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ENCEPHALITIS IN LOA-LOA FILARIASIS

BY

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"*L'étude des filarioses offre encore maints aspects inconnus dont l'examen réserve à ceux qui s'y consacreront des observations captivantes.*"

J. RODHAIN (1953)

Filariasis is usually regarded as a benign disorder and its neurological manifestations have rarely attracted attention. This may be due to the frequency with which the malady is superimposed upon other diseases with meningo-vascular involvement, to which the fatal complications have been attributed. Viewing the scene from a greater distance, we have felt that these complications might be related to filariasis itself. The subject is of some importance in view of the increasing availability of highly potent anti-filarial drugs.

REVIEW OF THE LITERATURE

The first *Loa loa* was extracted from the eye of a negress in 1770 by Mongin at San Domingo. The disease was described in West Africa by Guyot in 1777 as quoted by Lorenz (1890) and by Manson later (1904).

In 1908, Broden and Rodhain reported that in exceptional cases they had found a filarial embryo in the cerebrospinal fluid, admitting the possibility that a blood vessel had been injured by the needle.

The same year, Külz (1908) reported that in the Cameroons he had observed for four months a patient showing all the motor and psychiatric manifestations of sleeping sickness, but in whom it had not been possible to demonstrate the trypanosome in the blood or cerebrospinal fluid, or by lymph node puncture. The results of inoculation were negative and treatment was without effect. The blood of Külz's patient (not the cerebrospinal fluid as quoted by Chalgren and Baker, 1946 and 1947) was swarming with microfilariae.

Brunetière (1913) recorded a case with paralysis of the tongue and hand followed, seven months later, by paralysis of the entire left side of the body. He envisaged the possibility of a terminal filarial (mf. Loa) embolism of the sylvian artery.

In 1919, Robles noted in acute onchocercosis at Guatemala the possibility of profound prostration, delirium, convulsions, trigeminal involvement, and intermittent sweating. He also described a case of chronic onchocercosis with epilepsy resulting from perforation of the skull by a tumour.

Anderson's (1924) report from British Guiana was more complete. His case concerned a coloured girl aged 7 years affected by filariasis, who presented at necropsy a marked cerebral congestion with pericapillary leucocytic infiltration. He found numerous microfilariae (*M. bancrofti*) of normal appearance in the cerebral and cerebellar vessels. This was the only case of the six he reported in which he was able to make a post-mortem examination. He classes the frequency of microfilariae in the different organs in this order: kidneys, lungs, spleen, brain, liver, cerebellum, and myocardium.

Tha Mya (1928) reported a case with hemiplegia and contracture of the arm following a coma lasting four hours. There were unidentified microfilariae in the cerebrospinal fluid, which also contained blood. Microfilariae have also been recovered from the cerebrospinal fluid of an advanced case of trypanosomiasis (Chambon, 1933, *M. perstans*) and from the sheath of the optic nerve in a young Mexican Indian woman (Giaquinto Mira, 1934).

Rodhain (1937) recalled that in Hissette's case he had observed *M. perstans* in the capillaries of the choroid plexus. (Chalgren and Baker in 1946 refer wrongly to this case as one of onchocercosis with meningeal involvement.)

Meanwhile Peruzzi (1928) had observed cerebral filariasis in five monkeys suffering from trypanosomiasis, and Hashimoto (1939) found a microfilaria in the vessels of the anterior lobe of the pituitary of a dog.

There exists, however, experimental work which is little known, that of Wail, Popow, and Prjadko (1926). It concerns guinea-pigs infected with *Diopthol riaena tricupsis Fedschenko* 1874. This parasite was found in the capillaries which were permeable though filled with the filariae. They

described acute neuronal lesions, with neuron aphasia, phantom cells, and proliferation of the pericapillary glia. The lesions were thought to be due to disturbance of the capillary circulation dependent in turn upon the mechanical and obstructive effects of the microfilariae and to the toxic effect of the metabolic products of the parasites. This work is the first in which neuropathological studies of the disease were carried out with modern techniques.

The possible appearance of neurological and psychiatric symptoms in microfilariasis is now well recognized and several reports have appeared in recent years. That of Bonnet (1943) concerned a man of 42 years whose illness had begun five days before coming under observation, with rigors, fever, headache, and vomiting; this was accompanied, two days before admission, by torpor interrupted by periods of agitation. On admission, his respiration was rapid and there was a marked meningeal syndrome without any apparent motor defect, but with absent knee and ankle jerks and a right-sided Babinski response. Lumbar puncture yielded a fluid with 26 cells and 40 mg. of protein. There were no trypanosomes but 5 to 6 *M. loa* per field. A thick drop of blood showed *M. loa*. The blood urea was 170 mg. and the urine contained 0·25 g. of albumin per 100 ml. He died three days later with hyperpyrexia. He showed an aortitis probably due to old syphilis, of which, however, there was no further evidence. In this case the unilateral Babinski response probably indicated an accentuation of the lesions in the one hemisphere.

Bonnet related the meningeal syndrome in his patient to the filariasis but believed that the finding of microfilariae in the cerebrospinal fluid was fairly common. It is admitted, he said, that they are too bulky to pass the meningeal barrier and that it is the needle that introduces them into the subcutaneous tissues or into a small vessel. The frequent finding of red blood cells in the cerebrospinal fluid and the small number of microfilariae that one finds there is in favour of this interpretation. However, contamination by a needle is improbable even in the case of *M. loa* and *perstans* which invade the circulation, since the blood contains few of these parasites: three or four is the maximum in a thick drop. In any case injury to a vessel is rare during lumbar puncture and Bonnet believes that the passage of the parasites is the result of damage to the vessels by another disease. He emphasizes only the meningeal syndrome in his article; he leaves in the background the severe involvement of the central nervous system revealed by a symptomatology that we shall meet again later.

In his book, Napier (1946) mentioned "the possibility of psychoneurotic disorders". The possibility of a cerebral invasion was also mentioned by Chalgren and Baker (1946).

Bertrand-Fontaine, Schneider, Wolfromm, and Cagnard (1948) reported a case with double hemiplegia and a progressive course, reacting to treatment with "hetrazan". The patient was a man aged 30 years without previous illness, who developed a progressive hemiplegia, though in the course of its development there were several remissions. It was accompanied by periods of confusion and agitation with variable and transient ocular signs. There was a partial regression of symptoms spontaneously and then an improvement with treatment. The patient had an old loasis with oedema, marked eosinophilia in the blood, subjective ocular symptoms, a positive intradermal reaction, and living *M. loa* in the peripheral blood.

During the first few hours of treatment the symptoms increased, but after three courses of 3799 R.P. there was a considerable improvement suggesting that the symptoms arose from the filariasis. The cerebrospinal fluid was normal. As for the mechanism of the neurological signs, the authors were undecided as to whether there was an adult filaria in the subarachnoid spaces at the base of the brain (localization of choice) or whether there had been a migration of microfilariae in the vascular bed, causing obstruction with an oedematous reaction.

In their work of 1950, Kenney and Hewitt give as psychoneurotic manifestations of loasis, insomnia, headache, nervous depression, and abnormal irritability. The report is based on four observations. The first concerned a man aged 28 years with a change in personality accompanied by torpor. These symptoms were sufficiently severe for him to return to Europe. During this leave he again suffered from headache with acute mental symptoms and an eosinophilia varying from 50 to 56%. The removal of a worm (*M. loa*) from the eye led to an amelioration of all his symptoms and a fall in the eosinophilia to 3%. In the second case the symptoms were less marked and were also improved by extraction of the filaria. These two cases in Europeans were caused by *Loa loa*. The third case concerned an Indian suffering only from depression. The fourth was a negro in whom irritability and abnormal aggression, accompanied by a right hemiplegia, appeared suddenly. These two cases were caused by *M. bancrofti*. A state of apathy followed the initial symptoms. With "hetrazan" treatment the headache increased, and there was mental confusion and vomiting. He died on the seventh

day. There was no necropsy. These last two cases were observed in Central America.

In 1952, Kivits reported four new cases with " invasion of the cerebrospinal fluid " by *M. loa*. His first case was that of a woman who had suffered several times from headache and after a loss of speech had entered into coma. Lumbar puncture showed 50 vigorous living microfilariae per c.mm. of cerebrospinal fluid. She died in hyperpyrexia after five days in coma.

His second observation concerned a woman who had had an abscess in the popliteal fossa for 15 days and then suffered convulsions followed by coma ; there was generalized hypertonia and myosis. The optic fundi were normal. The cerebrospinal fluid contained 18 microfilariae per 50 c.mm. Four days later she died with hyperpyrexia. At necropsy, there was oedema of the pia mater with flattening of the convolutions and, on section, punctate haemorrhages without gross haemorrhage or softenings. Histologically, Kivits described foci of infiltration, with occasional small necroses, giant cells, and a few haemorrhages. In one area, microfilariae were found inside a giant cell. Some foci were perivascular. The choroid plexus and pituitary were free from abnormality.

His third case was that of a girl of 13 years with mental confusion, choreoathetoid movements, and generalized tendinous hyperreflexia, more marked on the right. The cerebrospinal fluid showed 8 actively motile microfilariae per 50 c.mm. At the end of four days the patient died with a temperature of 38° to 39° C. terminally.

The fourth case was that of a boy aged 12 years, with a history of six days of progressive prostration with generalized hypertonia. The first lumbar puncture showed 6 microfilariae per c.mm., 8 cells per c.mm., and 20 mg. per 100 ml. of protein. Two days later there was somnolence with myosis. Lumbar puncture then yielded a fluid with 48 white cells, 4 red cells, and 4 microfilariae per c.mm. The fluid improved, containing first 3 and then 1 microfilariae per c.mm. but it remained bloodstained. He died 17 days after admission in a deepening coma.

There are thus four cases in which coma, accompanied by hypertonia, appeared suddenly followed by death in four to seven days. In a single case there were focal cerebral signs in the form of choreoathetoid movements. Only in the last case was the cerebrospinal fluid bloodstained. In the remaining cases the microfilaria had not modified its composition.

We see no reason for putting the cases of encephalitis in a separate group. They also consist of an acute neurological syndrome, with the characteristics of a vascular disorder sometimes manifested as hemiplegia. In Kivits's last observation, as in Tha Mya's case, microfilariae were found in bloodstained fluid.

Kivits also wondered how the microfilariae had penetrated into meningeal spaces. The patients, all of whom were negroes, were not suffering from trypanosomiasis. It was not known whether they were syphilitic, but in view of the age of two of them (12 and 13 years), it is difficult to envisage meningovascular syphilis. He wondered whether a pre-existing encephalitis might not facilitate the passage of the microfilariae. Their presence would then be fortuitous. He noted, however, that at the time that he observed these cases there was no encephalitis in the Mayumbe.

In considering these observations as a whole, two questions immediately spring to mind. The first is the significance of microfilariae in the cerebrospinal fluid; the second is that of the structural basis of these severe neuropsychiatric manifestations, the majority of which are fatal and without any suggestion that an active treatment has provoked the symptoms.

(1) The fact that the cerebrospinal fluid remains normal in composition when microfilariae are present (Hissette, 1932 ; D'Hooghe, 1935 ; Manson-Bahr, 1950) and that in proved filariasis, lumbar puncture often yields a normal fluid (Pourbaix, 1952, quoted by Janssens, 1952) suggests an accidental penetration. The presence of microfilariae in the cerebrospinal fluid does not, therefore, in itself constitute a meningeal syndrome. One must also envisage the role of accessory factors such as meningovascular inflammations at the base of the brain favouring the penetration of the microfilariae in the monkey (Peruzzi, 1928) and even in man (Chambon, 1933) ; syphilitic lesions facilitate the passage of microfilariae not only into the cerebrospinal fluid but also into the parenchyma of the brain. The lesions of the vessels in these cases invite the penetration of the vessel wall. The coexisting meningeal reaction permits the microfilariae to remain in an environment normally unfavourable to them.

(2) As far as the anatomical basis of these states is concerned, we have only the reports of Wail and others (1926), Anderson (1924), and Kivits (1952) on which to build a hypothesis. From the clinical point of view, we have distinguished meningeal (Bonnet's main observation, 1943) and psychiatric disorders (Kenney and Hewitt, 1950) but above all cerebrovascular syndromes, sometimes focal (Brunetière, 1913 ; Mme. Bertrand-Fontaine and her

collaborators, 1948) with a bloodstained fluid (Tha Mya, 1928) and sometimes presenting as a coma of insidious onset but steadily progressing to a fatal end.

It will have been noted earlier that in certain cases (observation 4, of Kenney and Hewitt, 1950, for example) the initiation of the modern treatment for the disease is followed, at first, by an exacerbation of the neurological and psychiatric signs, as if the therapeutic lysis of the parasite gave rise to an acute toxicosis. On the other hand, if one views the fatal cases as a whole, it is clear that the " natural " evolution in certain cases, especially in young patients, follows a constant pattern. Since the general effects of filariasis (fever and urticaria) are at present considered as allergic manifestations (Napier, 1946), may not the cerebral signs also be interpreted as the effects of individual neural sensitization ?

We first report the clinical and electroencephalographic observations and then discuss the visceral and neurological lesions.

CASE REPORT

The patient, aged 34 years, was a man of unusual strength (height 6 ft. and weight 14 st. 6 lb.). He had been repatriated eight months before the end of his second term on account of a variety of complaints, especially a loss of weight (30 lb.) in three months, dyspepsia, and repeated bouts of dysentery.

The illness began with malaria, bacillary dysentery, and furunculosis during his first term spent in the east province of the Congo constructing roads as a supervisor of public works. The second term was spent in the Bas-Katanga. This time he had three attacks of bacillary dysentery, and was particularly troubled by echythematous lesions which were still present when he arrived at hospital. Albuminuria had been observed in Africa but was not considered of importance.

Clinical examination showed a slight enlargement of the liver, the lower border of which descended about 3 cm. Both the liver and gall bladder were tender. The spleen and other abdominal organs seemed normal. The breath sounds were harsh but there were no rales. The heart sounds were muffled and there was a slight reduplication of the second pulmonary sound. An exercise tolerance test gave a normal result. The blood pressure was 125/80 mm. Hg. The pulse was 80 per min. Electrocardiographic examination (Dr. G. R. Vleeschoouwer), on the other hand, showed a moderate sinus bradycardia, a *coeur couché*, with marked left ventricular preponderance (angle −15°). The auricle P wave was of normal form and duration but P3 was inverted, the P-Q interval 0·16, and the ventricular Q-R-S complex of normal duration 0·07, broadening of R in D2, Q-R-S inverted in D3 ; D1-D3 were mirror images. The S-T interval was normal. The T wave was reversed in D3. The perfectly symmetrical, mirror-like appearance of Q-R-S in D1-D3, even in the absence of alteration of this complex in D2, suggested an arterial and especially a coronary cardiopathy.

Radiographs of the chest confirmed the presence of a large heart with left ventricular hypertrophy. The lung fields were clear but there were heavy hilar shadows. Examination of the urine showed 100 mg. % of albumin but no reducing substances were noted. The specific gravity was 1026 and the *p*H 6·5. The deposit contained hyaline and granular casts, abundant microfilariae, but no red blood cells. A second examination two days later showed, in addition to much mucus, a deposit containing red and white cells, numerous small round cells and two granular casts, and a pure growth of *Streptococcus faecalis* (Dr. Brutsaert).

Tests of renal function were satisfactory : phenolsulphone-phthalein 62% and urea clearance 126%. Intravenous pyelography was entirely normal.

A blood examination gave the following results : Thick drop, *M. loa* +++, haemoglobin, 16·4 g. (103%), red blood cells, 4,841,000 ; volume index 1·07 ; volume of packed red cells 48% ; colour index 1·1 ; diameter of red blood cells 84 ; basal sedimentation rate, 25 mm. in one hour (Westergren) ; leucocytes, 8·200 (eosinophils 15·5%, non-segmented neutrophils 0·5%, segmented neutrophils 55%, lymphocytes, 25%, monocytes 2%). The Mazzini, Wassermann, Kahn, and Kline reactions were negative.

Analysis of urine gave urea, 35 mg. ; uric acid, 4·5 mg. ; total protein, 8·19 g. ; total cholesterol, 300 mg.

Tests of hepatic function showed thymol turbidity to be 7·77 ; zinc sulphate (Kunkel) 9·03 ; calcium sulphate, +1 in distilled water 9·03 ; cephalin-cholesterol (Hanger), Lugol, ++.

The bromsulphthalein test was negative and the provoked elimination of galactose 0·4 g.

A routine neurological examination was negative apart from abolition of the right knee jerk which, the patient declared, dated from an accident to the knee at football.

A diagnosis was made of hyperfilarization with disturbance of the proteins, together with intestinal infestation by schistosoma, giardia, and oxyuris.

The patient was admitted on March 19, 1953, felt definitely improved by the rest, but later his wife informed us that he had suffered for several days from violent headaches. He received at the same time as his wife a tablet containing diethyl carbamazine, 50 mg., and 22·5 mg. of histaphene maleate (Carbilista U.C.B.). On March 20, he was given a tablet three times, on March 21 and 22, the same dose, on March 23 again one tablet in the morning, a total of 550 mg. for the five days. The day after the first dose, the patient complained of headache and violent pain in the left flank with the characteristics of renal pain. On March 20, in the evening the temperature was 99·4° F. The next two days the patient's condition and temperature were the same. On the evening of March 22 the temperature rose to 100·2° F. On March 22, in the hope of diminishing the reaction, he was given at 6 p.m. and 10 p.m. a tablet of " postaphène ". During the day of March 23, he felt worse, the headaches were almost intolerable, especially

at the back of the neck ; he complained of mistiness of vision and a desire to vomit.

Until this moment, the reactions appeared reasonable considering the severity of the filarial infection, and we had under observation an almost perfect control in the wife, who had received for the same filariasis the same doses at the same times. We stopped the specific therapy after the morning dose, but again gave a tablet of " postaphène ".

In spite of stopping the treatment, his condition slowly deteriorated during the night and on the morning of March 24 he passed from somnolence into coma. This we attributed, rightly or wrongly, to the histamines. According to his wife he had not had hallucinations, or disturbance of speech, or convulsions. He slowly and progressively lost consciousness. Since the coma was accompanied by slight stiffness of the neck, a lumbar puncture was performed on the morning of March 24 with considerable difficulty as the patient was struggling violently. The fluid was clear and colourless (total protein 30–35–38 mg.). The Pandy test was negative, the Weichbrodt reaction ++, and the Lange curve 11222100000. The microfilariae obtained by lumbar puncture as well as those in the circulating blood were incontestably *M. loa*. They possessed all the essential morphological characteristics and also had an unusual structure, namely a central body. Finally, they showed evidence of attenuation by the diethyl carbamazine.

On March 13, Dr. E. van de Briel reported slight conjunctivitis and slight dryness of the conjunctival mucosa. The corneae were normal on examination with the corneal microscope. The media were transparent and the visual fields normal. Visual acuity was 10/10 in both eyes. A second examination on March 25 showed normal eyes with normal fields.

On March 24 at 5 p.m. he was semi-comatose but could easily be aroused by pinching his skin and could be made to put out his tongue. His face and head were red and swollen ; the latter was slightly retracted but in the midline. He did not show any involuntary movements. The tendon reflexes were absent. The plantar responses were flexor but difficult to obtain. The abdominal reflexes were present but feeble. The masseteric reflex was present. The left limbs seemed more hypotonic than the right. It was impossible to elicit a voluntary movement but at the moment of lumbar puncture, the patient protected himself with both hands. There was no Lasègue sign. On the other hand, there was a characteristic stiffness on trying to flex the neck.

The eyes were in a central position. Automatic movements were possible but not voluntary movements. The pupils were equal and reacted briskly. The corneal and conjunctival reflexes were present and the patient blinked when pain was caused by pressure on the infra-orbital branch of the trigeminal nerve. On command, the tongue was protruded forwards in the mid-line, but not beyond the dental border. It appeared to be parched. The right facial muscles contracted less well than the left and there was the same asymmetry in the contraction of the palate. The sensory and motor functions of the trigeminal nerve could not be assessed. According to his wife, there was no difficulty in swallowing. He was incontinent of urine but not of faeces ; the bladder was not palpable.

On March 25 his general condition was about the same, but he was breathing more stertorously. He had more difficulty in swallowing. Babinski's sign was not present. There was no marked hemiplegia, and the weakness of the left limbs was no greater. The fundus oculi was normal (Dr. van de Briel).

At this time we made a diagnosis of acute meningo-encephalitis, probably an acute haemorrhagic and oedematous encephalitis reminiscent of the so-called post-salvarsan encephalitis which often showed the features of a brain purpura. We imagined that such a picture might also occur with multiple emboli.

Fresh examinations of the blood on March 24 and 26 showed that microfilariae had disappeared from the peripheral blood. The haemoglobin had fallen to 14·8 g. (92·5%), there were 4,760,000 red blood cells, the colour index was 0·96. The volume of packed red cells was 45%, volume index 1·04, the mean cell diameter was 7·5, and the sedimentation rate more than 50·5 mm. in one hour. The leucocyte count was 11·2 with a fall in the eosinophils to 1·5% and a neutrophilia of 84%. There were only 9·5% lymphocytes and 5% of monocytes. The urea had risen to 78 mg., the uric acid remained at 4·8 mg. There was 1·9 mg. of creatinine ; the non-protein nitrogen was 54 mg. The total protein was 8·47 g. and the cholesterol 333 mg.

Examination of the urine showed 0·46 g. albumin per 100 ml. with a specific gravity of 1045 and a *p*H of 6. This time there was much urobilinogen and the deposit contained numerous hyaline and granular casts and red blood cells but only a few microfilariae.

In spite of classical treatment the patient became progressively worse and the coma deepened. His temperature was 101·6° F. on the evening of March 25. The next morning there was in addition a pulmonary oedema which overcame the patient after a few hours. He died in hyperthermia (105·4° F.) at 4 p.m.

In summary, our patient, although of an unusually strong constitution, returned from Africa in a state demanding attention ; there had been loss of weight, digestive disorders, exacerbated bacillary dysentery, and a subacute nephritis with cardiac and moderate hepatic failure. He showed a hyperfilariasis with *Loa*.

On admission, he complained of nausea and violent headaches which became worse with the institution of treatment and were accompanied by pain in the left side and kidneys. The patient complained of a mist before the eyes ; he became somnolent and then comatose. Death occurred six days after the start of treatment and three days after the appearance of the first poorly localized but severe signs of involvement of the nervous system.

An electroencephalogram (Fig. 1) recorded on March 25 showed almost continuous bursts of slow irregular waves of 1½ to 3 c. per sec. reaching 120 μv., and most marked in the anterior and temporal leads. From time to time, and especially when the patient became more drowsy, a rhythm of 6 c. per sec. and 50 to 120 μv.

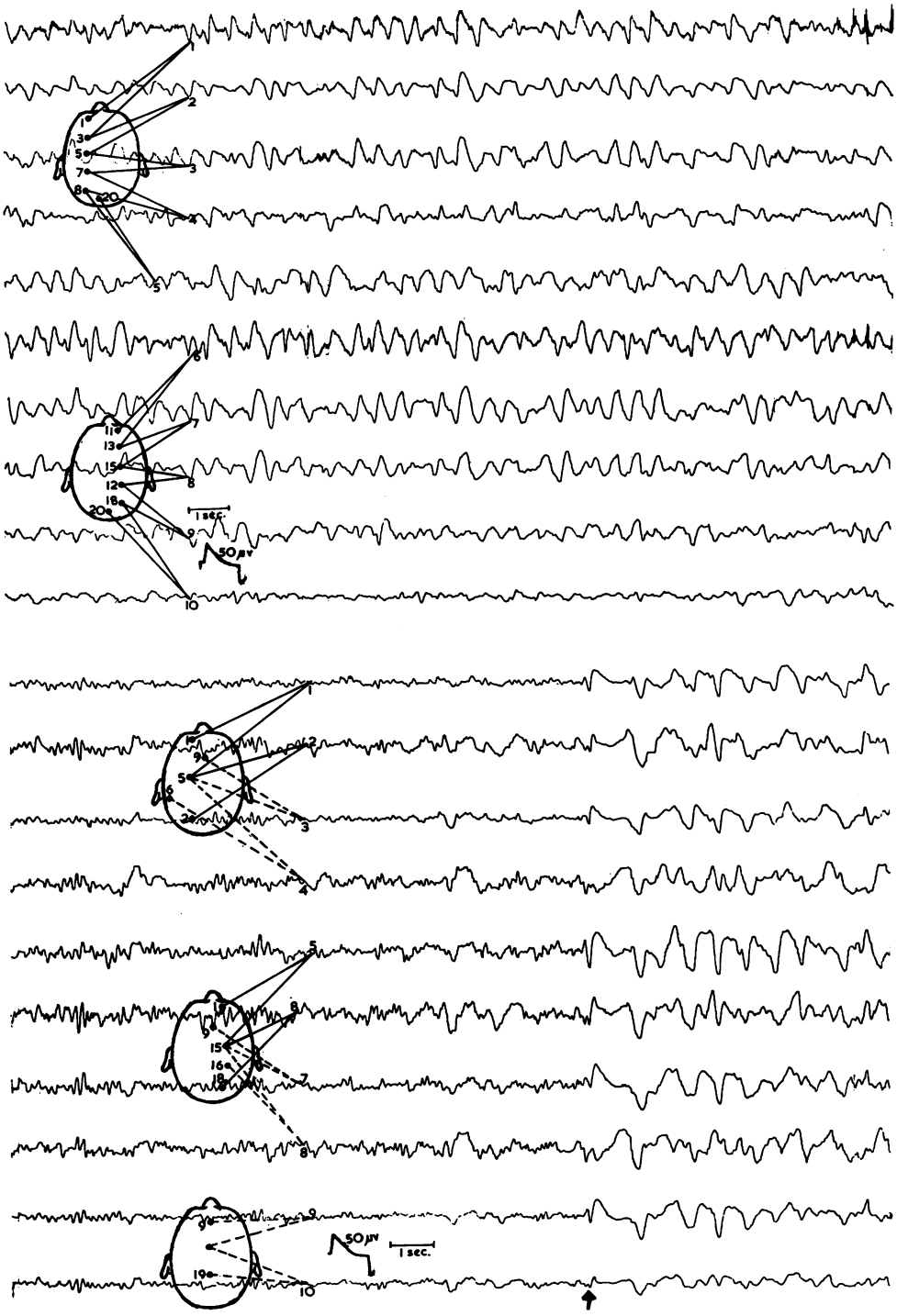

FIG. 1.—E.E.G. records.

appeared in all leads ; there were also some even more rapid waves reaching 7 to 9 c. per sec. but not exceeding 30 μv. When an external noise was made a burst of very slow waves—1½ to 2 c. per sec.—appeared and was often preceded by a flattening of the tracing ; the patient then relapsed into drowsiness and the 6 to 7 c. per sec. rhythm again became dominant. When the noises became louder and one attempted to rouse the patient the first recorded tracing, very disorganized and very slow, reappeared. With the intravenous injection of 50 ml. of hypertonic saline, numerous muscular potentials appeared mixed with the slow and irregular rhythm of the base. There was scarcely any improvement in the record, but the patient awoke and brought up a considerable amount of wind.

Dr. Radermecker reported as follows :

" This is a grossly abnormal record with symmetrically distributed, very slow polymorphous delta waves. When the patient went to sleep and began to snore, this type of record gave place to a basal rhythm of more rapid and synchronized waves at 5 to 6 c. per sec. The tracing indicates a diffuse and deeply situated encephalitic process. The modifications of the rhythm in the course of sleep recalls the synchronization which is encountered in very young children."

NECROPSY REPORT

Necropsy was performed 17 hours after death by Dr. Tverdy.

The body was that of a well built man in a good nutritional state. The lungs were severely oedematous and showed slight purulent bronchitis. The heart was dilated and filled with blood, the myocardium pale and flabby, with petechiae on the endocardium, slight atheroma of the coronary arteries, and normal valves. The liver was larger than normal and with a marked lobular pattern, but normal biliary passages. The spleen was moderately enlarged with a wrinkled capsule showing many petechiae and a pitted surface. The pulp was black in some areas and brown in others. It did not yield to the knife. The Malpighian corpuscles were not very obvious. The gastric mucosa was atrophic, had lost its folds, and showed many petechiae. The thyroid was large and fleshy. The kidneys were of normal size, the cortex smooth and a little pale, and the cortical vessels congested. The bladder, ureters, and adrenals appeared normal. The aorta was slightly atheromatous. The brain and the spinal cord were removed and fixed *in toto*.

No adult filariae were found in the loose connective tissue of various organs nor in the subcutaneous tissue of this very fat man.

Histology of the Organs

Kidneys.—The proximal convoluted tubules are severely degenerated, the cells being greatly swollen so as to obliterate the lumen almost completely. The nuclei scarcely take the stain while the brush border is almost everywhere defective. The nuclei of the distal nephron, however, are preserved. There are occasional red blood cells and hyaline casts in the tubules. The glomeruli show a definite increase in nuclei, this cellularity being partly due to the presence of polymorphonuclear leucocytes and partly to a proliferation and turgidity of the endothelial cells. The basement membrane is not thickened. The capsular cells of some glomeruli have hypertrophied and desquamated. The walls of some arterioles show fatty infiltration. There are microfilariae in the intertubular capillaries in the glomerular loops and in the tubules (Fig. 2).

Lungs.—There is oedema and intra-alveolar haemorrhage, severe vascular congestion, and desquamation of alveolar cells loaded with carbon pigment. Within the vessels there are irregular cells suggesting at first sight giant nuclei 20 to 40 μ long by 5 to 10 μ broad.

Liver.—Frozen sections stained with sudan stain show a moderate centrilobular fatty infiltration. The portal spaces are heavily infiltrated with lymphocytes, histiocytes, and a few polymorphonuclear leucocytes. In some areas the cellular infiltrations surround necrotic foci containing the microfilariae (Fig. 3). These foci develop into fibrous nodules (Fig. 4). In the adjacent sinusoids in contact with the walls of the centrilobular veins there are multinucleated giant cells. The biliary canaliculi in the portal spaces often contain bile casts. Occasionally there is a slight atrophy of the periportal parenchyma, followed by proliferation of fibrous tissue so that a few parenchymal cells within the enlarged portal spaces are cut off. Outside the portal spaces there are cellular infiltrations which are sometimes associated with the presence of microfilariae.

Heart.—The interstitial tissue of the myocardium shows the same cellular infiltrations as those seen in the liver, with lymphocytes, histiocytes, and here and there a few polymorphonuclear leucocytes. In the midst of the infiltrations there are microfilariae. The cardiac fibres are fragmented. The fibrous tissue is thickened at the expense of the atrophying muscular fibres with a resulting moderately severe perivascular fibrosis.

Adrenals.—Cellular infiltrations are found in the medulla and cortex similar to those seen in the heart and liver, sometimes associated with the presence of microfilariae.

Spleen.—In several areas, especially under the capsule, there are foci of necrosis in the centre of which are large numbers of microfilariae. The

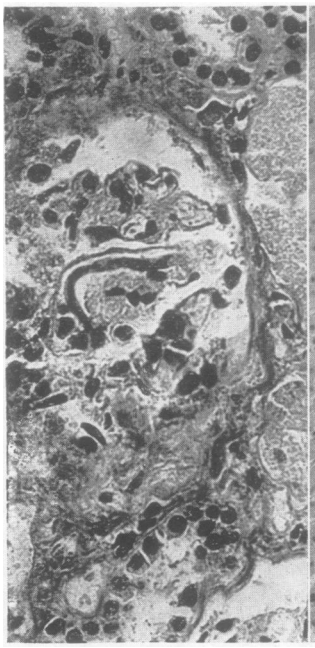

FIG. 2

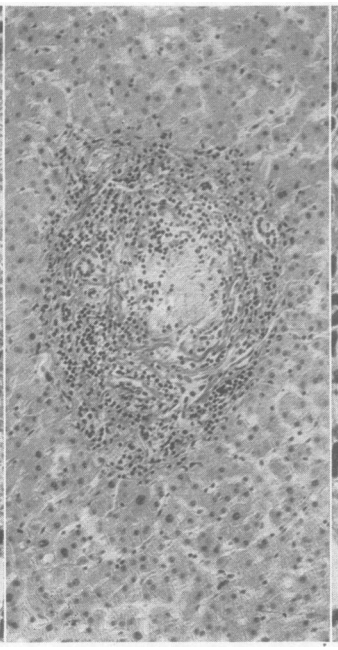

FIG. 3

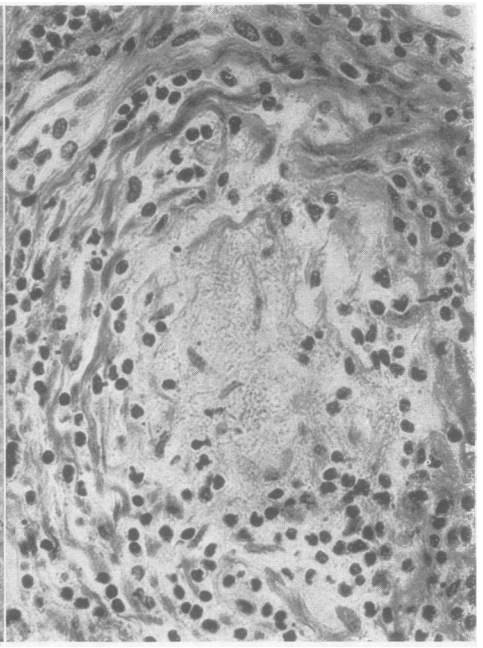

FIG. 4

FIG. 2.—Kidney, showing a microfilaria in one of the tufts of a glomerulus. There is also cloudy swelling of the proximal convoluted tubule. Haematoxylin and eosin.

FIG. 3.—Liver showing necrosis in the centre of a portal space.

FIG. 4.—Debris from microfilariae in the centre of an area of necrosis.

necrosis is limited by a zone of fibrous reaction. Within the fibrous tissue there are several multinucleated giant cells. There is a diminution in the cells of the germinal centres, those remaining lying in an acidophil, fibrillary substance. The sinusoids are poorly demarcated and the endothelial cells as well as those of the pulp are enlarged. Within the sinus as well as the trabeculae of the pulp there are moderate numbers of plasma cells.

Lymph Node.—A lymph node taken at the bifurcation of the trachea shows severe congestion ; the sinuses are distended and filled with histiocytes, polymorphonuclear leucocytes, and endothelial cells. The germinal centres show the same changes as were seen in the germinal centres of the spleen.

Considering the histological findings as a whole, the microfilariae pass the vascular barrier and penetrate deeply into the tissues. Their presence seems to cause, in the spleen and the liver, for example, a central necrosis followed by a peripheral fibrous tissue reaction with formation of multinucleated giant cells.

The subcapsular region of the spleen is particularly affected. In the liver, the necrosis associated with the presence of microfilariae is located in the portal spaces. With older lesions, fibrosis takes the place of necrosis. As well, the bile canaliculi are plugged with bile casts, without jaundice or macroscopic changes in the biliary passages. In the liver the picture is completed by the appearance of giant cells in the vicinity of the centrilobular vein and sometimes in the portal spaces. In other sites (myocardium, suprarenal glands) the microfilariae cause a reaction characterized by aggregations of lymphocytes and histiocytes. The passage of the microfilariae through the glomerular tuft produces very little reaction. The changes in the kidney are most marked in the proximal convoluted tubules, the picture in fact being that of a nephrosis rather than of a nephritis. In the foci of necrosis and tissue reaction, the microfilariae fragment before disappearing, but nowhere is there any evidence of parasitic phagocytosis.

In the extra-cranial organs two types of lesion can be demonstrated : (1) Nodular infiltrations of lymphocytes and histiocytes with a few polymorphonuclear leucocytes, usually in the vicinity of a microfilaria ; (2) foci of necrosis, probably due to the presence of microfilaria. The latter can be found in various stages of degeneration without giving rise to any phagocytic reaction. These foci are surrounded by a zone of inflammatory and

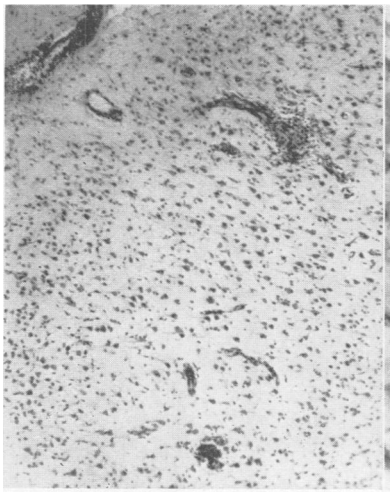

FIG. 5

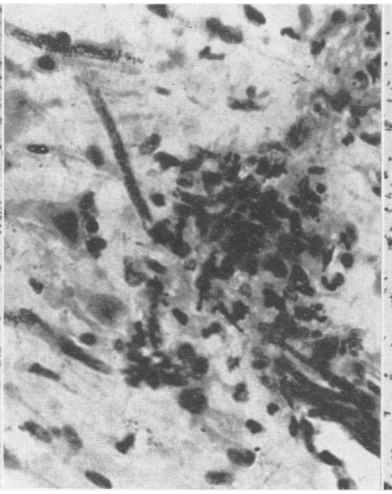

FIG. 6

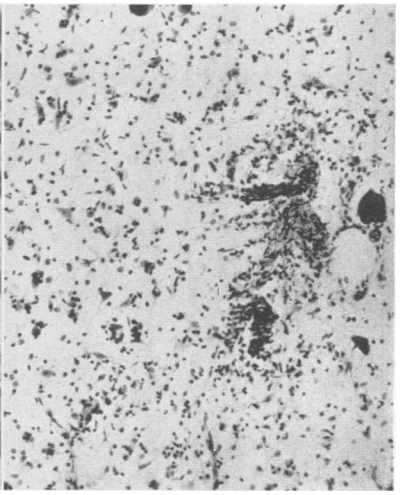

FIG. 7

FIG. 5.—Coronal section of brain passing through the superior frontal convolution. The lesions are of moderate severity. The meninges are patchily infiltrated, especially in the vicinity of a heavily cuffed vessel. The moderate-sized veins are surrounded by cuffs which at intervals show fusiform enlargement. On the left there is a small granuloma. Some capillaries and small veins show a marked stasis with lymphocytic cuffing. There are a few ghost nerve cells and also cells with ischaemic degeneration. There is a moderate diffuse microglial hyperplasia. Nissl.

FIG. 6.—Hippocampus. There is a nodule in the middle of the pyramidal zone close to a vessel stuffed with microfilariae (below and to the left, they appear like faggots in the lumen of the vessel). There are microfilariae lying free in the tissues. The nerve cells show ischaemic degeneration. There are regressive changes in the neuroglia. Frozen section, stained with cresyl violet.

FIG. 7.—N. reticularis. General view of a commencing diffuse perivascular reaction. The remainder of the section shows numerous microglial cells and satellitosis of the small nerve cells. Frozen section, stained with cresyl violet.

fibrous tissue reaction. With increasing age of the lesion, the cellular elements give place to fibrous tissue. Multinucleated cells participate in the reaction. Between the two types of reaction there are all intermediate grades; the small granulomas with central necrosis and the cellular nodules cause little change in the parenchyma in which they lie. They injure without doubt the myocardial muscle fibres and the periportal tissues. At a distance from these focal lesions a more diffuse reaction is observed, but it is difficult to prove a relationship with the principal disease. The finding of the microfilariae constantly in the neighbourhood of the nodules or in great numbers within the necrotic foci strongly suggests that there is a relationship between the two types of lesion and the presence of the embryos of the parasite. We have not been able to show the parasite in the lungs.

Examination of the Nervous System

Naked-eye Examination of the Brain.—Moderately severe meningitis was found over the convexity and particularly around the interpeduncular and cerebellar cisterns, the vermis, and the sylvian fissures. The meninges were markedly adherent at the Pacchionian granulations. There were no obvious vascular lesions. The optic nerves appeared normal. The olfactory bulbs were turgid.

On coronal section of the brain, there was a tendency to petechial haemorrhage equally marked in the cortex and centrum semi-ovale. It was rather less marked in the thalami and around the third ventricle. There were no softenings but there were greyish areas in the peduncle and the tegmentum of the pons. At the level of the inferior olives the whiteness of the latter was striking. In the roof of the fourth ventricle there were abnormal greyish streaks around the ependymal canal and the neck of the medulla.

In summary, there was little to be seen apart from focal vascular changes and an accentuation of capillary stasis, sometimes with small diapedeses of red cells in the cerebral hemispheres, cerebellum, and brain-stem, and a pearly appearance of the olives.

Histology of the Brain.—The distribution of the lesions has been demonstrated by a series of blocks cut in the coronal plane embedded in celloidin and stained with cresyl violet. The first block passes through the prefrontal region. There is a meningeal reaction, especially in the neighbourhood of the veins. Beneath the infiltrated meninges the molecular layer shows the moderate glial reaction one would expect. Occasionally there is exuded plasma.

The cytoarchitecture of the cortex is everywhere recognizable (Fig. 5). There are pericapillary infil-

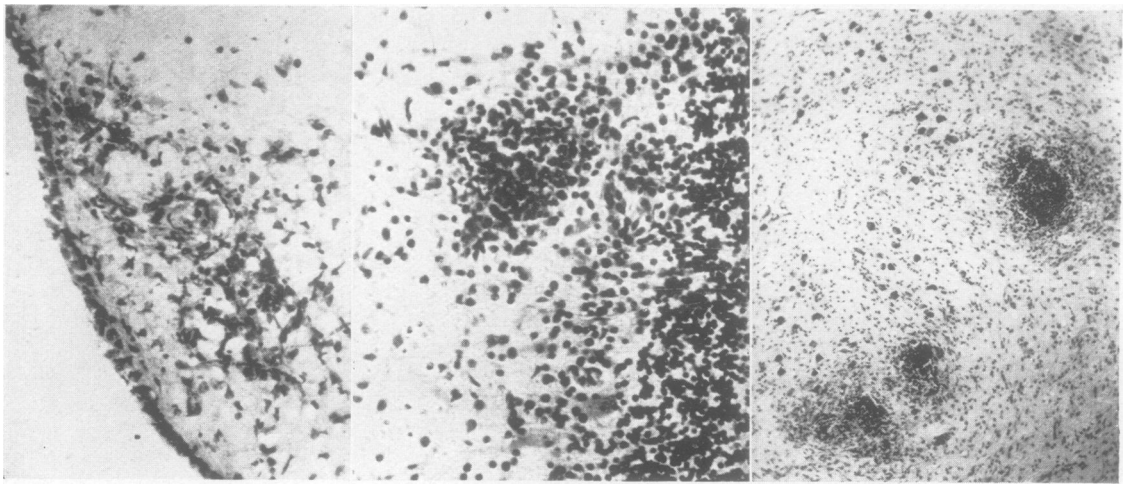

FIG. 8. FIG. 9. FIG. 10.

FIG. 8.—Thalamus. Subependymal infiltration. In the centre there is again a dilated capillary with its wall packed with cells and a few microfilariae ; on the left there is only a network of debris ; the infiltration consists of microglial cells, lymphocytes, and, occasionally polymorphonuclear leucocytes (frozen section, stained with cresyl violet).

FIG. 9.—Cerebellum showing granuloma in the molecular layer, composed of lymphocytes and an occasional polymorphonuclear leucocyte. No microfilariae can be seen. Homogenizing cell change in the adjacent Purkinje cells (on left). Nissl.

FIG. 10.—Brain-stem at the level of the inferior olives. Several granulomas are visible to the naked eye. Nissl.

trations, but on the whole it is the veins of medium size that are surrounded by cuffs which may be very thick and either discoid or fusiform in shape.

All intermediate forms between infiltrating processes and granulomatous nodules can be seen. The perivascular infiltrations are particularly prominent in the third and sixth layers of the cortex and in the subcortical region. They are equally developed in the depths of the sulci and the summits of the gyri ; they can also be seen, but less frequently, well within the molecular layer.

The same infiltrations are present also in the white matter. In their centres there are concentric spongy zones several times the width of the vessel, and usually staining yellow with Nissl, no doubt due to a hyaline change in the ground substance around an affected vessel. Indeed, there are quite frequently within the vacuolated areas vessels with hyaline walls, thickened eccentrically, or, on the other hand, a vessel surrounded by a lymphocytic exudate of no great density.

A smaller block passing through the anterior part of the basal ganglia shows several foci in the thalamus, in the globus pallidus—especially the inner segment—and in the parts of the caudate nucleus bordering on the ventricule. The claustrum is intact. The insular cortex shows the same changes as the frontal region, but they are less severe. The substantia innominata is intact.

A more caudal block shows a few more foci distributed within the thalamus. The red nucleus and the substantia nigra are intact. The nucleus of Luys is lightly affected ; there, as well as in the internal capsule, a few infiltrations are seen. The putamen and external capsule are intact. There is a very light infiltration of the medial geniculate body. The choroid plexuses, enclosed within the hippocampal sulcus, show an increase in the nuclei in their taeniae. The plexuses themselves show no changes. The cortical infiltrations become less frequent on passing from the superior to the middle temporal convolutions. They can still be found, though in far fewer numbers, in the inferior temporal, fusiform, and hippocampal gyri. They are present in all parts of the white matter. In certain parts, for example, in the digitate white matter of the supramarginal gyrus, there is an extensive infiltration with a softened centre. In other areas, for example, the inferior temporal convolution, the glial infiltrations follow the fibre tracts. The meningeal reaction is most severe over the lobule and precentral convolution. At the outer ends of the sulci the dilated vessels are often ensheathed in well developed cuffs. The striothalamic vein shows the same perivascular cuffing.

The hippocampal gyrus is free from gross change in its architecture. The fimbria and white matter of the hippocampal gyrus show numerous infiltrations. The fascia dentata and pyramidal zone are severely affected. Severe ischaemic or acute lesions are seen in the pyramidal layers together with microglial hyperplasia and pericapillary cuffing with a variety of cells, nodules, and even free microfilariae (Fig. 6).

There are also a few infiltrations in the peri-aqueductal grey matter (Fig. 7). The insertion of the choroid plexus shows a moderate increase in nuclei. There is a granular ependymitis with, in parts, a desquamation of the ependyma. The infiltrations are not, however, very intense in the subependymal region (Fig. 8). There are a few foci of infiltration where the fibres of the centrum semi-ovale enter the corpus callosum. In the white matter underlying the inferior temporal convolution, there is a diffuse glial infiltration and pericapillary infiltrations spreading from the digitate white matter into the centrum semi-ovale.

In the cerebellum the structure of the cortex is everywhere preserved. There is a discrete lepto-meningitis with a few foci of infiltration in the molecular layer, in the midst of the granular layer, or at the point of branching of foliae. Occasional lamellae show the atrophy encountered in vascular disorders. In the vicinity of the small granulomas (Fig. 9) in the molecular layer, there are glial bush formations indicating that Purkinje cells have disappeared. In the white matter nodular infiltrations are particularly to be seen near the " V " fibres in the dentate nucleus itself and in the hilum of this nucleus. The dentate nucleus also shows a diffuse gliosis. There are a few nodular infiltrations at the junction of the pons with the midbrain, especially in the reticular nucleus, the oculomotor nuclei, the median nucleus of Reil, and the pontine nuclei situated close to the raphe. The marginal region of the pes pedunculi and the ventral nuclei are intact.

There is a slight aqueductal granular ependymitis with some infiltrations.

The brain-stem is not severely affected. In the pons there are numerous small foci in the nucleus of the mesencephalic root and in the reticular zone, but there are fewer in the tectum than in the crus. Moderately severe, sheet-like infiltrations are to be seen in the ventral nuclei of the pons and in the pyramidal tracts. Section through the upper part of the medulla shows a few infiltrations in the olives and in the floor of the fourth ventricle. On the whole, existing structures are not destroyed. There are also small foci of infiltration in the pyramidal tracts, in the reticular substance, in the lateral nuclei of the medulla, and immediately beneath the ependyma of the floor of the ventricle. They have everywhere the same appearance. The olives show a moderately severe diffuse gliosis (Fig. 10). A few of the nerve cells in these nuclei show acute changes. In the upper part of the medulla both pyramids show a few glial stars ; there are more prominent foci in the middle cerebellar peduncle, in the superior olives close to the facial nerve, and in the nuclei of IX and XII. The appearances are similar in the lower part of the medulla. Here there are nodules in the intercellary nuclei, the lateral nucleus of the medulla, and the dorsal para-olive. At the cervico-medullary junction there are a few infiltrations in the nuclei of the posterior columns and in the substantia gelatinosa of Rolando. The roots themselves show only a moderate infiltration. In the cervico-medullary region and sacro-lumbar part of the spinal cord the infiltrations are situated most prominently in the pyramidal tracts and to a lesser degree in the grey matter and nuclei of the posterior columns. Sections stained for myelin show everywhere the same changes. The spongy foci described in the centrum semi-ovale appear in these sections as a mushroom-like budding centred on a blood vessel. The myelin has been lysed throughout these polycyclic pale areas. Near these foci there are simple haemorrhagic softenings revealed by pallor of the myelin sheaths involved in the areas of diapedesis. It is easy to distinguish these two types of lesion from each other. They are not the result of celloidin embedding, for they can also be seen in frozen sections stained with Spielmeyer, but here the borders are less sharp. The olfactory bulbs show occasional infiltrations. The dura mater is intact. The pituitary and pineal glands and the stalk of the infundibulum, the chiasma, and the optic nerves are normal.

Muscles.—The fibre bundles, the interfascicular connective tissue, the intramuscular nerves, and the vessels show no abnormality in any of the five pieces of muscle examined.

The peripheral nerves (sciatic, external popliteal, ulnar, radial, and an intercostal nerve) show no loss of myelin sheaths, while sections stained with scharlach R reveal no products of degeneration. There is some infiltration of the perineurium, especially around the vessels, by haematogenous elements which have penetrated the perivascular connective tissue. This exudate is uniform and consists largely of lymphocytes, with a few large mononuclear cells and occasional plasma cells. The walls of the capillaries are particularly rich in nuclei, while the endothelial and adventitial cells also have very darkly staining nuclei with numerous well impregnated chromatin fragments. Nowhere are there any microfilariae. Spinal ganglia and the ganglion of Gasser are normal.

The distribution of the inflammatory lesions may be summarized as follows. In the cortex and the centrum semi-ovale, the focal perivascular infiltrations are found in all areas. Nevertheless, there is a predominance of lesions in the medial surface of the frontal lobes, the paracentral lobule, the frontal and

ascending parietal, inferior temporal, and fusiform convolutions. Of the basal ganglia, the thalamus and the inner segment of the globus pallidus are the most affected. The dentate nuclei, inferior olives, and the nuclei of the floor of the fourth ventricle are similarly involved. In the spinal cord, infiltrations are particularly to be found in the posterior horns and lateral columns. The spinal roots show patchy, moderate infiltration. The spinal ganglia and the muscles are spared. With careful searching lymphocytic infiltrations can be found in the peripheral nerves.

The Structure of the Histopathological Process

A general view of the cortex shows at once that the cytoarchitecture is preserved, a diffuse and uniform microgliosis with red cells, a series of small foci of infiltration with necrotic centres and perivascular situation, and an abnormal visibility of some capillary branching with, in places, little clusters of adventitial cells. A fair number of nerve cells, especially in the vicinity of the perivascular foci, show acute cell change, namely, disappearance of the Nissl bodies, abnormally prominent and swollen dendrites, sometimes a vacuolation of the cytoplasm at the periphery of the cell, and an early pyknosis of the nucleus. In addition there are a few phantom cells. The rod cells, which are noticeable throughout the cortex, rarely show degenerative changes except in the necrotic foci, where both the microglial and oligodendroglial satellites are increased in number. The astrocytes show little reaction, but are sometimes markedly and diffusely increased in layers II and VI and in other regions (thalamus, pulvinar, and hypothalamus).

The vascular lesions are striking; they affect particularly the veins and capillaries. The vessels are much more prominent than usual; within their distended lumen red blood cells piled *en rouleaux* indicate stasis.

The lesions around the veins are more marked than those around the arteries. This can be seen when both types of vessel are present in the one focus. For example, in the hippocampal gyrus one may see a vein with a thinned-out hyaline wall with scarcely visible nuclei and a microfilaria apparently passing across it. The artery is less affected; the adventitial space is filled with plasma or there is the loosely attached debris of an adventitia infiltrated with haematogenous elements, histiocytes, compound granular corpuscles, and microfilariae.

The foci of infiltration and necrosis are of different types according to their stage of development: (1) The walls of veins and capillaries can no longer be seen and are replaced by a series of cells with eosinophil cytoplasm and a large, lobed vascular nucleus (histiocytes), nuclei of lymphocytes, activated microglial cells, a few cells, probably polymorphonuclear leucocytes, and runs of red blood cells. One can also see the interrupted filaments of the microfilariae. (2) The endothelial cells of the capillaries are turgid, their lumen being occupied by festoons of microfilariae (Fig. 11). The adventitial space can only be recognized with difficulty, for within it are the same cells described above. Within the syncytium formed by them are vacuoles either empty or packed with red blood cells or nuclear debris. Some of the cells in these foci show degenerative changes. Microfilariae may be seen with one of their ends within a granuloma while the other lies free in the parenchyma. (3) The appearances resemble those just described but there are also dense intra- and extra-adventitial lymphocytic

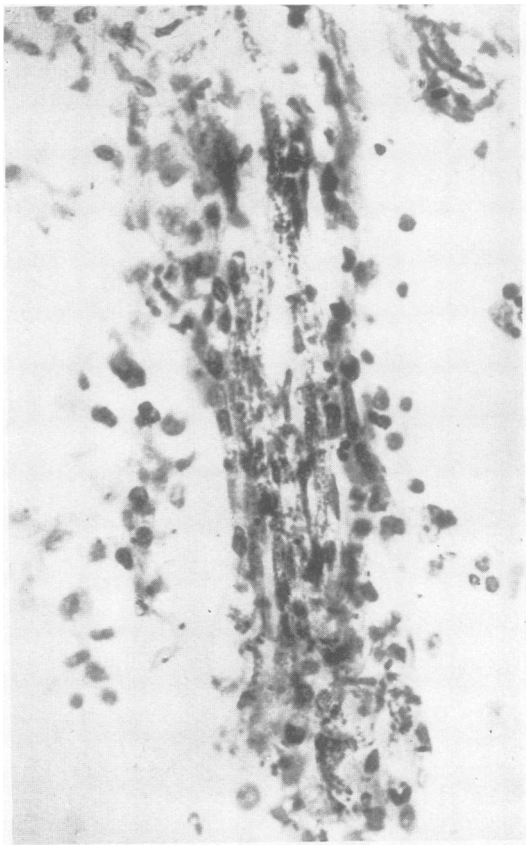

FIG. 11.—Aggregations of microfilariae in the lumen and on the surface of the vessels in the upper part of the photograph. They can also be seen in the capillary on the left, and below a microfilaria can be seen leaving the largest vessel. Frozen section stained with cresyl violet.

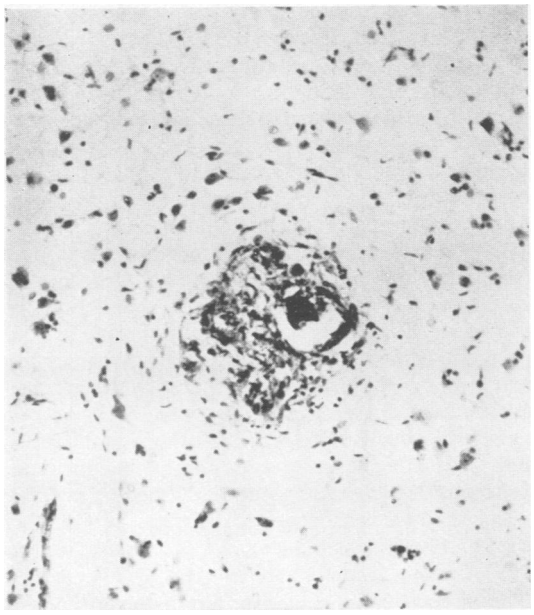

FIG. 12a

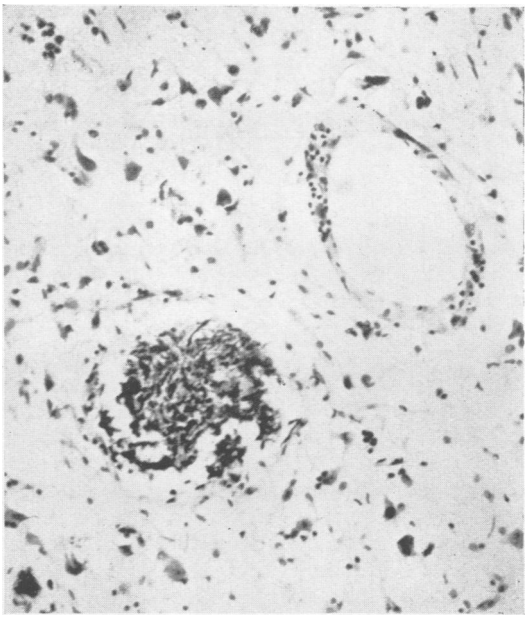

FIG. 12b

FIG. 12.—(*a*) Precentral convolution: early stage in the formation of a granuloma. Several microfilariae can be seen (frozen section, cresyl violet). (*b*) Precentral convolution; granuloma at a more advanced stage in its formation. There are several microfilariae (frozen section, cresyl violet).

infiltrations. (4) The infiltrations may form an actual granuloma around, or, more often, to one side of, a vessel. The lumen of the vessel may be still recognizable but occupied by an adherent thrombus (Fig. 12), or it may be completely unrecognizable (Fig. 12b). Within the granuloma the cells lose their distinctiveness while the nuclei show degenerative changes, but everywhere one can recognize the lacework of the microfilariae.

Within the centrum semi-ovale there are similar granulomas. Where the plasma is coagulated within the vessels, there is marked cavitation of the adjacent parenchyma. Other areas show a spongy liquefaction. On one side of the vessel there is a triangular or oval honeycombed area in which the delicate trabeculae take the blues so as to appear slightly violet. The vessels may be central or represented only by a skein of fibrin filaments, its wall being no longer recognizable. Its fragments are mixed with sheets of glial and haematogenous cells, together with fragmented glial nuclei and free microfilariae.

Aggregates of nuclei can be seen within agglutinated masses of protoplasm where there are abundant microfilariae. These syncytiae correspond to the giant cells mentioned in the literature. The glial or histiocytic origin of these giant cells we regard as debatable.

In some areas, such as the basal ganglia and the hypothalamus, the nerve cells are more affected; hyperchromatosis with shrinkage and loss of dendrites, a hyaline appearance of the cytoplasm and apical dendrite, a turbid vacuolar degeneration and an increase and degeneration of the satellite neuroglia are all noticeable. In these regions there is a diffuse increase in microglia and also of astrocytes, which have large clear nuclei and are to be found in isolated groups. The situation is the same in the cerebellum; the Purkinje cells have, in places, a hyaline appearance.

The leptomeninges show focal infiltrations mostly related to the adjacent parenchymatous foci, so that the microfilariae occupy the capillaries of the molecular layer of the cerebellum and the foci are in the Purkinje cell layer. There are unmistakable nodules swarming with microfilariae immediately beneath the ependyma.

Regarding the lesions as a whole, one may classify them as follows: (1) Very prominent lesions associated with vascular stasis with evidence of vasoparalysis, oedematous transudation, thrombosis and a spongy state, especially in relation to the capillaries and small veins; (2) Nodular infiltrations with adjacent necroses expanding into small spherical granulomas around degenerating blood vessels packed with microfilariae. The nodular or

fusiform infiltrations, the spongy change in the ground substance and the vascular changes due to vasoparalysis are all interrelated. They are always found together and it is this association of lesions that gives the disease its distinctive character. (3) As the foci are disseminated throughout the brain above the peduncle, without predilection for white or grey matter (though the former may be little affected), the reaction of the parenchyma to the effects of the circulatory disturbance is microgliosis with rod cells, a macroglial proliferation, and involvement of nerve cells varying according to locality. The nerve cells only occasionally show neuronophagia. Nowhere are there large areas of cellular devastation. There is an increase in satellites and apparently reversible changes in the cytoplasm. (4) Finally there are sheets of microglia spreading out in a fantail manner near vessels undergoing necrosis or showing reactive changes in their walls, in which can be seen lymphocytes, plasma cells, and polymorphonuclear leucocytes. In their neighbourhood there is neuronophagia, acute nerve cell changes and a diffuse micro- and macro-glial proliferation.

DISCUSSION

Viewed as a whole, the encephalitis under discussion presents the following picture.

Large numbers of microfilariae are present in the lumen of the vessels and insinuate themselves into the smallest capillaries. Nevertheless, we have nowhere seen any histological changes suggesting the purely mechanical effects of obstruction, such, for instance, as the ring haemorrhages characteristic of traumatic fat embolism, of which the fatal outcome is often as rapid as in the case under discussion.

The microfilariae traverse the wall of the vessels, and are also to be found in the adventitial space. They are without any doubt to be found in the parenchyma but always in the vicinity of necroses where it is difficult to say whether or not the vessel wall had been lysed. They produce no reaction in the adventitial space.

In fact the reacting elements of the Virchow-Robin space appear to ignore their presence. We did not find them within giant cells or isolated histiocytes. They are to be seen, however, grouped together in granulomas and in the glial syncytia, but it is impossible to say whether they are within the cells or simply agglutinated within the granuloma. In the vessels and in the parenchyma they are present in large numbers, but always free and little changed as far as one can judge by their appearance and outline.

Yet the microfilariae assuredly cause a violent but well localized gliomesenchymal reaction, of which the spherical granulomas described in the report are the most typical. The glial infiltrations whether sheet-like, *en bouquet*, or nodular as well as the subependymal pericapillary glial networks, are expressions of the same reaction. These glio-mesenchymatous reactions have a tendency to rapid necrosis. The other changes in the ground substance, namely, spongy degeneration with honeycomb appearance, " rain-drop " microcavitation and concentric spongy appearance with or without glial reaction, the diffuse glial infiltrations with a delicate capillaritis in the centrum semi-ovale, and the cellular rarefactions in the pyramidal layer of the hippocampus, all can be regarded as evidence of a functional disorder of the circulation. All this suggests that the granulomatous, nodular, parenchymatous reaction is only a response to a toxin derived from the microfilariae, whether or not the latter are present in enormous numbers in the circulation and whether or not the beginning of their therapeutic lysis has initiated an exceptionally violent and generalized reaction on the part of the organism.

The visceral lesions are similar to those that we have shown in the central nervous system. Here also there are necroses or granulomatous reactions tending in their centres towards necrosis. The microfilariae are intact or in course of fragmentation or lysis. In the central nervous system it is not possible to demonstrate fragmented forms but some have a retracted and atrophic appearance suggesting that they have died. Such appearances are accompanied by diffuse changes, which are probably related to the final toxaemia or to oedematous reactions with the same origin. The necrogranulomatous changes appear, particularly from the histological evidence in the extra-cranial organs, to be not of recent origin but to have preceded the terminal event. The presence within their centres of the remains of microfilariae indicates that they are almost certainly reactive.

It may be asked whether the patient had not succumbed to the combined effects of a microfilarial invasion together with some other cerebrovisceral granulomatous process. This recalls the hypothesis put forward by other observers that the microfilariae would only pass through the blood-brain barrier if this had been damaged by some other infection, for example, trypanosomiasis or syphilis. The fact that the embryos of the parasite found within the granulomas were more or less digested is strongly suggestive of a connexion between their lysis and the reactive process.

An attempt at integrating the cerebral " accidents " can only be achieved against the background of the general pathogenesis of filariasis. We have found

in the recent reports of Rodhain (1953) and Wanson (1953) a complete exposition based on a large personal experience. Their conception is reflected in this paper. *Loa-loa* filariasis has, in common with other types of filariasis, an insidious character of penetration by the organism ; this invasion elicits no local or general reaction over the course of many years although antibodies are formed which may be demonstrated by their deviation of complement. One should distinguish (1) disorders arising from a local reaction to adult filariae ; (2) a second type of local reaction consisting in a lymphatic disorder, suggesting partial obstruction with stasis and oedema, and may have played a role in the production of some of the features we have just reported ; (3) a third type of reaction consisting in allergic cutaneous manifestations (without filariae or with microfilariae *in loco*), revealing themselves as transitory oedemas corresponding to acute attacks of filarial lymphangitis.

Lysis of microfilariae alone cannot be the cause of these phenomena. It is admitted that the presence of the microfilariae has a chronic irritant effect on the lymphatic and connective tissue, but it is still not known whether the lesions result from the direct irritant effect exerted by the microfilariae alone or whether they are conditioned by a previous sensitization of the organism to the microfilariae. Rodhain maintains that in the course of the parasitosis of the human organism by the filariae, the former is sensitized by the adults who produce embryos endowed with antigenic properties. The destruction in large numbers of these embryos provokes the local and general allergic reactions varying in form and intensity according to the number and the specificity of the microfilariae destroyed. In the course of evolution of a filariasis, we see these manifestations produced in various forms. The best known are, without doubt, the filarial lymphagitides, elicited by *Wuchereria bancrofti* and related species (Wucherer, 1868). Their repetition is the cause of the various types of elephantiasis.

As far as *Loa-loa* filariasis is concerned, the best known symptom is Calabar oedema (which in certain individuals recurs with great frequency). One can only say that it bears all the hallmarks of an anaphylactic reaction. There is no fact that proves a direct connexion between the oedema and either a sudden massive destruction of microfilariae or the birth of many embryos. The oedema may occur without detectable filarial embryos in the circulation. It is a typical example of sensitization of the organism by the adult nematode, a sensitization revealed by anaphylactic phenomena whose inception may be manifested under the influence of greatly varied circumstances with differences in intensity dependent upon the parasitosed subjects themselves.

We have shown above that grave complications can supervene without any treatment, and that they can manifest the same symptomatology and the same fulminant evolution as cases in which they appear in the course of or after treatment. This, of course, supposes that the recorded cases to which we have made reference were uncomplicated by the presence of any coexisting disease. Certainly, this applies to the cases of Bonnet (1943), and Cases 1, 2, 3, and 4 of Kivits. On the other hand, in Kivits's second case, the cerebral syndrome appeared 15 days after a local suppuration. Perhaps this is an example of one of the precipitating " circumstances " referred to by Rodhain. It is not impossible that a syphilitic (Bonnet's case, 1943) or trypanosomal (experimental observations of Peruzzi in the monkey, 1928) vascularitis of the central nervous system favours not only the penetration of the microfilariae but also the extension of the allergic reaction to the nervous parenchyma itself.

The encephalitis of *Loa-loa* does not necessarily betray the same fulminant character seen in the cases we have just recalled. It may evolve in bursts ; this phasic development is most marked in the observation by Mme. Bertrand-Fontaine and her collaborators where the deterioration in the patient's condition was interrupted by the treatment.

The encephalitis may be insidious with a psychoneurotic presentation, as in Kenny and Hewitt's (1950) third case, and in the first two observations of these authors, where the removal of an adult filaria had terminated the psychiatric symptoms and eosinophilia.

The cerebral localization of a filariasis can, then, reveal itself simply by vague headaches with depression and apathy or torpor with nothing else to suggest the underlying filarial allergy until the day when an active therapy is instituted. That is what happened in our case. It was the same in the case of Mme. Bertrand-Fontaine and her collaborators and also, with a fatal result, in Case 4 (*M. bancrofti*) of Kenney and Hewitt (1950).

This is all consistent with the view of Rodhain who said of the local and general allergic reactions that they were so characteristic that the therapeutic test, which determines their appearance, indicates a filarial aetiology in cases where the diagnosis is in doubt.

However, the carbamazide used in our case is essentially a microfilaricide or macrofilaricide for *Loa-loa*. The use of this drug in loasis initiates a variety of reactions of variable intensity and

duration affecting the skin, liver, stomach, and joints usually without fever—a reaction assuredly anaphylactic and reacting to antihistamines. These accidents begin on the second day and, as a rule, last for two days. By their rapid lytic action these new drugs can thus bring impressive evidence of the allergic origin of a part of the filarial symptomatology.

Without doubt, the clinical manifestations in all forms of filariasis (*M. loa*, *bancrofti*, and *volvulus*) are irregular and, taking everything into consideration, infrequent, but it is worth while to consider some of them in the light of our present knowledge of allergy.

The changes that we have encountered in the liver, spleen, adrenals, etc., and especially in the central nervous system, are of two types : granulomatous reactions with a variable necrotic component and lesions indicative of an acute, diffuse oedema. The membranes both of the nervous system and the extra-cerebral organs are only involved to the extent that the underlying tissues show granulomatous or oedematous reactions. These two types of reaction are not contemporaneous. The first named are the older and the more striking while the second are terminal, but for the reasons given above we consider both to be connected with the presence of microfilariae, living or lysed. We regard them as evidence of a subacute or chronic allergic affection of the nervous system, depending directly and solely upon the presence of microfilariae and comparable to the relapsing lymphangitides terminating in elephantiasis.

The reactions to microfilariae seen in the cerebral tissue are almost exclusively in the adventitial and glial tissues surrounding the Virchow-Robin space. This is true not only in our case but in the sections from Kivits's case, which, thanks to the kindness of this author, we have been able to re-examine.

Either spontaneously or under the influence of an active chemotherapy, an adventitial reaction or extra-adventitial nodules make their appearance. Then the exudation of plasma or changes in the ground substance characteristic of oedema are seen. It is probable that changes in the walls of the vessels or the adventitial spaces of the brain from other causes (syphilis, trypanosomiasis) play a role, and it is known that all inflammations of the walls of the vessels have an important effect on the blood-tissue barrier, resulting in increased permeability to both antigens and antibodies.

The acute phase of the disease begins with the explosiveness characteristic of other allergic conditions (involvement of the nervous system in serum sickness, in polyarteritis nodosa, in the exanthemata), that is, clinically resembling apoplexy or a cerebral illness with focal symptoms, frequently and fortunately transient, but the histological picture is entirely different from that seen in, for example, post-vaccinial encephalitis. It may, from certain points of view, resemble that seen in polyarteritis nodosa but recalls much more certain experimental encephalomyelitides whose granulomatous character has frequently been stressed (Kabat, Wolf, and Bezer, 1948). Even if the role of this granulomatous reaction in the production of antibodies is debatable, its very constant, if not invariable, presence in certain types of experimental encephalomyelitis, has a significance. This approach indicates, perhaps, a line of treatment to be attempted in the serious accidents of cerebral loasis.

SUMMARY

In filariasis with *Loa-loa*, theoretically, two types of neurological accident may be seen : the first, due to the presence of macrofilariasis, of focal character, the second to the presence of microfilariae, and presenting with subjective mental symptoms and vague neurological features until there is a dramatic complication in the form of hemiplegia or double hemiplegia. On this basic phenomenon, apparently focal and suggesting a thrombosis, there are grafted, in a few cases, other neurological signs, though these are always scanty. This dramatic accident, terminating fatally in a few days, is accompanied by microfilariae in the cerebrospinal fluid, which in other respects shows quite non-specific and minor abnormalities. The neurological complication is part of a generalized disease.

As seen in Kivits's case and in our own, the cerebral complication is the expression of a subacute or chronic encephalitis with a terminal phase representing a fulminant allergic reaction. This terminal phase may supervene spontaneously, though its appearance may be accelerated by a septic incident, by injury to the blood vessels by some other infection, or by the sudden introduction of a large amount of microfilarial antigen consequent upon the initiation of a lytic chemotherapy. The basis of the encephalitis is a diffuse inflammation of the adventitial and vascular apparatus, accompanied by a not inconsiderable glial reaction. This inflammation elicits a nodular reaction with granulomata tending to become necrotic and to be disseminated though with a predilection for certain areas.

In a few areas, the leptomeninges showed local reactions corresponding to those of the vessels, but there was no primary meningitis, ependymitis or infiltration of the choroid plexuses. The peripheral

nerves participate in the disease only to the extent that the perineural lymphatics may be involved.

The electroencephalographic changes may be primarily determined by a pre-existing filarial encephalitis for the changes we have described are not seen in this form in oedema nor in coma.

The question of prevention of such dangerous and insidious neuroallergic reactions is obviously of great importance, especially with the use of heroic doses of antifilarial remedies. It would seem wise in those cases suspected of neural loasis, to attempt a desensitization at the start of treatment either by fractionating the doses of the lysing drug or by combining the drug with antihistaminic substances which appear to act on the tissues taking part in the allergic reaction.

Another approach to treatment might be devised by taking into consideration the granulomatous form of the perivascular reaction which is characteristic of certain types of " allergic vasculitis." It is known that an appropriate dose of A.C.T.H. protects an allergic guinea-pig against the allergic encephalomyelitis which follows injections of heterologous brain substance (Moyer, Jervis, Black, Koprowski, and Cox, 1950) and probably acts at the side of the antigen-antibody reaction. On the other hand, cortisone prevents the development of an experimental encephalomyelitis in the rhesus (Kabat and others, 1947; Morgan, 1947); probably the cortisone suppresses the granulomatous reaction to the antigen at the site of inoculation. There can be no doubt that cortisone is less easily controlled than the antihistamines which have, to a certain extent, an inhibitor effect on experimental encephalomyelitis (Lumsden, 1949), as have also the salicylates (Good, Campbell, and Good, 1949) and mustard gas (Koprowski quoted by Moyer and his collaborators, 1950) but its action is certainly more effective. With cerebral complications as severe as those that we have described, no delay in instituting treatment can be permitted, so when chemotherapy is instituted for the neurological or psychiatric manifestations of filaria, the physician should be prepared, at the first hint of cerebral involvement, to control the allergic reaction by a massive dose of cortisone, possibly combined with antihistaminic substances.

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