KATAYAMA DISEASE, EARLY TOXAEMIC STAGE OF BILHARZIASIS

WITH A REPORT ON A CASE SHOWING
PULMONARY INFILTRATION

BY

J. RITCHKEN, M.D.

AND

MICHAEL GELFAND, M.D., F.R.C.P.

Salisbury, Southern Rhodesia

It may be many months after the bilharzial parasite has entered the body that the disease becomes recognized. However, in a small number of cases symptoms and signs develop after the first month, and these manifestations are referred to as the Katayama syndrome or the early stage of toxæmia. Though reported as occurring more commonly in patients infested with *Schistosoma japonicum*, this syndrome is seen in *S. mansoni* but only occasionally in *S. haematobium* infection.

We have had occasion to treat a child soon after initial exposure to bilharzial infestation. He displayed the classical signs of the Katayama syndrome. We record this case as the literature on the subject is extremely sparse, particularly concerning the pulmonary changes. The pathogenesis and clinical features of this interesting condition are also reviewed.

Case Report

A boy aged 7½ years paddled on a single occasion (December 8, 1952) in a river known to be infested with bilharzial snails. He could not recall any itching of the skin at that time and remained in good health until January 3, 1953. On that day he felt tired and had no appetite; his temperature was 100° F. (37.8° C.). During the following five days his temperature ranged from 100 to 104° F. (37.8 to 40° C.), but, apart from recurrent vomiting attacks, he did not complain of any specific symptoms.

Physical examination was entirely negative. A blood slide showed no malaria parasites, but revealed a marked increase of eosinophils. He was thereupon admitted to hospital for further investigation. Soon after admission he developed a persistent dry cough and became slightly cyanosed and breathless. Examination showed coarse rales scattered over both lungs, but no other physical signs. Without any specific treatment his temperature fell by lysis to normal ten days after the onset of illness. The cough and vomiting rapidly improved, and apart from loss of weight and a pallid complexion he appeared perfectly normal.

Laboratory Investigations.—On January 9 the white blood cells numbered 36,100 (neutrophils 42%, lymphocytes 11%, monocytes 3%, eosinophils 44%), and on January 12 27,400 (neutrophils 42%, lymphocytes 8%, monocytes 1%, eosinophils 49%). Repeated urine tests revealed no abnormalities. No pathogenic cysts, ova, or parasites were seen in numerous tests of the faeces. X-ray examination of the chest on January 10 showed a diffuse miliary type of lesion confined mainly to the middle and lower zones of both lungs, especially the left, where the lesions appeared to be almost confluent. A cercarial skin test was negative.

A diagnosis of probable Katayama disease was made and the patient was discharged and kept under observation.

He was examined again on February 8. He complained of feeling tired, his appetite was poor, and his mother expressed concern at his listlessness and pallor. His cough had disappeared. A further chest x-ray film showed complete clearing of the focal pulmonary consolidation. On

February 10 the white blood cells numbered 16,900 (neutrophils 38%, lymphocytes 23%, monocytes 2%, eosinophils 37%). Examination of the urine and faeces was again negative.

On February 24 he again became pyrexial and complained of severe abdominal pain and diarrhoea. The spleen was now palpable and he was very tender over the liver area. On the following day diarrhoea persisted and the lateral spined ova of *S. mansoni* were found in the faeces. Treatment with "anthiomaline" was started, and within two weeks he showed a marked improvement. A follow-up examination four months later showed complete restoration of health.

Discussion

The clinical picture of the toxæmic stage in Southern Rhodesia is very variable. It may be mild or severe (Gelfand, 1942; Gelfand and Osburn, 1943). In many it may simply be labelled "urticaria due to food allergy"; in others the picture may cause undue alarm and the diagnosis of acute miliary tuberculosis may even be considered. The essential features comprising this syndrome are:

Age.—In our experience the toxæmic stage is seen in the child and not in the adult, and only a small proportion of infected children are so affected.

Pyrexia.—This may be prolonged over many days, but more often is characterized by periodic rises with long apyrexial intervals. In most cases, despite a high temperature, the child does not seem to be seriously disturbed.

Symptomatology.—General malaise, loss of appetite, and frequent vomiting are usually the only symptoms. With lung involvement a cough is characteristic, and in the later stages tenderness over the liver area is a frequent finding.

Loss of Weight.—This is often a noticeable feature, and appears to be mainly related to the frequent vomiting and poor appetite.

Urticarial Eruptions.—These often appear in crops and at times assume the features of angioneurotic oedema affecting the orbits, face, penis, and scrotum.

Splenomegaly.—Splenic enlargement is usually noted towards the end of the toxæmic stage, and subsides even though no antibilharzial treatment is given.

A High Blood Eosinophilia.—This is constantly present in all cases, and is the one feature which is maintained throughout the course of the disease. The actual count is usually between 20 and 60%. It is probable that the eosinophil count remains elevated until active treatment is started.

Lung Involvement with Radiological Changes.—It is probable, because of failure to examine the lungs radiologically and owing to the transitory nature of the radiological features, that these are rarely demonstrated. In the above case extensive miliary changes were shown, and it is probable that these reveal the severest degree of pulmonary involvement.

Pathogenesis

In view of the non-fatal nature of the early toxæmic stage of bilharziasis, there are no pathological data available. However, the general symptomatology and major signs such as urticaria, eosinophilia, and transient pulmonary infiltration suggest an allergic reaction to the developing schistosome.

In the case reported the toxæmic stage appeared 35 days after exposure. It is known that mature female schistosomes with fully developed ova in their uterine canals are found in the portal vein four to six weeks after the cercariae have pierced the skin or mucous membrane. It is therefore probable that 35 days after exposure the fully matured female has found her way via the mesenteric vessels to the small venules of the large intestine, and that ova deposition has begun. It is therefore suggested that the early bilharzial toxæmia is an intense allergic reaction towards this stage of the life cycle of the schistosome. This reaction occurs usually in children, and often, as in the present case, in a child known to suffer from other allergic conditions.

This concept of the nature of Katayama disease has received much confirmation in recent years by work done on closely

related subjects. Crofton *et al.* (1952) reviewed the entire subject of pulmonary eosinophilia. The latter they define as a condition in which pulmonary infiltration on the radiograph is accompanied by blood eosinophilia, but in which any of four conditions (the resolving stage of pneumonia, hydatid disease of the lung, Hodgkin's disease, and sarcoidosis) can be excluded. According to their classification of pulmonary eosinophilia, the Katayama syndrome would be grouped under that of simple pulmonary eosinophilia (Loeffler's syndrome).

The pathology in simple pulmonary eosinophilia has not been studied, as the condition is not fatal. However, Von Meyenburg (quoted by Crofton *et al.*) described changes which he considered to be those of Loeffler's syndrome in three soldiers who died from trauma. Irregular bronchopneumonic foci were noted which were seen microscopically to consist of small areas of alveolar exudate with many eosinophils. In one there was an eosinophilic infiltration of the interstitial tissue. In two cases ascarides were found in the intestine. Crofton *et al.* conclude that the entire group of pulmonary eosinophilias represent a hypersensitivity reaction of the body to various stimuli. When the hypersensitive reaction is brief and involves only the alveoli the manifestation is a simple pulmonary eosinophilia.

The breakdown of normal, abnormal, or foreign protein in the body tissues results in the release of histamine. Vaughn (1953), by injecting extracts of ascaris and of histamine into guinea-pigs, was able to demonstrate a great concentration of eosinophils in the pulmonary tissue. Twelve hours after the injection widespread thickened areas with a patchy consolidation were a common finding, and microscopical study showed a gross eosinophilic infiltration of the perivascular and peribronchial connective tissue. The changes, though similar, were more extensive after ascaris extract than after histamine injection. In Vaughn's opinion the biological purpose of this eosinophilic infiltration lies in the fact that the eosinophil, being in effect a carrier of histamine, is performing its function in delivering a substance to the lung, where it is inactivated by histaminase or another related enzyme.

In 1949 Sprent (quoted by Crofton *et al.*, 1952) sensitized mice to various ascaris extracts by parenteral injection and also produced striking pulmonary changes, including an eosinophilic infiltration. In a case of ascariasis it is known that the life cycle includes a stage of pulmonary migration, but as the result of Sprent's and Vaughn's experiments it is probable that the transitory pulmonary shadows seen in that condition are also better explained as an allergic phenomenon than as a reaction to the migrating larvae.

Further evidence of the allergic nature of this group of diseases is recorded by Wright and Gold (1945), who describe nine cases of pulmonary eosinophilia associated with creeping eruption, a local condition of the skin caused by the filariform larvae of *Ancylostoma braziliense*. Furthermore, in view of the similarity of the lung changes associated with eosinophilia which occurs in other parasitic diseases such as ascariasis, trichiniasis, cutaneous helminthiasis, amoebiasis, and liver-fluke infestation, the pulmonary changes seen in Katayama disease can best be accounted for on an allergic basis.

At this stage attention should be brought to the recent interest shown in the eosinophilia hepatomegaly syndrome of young infants and children caused by infestation with the larvae of *Toxocara canis*, a dog roundworm.

Beaver *et al.* (1952) and Milburn and Ernst (1953) have demonstrated the larvae in the liver of affected patients. The latter authors suggest that other diseases, such as Loeffler's syndrome and tropical eosinophilia, may also be due to visceral nematode larvae migrations. In this connexion Muhleisen (1953) demonstrated filariform hookworm larvae in a patient who developed asthmatic symptoms one week after the onset of creeping eruption. Such symptoms had previously been regarded as being of allergic origin.

To our knowledge, no sputum studies have been done on patients in the toxæmic stage of bilharziasis, but it is

thought most unlikely that the transient pulmonary infiltrations and other symptoms of the Katayama syndrome could be accounted for by cercariae trapped in the capillary bed of the lung or by migrating schistosomes. There is no evidence that the mature schistosome migrates anywhere but to the vesical and intestinal venous plexuses. All extra-urinary and intestinal forms of bilharzia are due to embolization of ova from the above sources.

If the syndrome was due to cercariae trapped in the lung capillaries, symptoms would be expected soon after infestation, and would not appear three to four weeks later.

Summary

A case of Katayama disease caused by *Schistosoma mansoni* is reported. Symptoms developed 26 days after a single exposure to infected water.

In addition to the well-known symptoms and signs of this condition, a marked transient pulmonary infiltration is demonstrated.

The pathogenesis of pulmonary eosinophilia in schistosomiasis is briefly discussed, and it is thought that the symptoms are best explained on an allergic basis.

REFERENCES

- Beaver, P. C., *et al.* (1952). *Pediatrics*, **9**, 7.
Crofton, J. W., *et al.* (1952). *Thorax*, **7**, 1.
Gelfand, M. (1942). *Clin. Proc.*, **1**, 247.
— and Osburn, H. S. (1943). *Ibid.*, **2**, 169.
Milburn, and Ernst, K. F. (1953). *Pediatrics*, **11**, 358.
Muhleisen, J. P. (1953). *Ann. intern. Med.*, **38**, 595.
Vaughn, J. (1953). *Blood*, **8**, 1.
Wright, D. O., and Gold, E. M. (1945). *J. Amer. med. Ass.*, **128**, 1082.

Medical Memoranda

Use of the Hodge Pessary in the Sling Operation

The use of a Hodge pessary in assisting diagnosis and as a test of the desirability, or otherwise, of carrying out a sling operation in cases of retroversion with symptoms is too well known to warrant further consideration here.

Its employment, however, as an instrument in the technique of the Baldy-Webster sling operation has never come to my notice, and I have not been able to find any such reference in the literature, nor have the many colleagues whom I have questioned. During the past 18 months I have used the pessary in 12 cases in which the Baldy-Webster sling operation has been carried out.

On the evening before operation the vagina is cleansed in the usual way and a Hodge pessary of suitable size inserted, or insertion may be left until the following day, when, with the patient anaesthetized and ready for operation, the pessary is introduced with adequate antiseptic precautions. At operation it is found that the uterus is maintained in good position, and the actual sling procedure is facilitated and simplified. In some of the cases the pessary has been removed 24 hours post-operatively, whilst in others it has been kept *in situ* for five days. In no instance has there been any indication of infection or other untoward effects, and the immediate results have been excellent. So far as can be judged at present by follow-up examination at the gynaecology post-operative clinic, the relatively long-term results leave nothing to be desired.

COMMENT

The use of a vulsellum forceps or a catgut traction suture in the fundus of the uterus to hold this organ forward in a reasonable position whilst operating is largely condemned, as damage may be done to the myometrium, and the punctures and knots may form points to which adhesions may attach, with possible unhappy results, especially for a woman of child-bearing age. An assistant's hand may support the uterus, but frequently this is found to be a doubtful