severe infiltration of the

retina of the right eye. The process had a variable character, and there was a considerable blood eosinophilia (49 per cent.). As the x ray of the lung showed a fugitive infiltration, a diagnosis was made of Löffler's syndrome with ocular complications. No intestinal parasites were found.

The shadow on the lung completely disappeared, two permanent lesions remained in the fundus, and were held responsible for two visual field defects of the Jensen type. Moreover a visual field defect of the left eye, where no infiltration was found, could be detected.

The possibility was shown that in conjunction with a reversible process as described by Löffler, more severe permanent lesions may result as found by Meyenburg in *post-mortem* examinations in cases of Löffler's pneumonia.

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