THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

JULY, 1949

COMMUNICATIONS

TOXOPLASMOSIS, A SUMMARY OF THE DISEASE WITH REPORT OF A CASE*

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PRE-NATAL infection of the eyes of human infants by toxoplasma has been reported with increasing frequency in the past ten years, mainly in America, and more recently in Holland and other European countries. There are now more than 50 recorded cases. The disease was introduced to British literature by Vail in 1942, but so far only two cases have been reported in England, one by Jacoby and Sagorin in December, 1942, and one since then by Wilson and Forest Smith. A third case may, therefore, be of interest, and will perhaps draw further attention to a disease undoubtedly present in this country and often overlooked. In retrospect it is certain that cases of this disease have been seen

* Received for publication, May 3, 1949.

in the past and pronounced correctly but inaccurately intra-uterine uveitis or pseudoglioma, or incorrectly congenital developmental abnormalities including macular coloboma.

Janku in 1923 reported choroido-retinitis in the eye of an infant in which he demonstrated a protozöon which he described as a sporozöon. It is now agreed that the organism was in fact toxoplasma, and this case is accepted as the first of human toxoplasmosis recorded. Similar cases were reported by Torres (1927), Richter (1936), and Wolf and Cowan (1937). In 1939 Wolf, Cowan and Paige recognised the infecting protozöon as toxoplasma from its resemblance to that organism which was previously known to affect rodents. Since then reports of human cases have been published by numerous authors, and the disease has been carefully studied by Cowan, Wolf, Paige and others in America, and by Binkhorst in Holland. A brief summary of their researches may be of value.

The organism.—Toxoplasma was discovered in 1908 by Nicolle and Manceau in the North African gondi. It is a protozöon now considered by Sabin and Olitsky to be an obligate intracellular parasite. In its "free" and pathogenic form it is a slender lunate or slightly curved body measuring 4-7 × 2-4 microns, becoming increasingly globular with age. Stained with Giemsa the cytoplasm is eosinophilic, and the nucleus hyperchromatic. It is also found in multi-nuclear clumps or "cysts" measuring 20-30 microns, and these probably represent aggregations of immature organisms. In this form it appears to cause no tissue-reaction so long as the enveloping cell-membrane is unbroken. The organism is demonstrated most readily in man in sections of *post mortem* material, heart, lung, muscle and testis, as well as in the brain and eye, but it may also be recovered in living patients in the cerebro-spinal fluid, and rarely in centrifuged blood serum.

Animal infections.—Toxoplasmosis has been recognised for more than 40 years as a disease of rodents. It also affects birds. It has been found in numerous wild animals, including squirrels and zoo animals in England, and it is important to note that spontaneous cases have been recorded in domestic animals, including the dog and fowl. Mice and rats are also susceptible, and undoubtedly there is an extensive animal reservoir of the parasite. How the infection is transmitted to man is not yet known. Possibly the mouse and rat, so numerous in this country, are important carriers, though spontaneous toxoplasmosis has not yet been reported in wild specimens. Ticks have been suggested as possible insect vectors between animals, and between animals and man.

Human infections.—In human infections the severity of the disease and its predilection for the eye and central nervous system appear to vary inversely with the age of the patient. In adults the disease is slight, and may even be sub-clinical, though more often there is a febrile disturbance with mild broncho-pneumonia and a papillo-macular rash resembling that of typhus. Rarely a chronic encephalitis may occur. In children the disease is manifested as an encephalitis, and in infants a severe intra-uterine or early post-natal encephalo-myelitis develops, and it is this type which has up to now interested the ophthalmologist, on account of the regularity with which the eyes are involved. The eye infection is probably directly transplacental, though possibly the organism may reach the eye from the infected brain *via* the cerebro-spinal fluid along the optic nerve. It remains to be discovered whether ocular involvement follows infection other than intra-uterine, for if children infected post-natally develop an encephalitis this would not seem improbable.

General manifestations.—In severe infections the infant may die before or shortly after birth. Advanced toxoplasmosis has been found in a stillborn baby. In milder cases there may be jaundice, convulsions, spastic deformities, splenomegaly, hepato-megaly and widespread focal encephalitis leading, if the child survives, to multiple areas of cerebral calcification. These calcified areas are clearly shown by X-ray, and provide a valuable aid to diagnosis. They are found scattered throughout the cortex of all the lobes, as well as in the basal ganglia and thalami, and are of two types—curvilinear streaks, and globular bodies some 3 mm. in diameter. Internal hydrocephalus generally results, but microcephaly may occur instead. There is a varying degree of mental retardation, which in the mildest cases may be little more than delayed development of speech. Severe involvement of the eyes still further impedes progress.

Ocular manifestations.—These are practically universal, and constitute a cardinal feature of the disease.

The lesions in the two eyes are generally strikingly similar. Searching nystagmus associated with macular lesions is usual. Microphthalmos and other effects of arrested or abnormal ocular development are common, though not invariable. Gross persistence of pupillary membrane may be a feature, and less frequently posterior cortical cataract, posterior lenticonus and other developmental abnormalities may be found. Strabismus is common.

The characteristic disturbances are found in the posterior segment, and consist of focal choroiditis affecting both macular regions as well as, generally, areas elsewhere in the fundi. Frequently the periphery of one or more quadrants is involved.

The active stage, not often observed, presents the appearance of one or more brawny red swellings in the fundus, particularly at the macula, in the centre of which there is a marked tendency towards necrosis. The inflammation is strictly focal, unaffected areas of the retina and the retinal vessels remaining normal. The vitreous likewise remains clear, except in close relation to foci of inflammation. The quiescent stage is, of course, more commonly seen. In this there are sharply demarcated, punched-out white areas of choroido-retinal atrophy, sometimes as much as 6 disc-diameters across. The edges may be scalloped, as often obtains in other forms of infantile choroiditis, and there is marked pigmentary disturbance, large masses of black pigment being found at the edge of the crater and, to a lesser degree, on its floor. Sometimes bands of grey connective-tissue, often very extensive, run in the vitreous from crater to crater. In this stage, too, the unaffected areas of retina and the retinal vasculature show no abnormality, and the vitreous in general is strikingly clear. Some degree of optic atrophy is usual. This may be consecutive and associated with retinal damage, especially at the macula, or post-papillitic as a result of encephalitis.

Histopathology.—Sections show areas of acute round-celled infiltration in the choroid and retina, with a marked tendency towards necrosis. The focal nature of the lesion is shown by the sharp margin between normal and inflamed tissues. The parasite has been demonstrated within inflamed areas. Following destruction of the retina there is a proliferation of glial tissue into the vitreous. Brain sections show similar granulomatous changes, and here the necrosis is followed by calcification. In the optic nerve slight perivascular infiltration may be seen.

Laboratory tests.—The cerebro-spinal fluid is usually xanthochromic, contains excess of protein, and may show a mild pleocytosis. In a proportion of cases the parasite has been found, but since most are seen only after the acute stage has subsided, a negative result may often be expected.

Serum reactions on the patient and mother are a valuable aid to diagnosis, and are of two types. A complement-fixation test can be performed, and the titre is an indication of the activity and severity of infection. An antibody fixation test (Sabin and Ruckman, 1942) is also employed. Tissue, usually mouse brain, known to be infected with toxoplasma is mixed with the serum of the patient, and also with that of a control, and injected intracutanously into a rabbit. A nodular necrotic lesion develops about the fourth day if no antibodies are present in the serum, and fails to develop if they are present.

In some cases this test has proved negative during the first ten

weeks of the disease, and such a result probably indicates a low degree of serum reaction at this stage. A negative report, therefore, does not disprove the diagnosis. Transmission of the disease to animals by injection of infected human cerebro-spinal fluid has also been performed.

Differential diagnosis. — The disease requires differentiation mainly from other forms of intra-uterine or neonatal uveitis, and "pseudo-glioma." Among these are congenital syphilis, metastatic choroiditis associated with pulmonary infections, and choroiditis secondary to meningitis. Multiple congenital abnormalities are usually present in toxoplasma owing to arrested development of the eyes, and the central areas of choroiditis may be mistaken for bilateral colobomata of the maculae of maldevelopmental or hereditary origin. Retinoblastoma may be suggested, though the findings are not very similar. Birth injuries involving the maculae with organisation in an extensive vitreous haemorrhage may be considered. Among rare conditions Tay-Sachs' disease may occasionally be suspected, and tuberous sclerosis has certain points of similarity, including areas of cerebral calcification, though its age-group is different. The diagnosis of toxoplasma will probably be reached if its possibility is considered, and it may be supported by the evidence of skull X-rays and serum reactions, or proved by demonstration of the parasite.

Treatment.—There is clearly no prospect of improving retina already destroyed, but the child may be treated in the active stage of the disease, and the mother during or before other pregnancies. So far chemotherapy has proved disappointing. Penicillin is ineffective, but sulphonamides, though inactive *in vitro*, seem to be effective *in vivo*. One cure has been claimed by the administration of sulphonamides and emetine. It is hoped that other drugs, especially organic preparations of arsenic and antimony, which are effective against other protozoal and Leishmania infections, may prove successful, since the organism is rather highly differentiated.

COMMENTARY

It is evident that any active or quiescent choroido-retinitis which may have originated in early life, especially if it is associated with convulsions and unusual skull size, or abnormal development of the eyes, should suggest the possibility of toxoplasmosis. The characteristic lesions in the eyes are bilateral areas of focal choroiditis, frequently multiple, and almost invariably affecting both maculae. The intervening retina and

the retinal vasculature are normal. The vitreous is clear, but extensive bands of connective-tissue may run through this structure between areas of choroiditis. Associated ocular deformities, particularly microphthalmos and marked persistence of pupillary membrane, are common. In addition to the eyes and brain, other organs, especially the liver and spleen, may be infected. In suspected cases skull X-rays and serum-reactions on child and mother and siblings should be performed. Among the many problems awaiting solution are the mode of transmission, the possibility of ocular toxoplasmosis occurring in other than congenital infections, and the treatment of the disease.

CASE REPORT

A. H., a boy now aged two years and eleven months, was first admitted to St. Thomas's Hospital, London, at the age of six weeks for investigation, having been fretful and irritable and suffering from vomiting attacks for three days. The mother, who is rather deaf, reported that her health during pregnancy was good, and that labour was normal. The child's birth-weight was seven pounds, and there was no neonatal jaundice. Though a cat and a dog are now kept, there were no domestic animals except racing pigeons at the home before the patient's birth, but the house was infested with mice. In the course of examination hepatomegaly and splenomegaly were found, and the lungs were normal. A convergent squint was present, and defective vision was suspected, since the child did not appear to notice surrounding objects. The blood count was as follows:—R.B.C. 3,520,000.

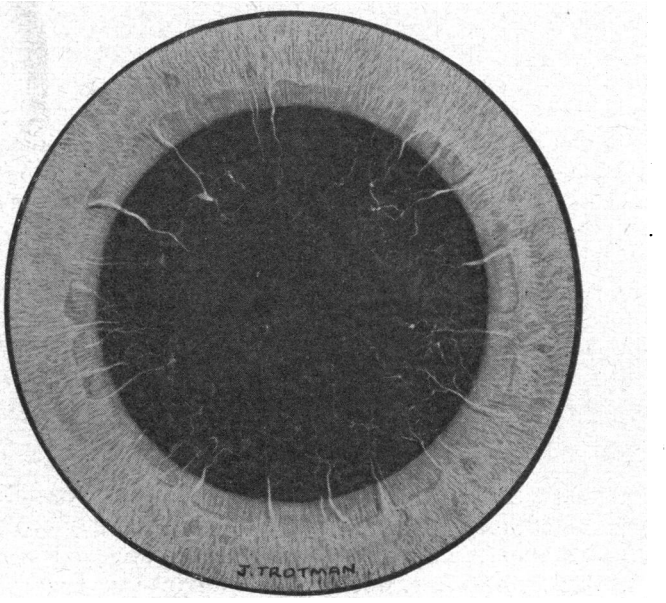

FIG. 1.

Persistent pupillary membrane in right eye.

Hb. 60 per cent. W.B.C. 20,600. Polymorphs 12 per cent. Lymphocytes 80 per cent. Mononuclears 4 per cent. Eosinophils 2 per cent. Pathological monocytes 2 per cent. Normoblasts 2 per cent. The blood-Wassermann reactions of mother and child were negative. One week later a gluteal abscess was incised, and three months later other septic blisters appeared on the buttock, and there was a sharp vaccination reaction. At the age of eighteen months there had been one convulsion, with foaming at the mouth.

The child was brought to the eye department when aged two-and-a-quarter years on account of squint and defective vision. He appeared rather backward for his age, but could see and grasp objects of moderate size, and would run by himself

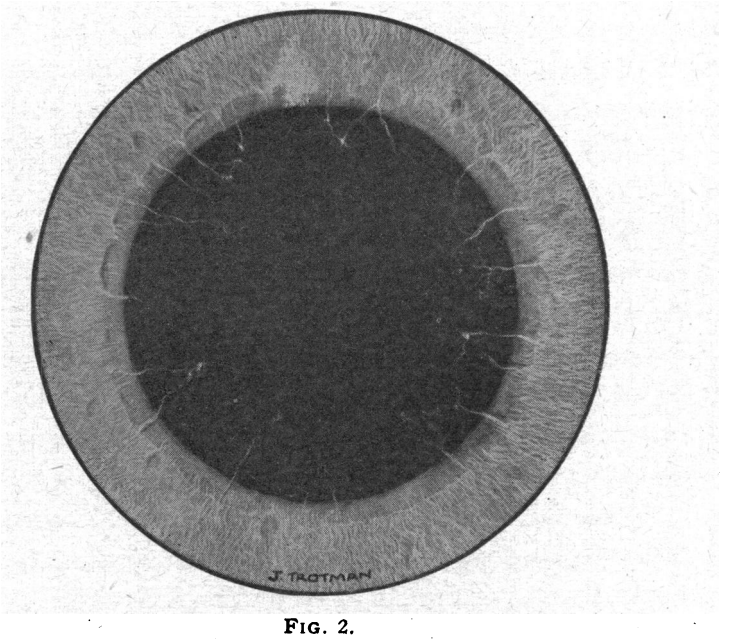

FIG. 2.

Persistent pupillary membrane in left eye.

around the room in play without knocking against furniture. On examination there was right convergent strabismus of about 25 deg., with apparent weakness of the external recti, and slight epicanthus on the left side, microphthalmos, persistent pupillary membrane, congenital lens opacities, and in the right eye what appeared to be a macular coloboma and a patch of connective tissue in the upper nasal quadrant. He was thought to be suffering from multiple congenital malformations. Unfortunately six months elapsed before he was seen again for examination under general anaesthesia. The child is hydrocephalic, the skull circumference being 19¾ inches. The fontanelles are closed. The eyes are slightly microphthalmic, the corneæ measuring 9·5 mm. in diameter. The right convergent strabismus is unchanged, and fixation is defective. In both eyes there is very marked persistence of pupillary membrane, and localised opacity in the anterior lens capsule. The pupils react to light, and there is no evidence of past inflammation in the anterior segment of the eyes. Owing to these abnormalities a clear view of the fundi is difficult to obtain. It is, however, evident that in the right macular region there is an area of choroido-retinal atrophy approximately 4 disc-diameters

in size. Large choroidal vessels are visible in the base of the crater, and there is considerable pigment disturbance, especially at the temporal edge. In the upper nasal periphery there is a patch of light grey connective-tissue lying in front of the retina similar in size to the macular lesion. So far as could be observed, there are no other abnormalities. In the left eye no definite macular lesion resembling that in the right eye could be seen but the area immediately temporal to the optic disc appeared somewhat pale, suggesting a milder degree of choroidal disturbance. Some glial tissue is visible in the upper periphery of the fundus. It was clear at this

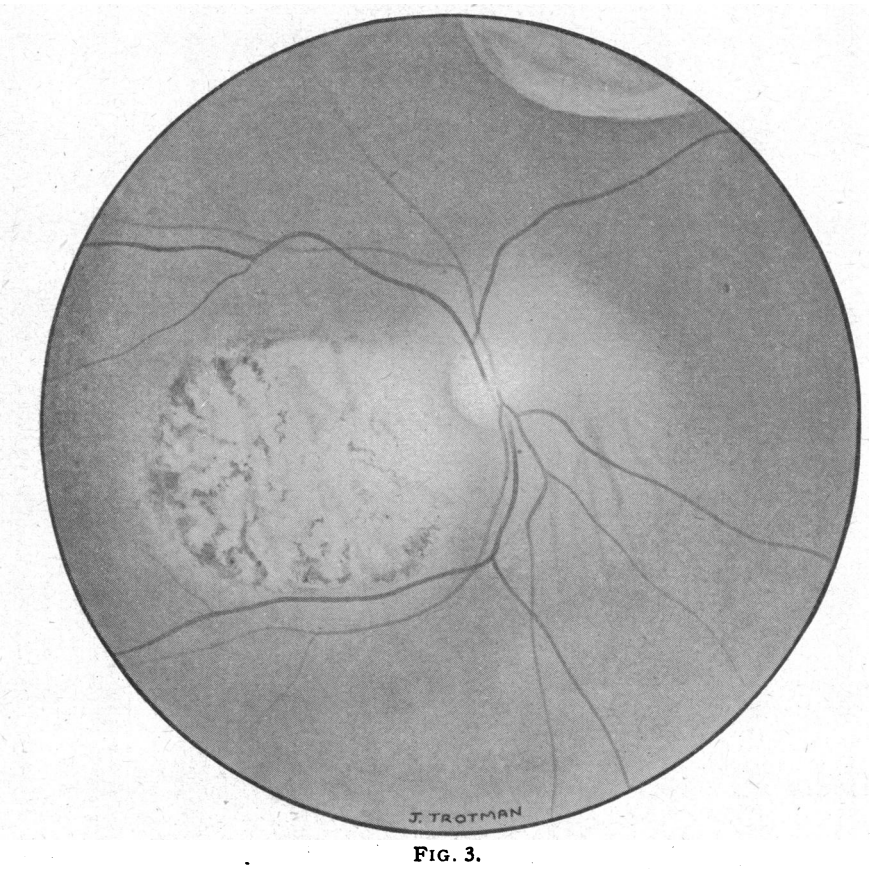

FIG. 3.

Right fundus showing macular and peripheral lesions.

stage that the case was probably one of toxoplasmosis, and that our earlier diagnosis was incorrect. X-rays of the skull, now performed, show multiple areas of calcification including one curvilinear streak in the brain. The serum-reaction to toxoplasma is strongly positive, the complement-fixation being 100 per cent. at the surprisingly high titre of 1/256. There is no fixation of normal antigens. The cerebro-spinal fluid is clear, and contains per millilitre 2 cells, 35 mg. protein with no excess of globulin, 738 mg. of chlorides and 0·069 per cent. of sugar. No parasites were found. The skull X-rays of mother, father and sister are normal, and their sera all negative to toxoplasma at a titre of 1/2.

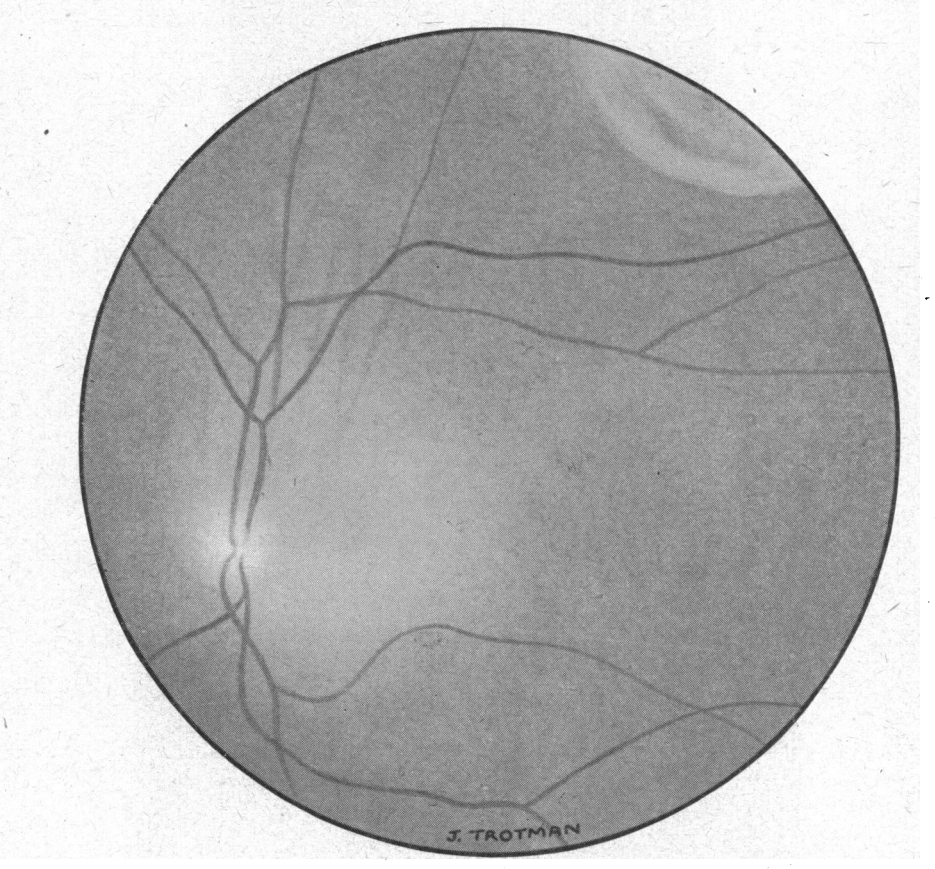

FIG. 4.

Left fundus showing similar lesions, but less conspicious than those of right eye.

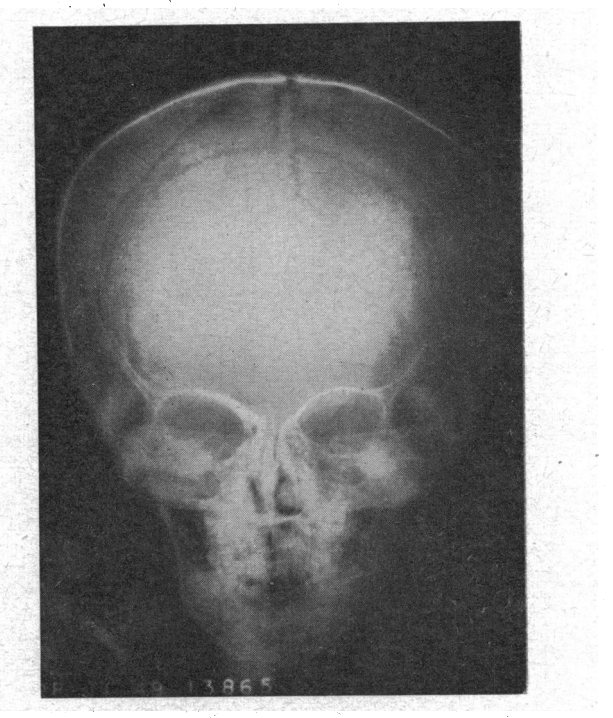

FIG. 5.

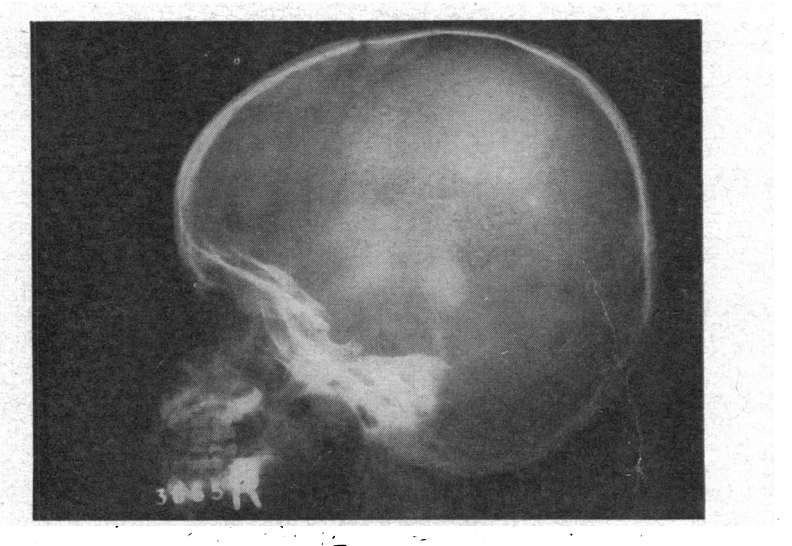

FIG. 6.

X-rays of skull showing multiple areas of calcification.

Though no toxoplasma parasites have been discovered, and it is perhaps rather late to expect a positive finding, there can be no doubt concerning the diagnosis. The mother's negative serum-reaction is difficult to explain. It is conceivable that the child acquired the infection after birth, but this would appear highly improbable in view of the extremely early age at which the sight was thought to be abnormal, and the presence of developmental abnormalities such as gross persistence of pupillary membrane. The mother is now seven months pregnant. X-rays of the foetal skull show no abnormal calcification at present, but this next child will be examined for toxoplasmosis soon after birth.

My thanks are due to Dr. J. A. Dudgeon for performing the serological tests, and to Dr. B. R. D. Wilson for information regarding the general condition of the patient.

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VASCULAR CHANGES IN DIABETES WITH PARTICULAR REFERENCE TO THE RETINAL VESSELS

Preliminary Report *

BY

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RECENT advances in pathological and clinical studies of diabetes indicate that at least some of the more important complications of this disease may have a common underlying cause, namely, a vascular degeneration. There is already an extensive literature referring to retinopathy, intercapillary glomerulosclerosis, peripheral neuritis and generalised athero-sclerosis in diabetes; their inter-relationship has been repeatedly emphasised and it is suggested that they should be regarded as different manifestations of the same underlying pathology.

Dedicated to Professor J. Meller.

* Received for publication, May 9, 1949.