NERVOUS MANIFESTATIONS IN EALES'S DISEASE*

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IN 1880 and again in 1882 Henry Eales of Birmingham described the clinical picture of primary recurrent retinal haemorrhage in young adults. His seven cases were all young men, whose ages ranged from 14 to 29. They had in common a history of headache, epistaxis, variations in peripheral circulation, dyspepsia, and chronic constipation. One was diagnosed as having mitral incompetence, and in two the urine contained the slightest trace of albumen, but otherwise they bore no stigmata of bodily disease. Eales regarded the condition as a very rare one, and believed it to be a vaso-motor neurosis which, by causing constriction of alimentary vessels and compensatory dilatation of those of the head, led to rupture of retinal and nasal vessels and consequent haemorrhage.

Eales's disease is now a well-recognized entity, though it is agreed to be rare. Characteristically its age of onset is between 15 and 40 years, affecting both sexes, but with a preponderance in males. In most cases both eyes are ultimately attacked, though symptoms may be unilateral for some while. The retinal haemorrhages are very frequently accompanied by bleeding into the vitreous body, and it is the latter occurrence which most often drives the patient to seek medical advice. The ophthalmoscopic picture ranges from one of obstruction of the central retinal vein with multiple haemorrhages and generalized venous distension to one of variation in calibre and local sheathing of a single vessel, often peripherally situated. The vitreous may be faintly hazy or so clouded with blood as to make the fundus invisible. At a later stage retinitis proliferans and permanent vitreous opacities may be found. The course of the disorder is unpredictable but generally unfavourable.

Many suggestions have been made as to its aetiology. Up to now there have been two main theories current, neither of which commands unqualified support: the first that it is a manifestation of tuberculosis, and the second that it is a localized and early stage of Buerger's disease. The idea that it is a tuberculous affection of the retinal vessels seems to have grown up about the turn of the 20th century (Simon, 1896; Noll, 1909; Axenfeld and Stock, 1911; Fleischer, 1914). It was based partly on evidence gained from the examination of eyes removed for secondary glaucoma, and partly

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on the demonstration of tuberculosis elsewhere in the body. It has been supported latterly by various writers, amongst them Safar (1928), Gilbert (1935), von Hippel (1935), Sukanuma (1937), Verhoeff and Simpson (1940), and Schmid (1945), but other ophthalmologists have contested this opinion on the grounds that in the majority of cases no history or signs of Koch's infection are present (Moore, 1925; Hutchinson, 1932; Ballantyne and Michaelson, 1937; Paton, 1938; Benedict and Wagener, 1940; O'Malley, 1943).

Its ascription to thromboangiitis obliterans of the retinal vasculature is a relatively recent development. Marchesani (1934, 1935) first put forward this conception on clinical and histological grounds, and since then (according to Benedict and Wagener) several other authors have reported agreement with his conclusions (for example, Ludwig, 1935; Mikuni, 1936; Uyama, 1936). Whilst there is no doubt that thromboangiitis obliterans may occasionally affect the retinal vessels (Gresser, 1932; Birnbaum and others, 1934), it seems likely that it seldom or never gives rise to the picture of recurrent intra-ocular haemorrhage as described by Eales. Schmelzer (1937) examined six cases of thromboangiitis obliterans, and though one had had closure of the central retinal artery some years before, none had symptoms or signs of vitreous bleeding. In a recent article, Schmid (1945) has published observations of 85 patients with typical Buerger's disease. In none was there history of ocular disturbance, and objective ophthalmological abnormality was present in only sixteen; in the majority it consisted simply in narrowing of the retinal arteries or alternatively of venous dilatation, and in a few there was mild macular degeneration. Conversely, in 25 patients with Eales's disease, he found not the least suspicion, either symptomatically or from careful physical examination, of thromboangiitis obliterans of the limb vessels. Schmid was unable to accept the vague symptoms of peripheral vascular disorder, of which some of Marchesani's patients complained, as of critical significance, and expressed the conviction that Marchesani's claim could not be substantiated from clinical evidence. Hager (1949) had written in similar vein; study of the case-records of 95 patients with Eales's disease proved that none had had symptoms or signs of peripheral thromboangiitis obliterans, and he argues that there are, in any case, notable differences between the two conditions, even when, as occasionally happens, the latter presents ocular manifestations.

Critical studies of the histology of the retinal lesions in Eales's disease cast considerable doubt on the correctness of both the tuberculous and the thromboangiitic interpretations of its pathogenesis (Ballantyne and Michaelson, 1937, 1947; Loewenstein and others, 1946). According to these authors, the lesions consist essentially in a patchy cellular infiltration, which at its outset is within the substance of the walls of blood vessels. The vessels attacked are predominantly but not exclusively veins, arteries

and capillaries occasionally being affected likewise; the small veins at the periphery of the retina are often those affected earliest. The character of the cellular accumulation is chiefly lymphocytic, but there may be, additionally or alternatively, a proliferation of endothelial cells; giant cells are lacking. Beading and dilatation of the veins from stasis of blood flow is a prominent microscopical feature, with overfilling of the capillary bed, and there is not uncommonly venous thrombus formation. The retinal and vitreous haemorrhages characteristic of the malady arise from rupture of vessel walls at points weakened by disease, where micro-aneurysms may develop. Signs of vascular pathology are not limited to the fundus oculi, but may be seen also in the optic nerve and its sheath (Safar, 1928; Verhoeff and Simpson, 1940; Loewenstein and others, 1946). In summary, the histological findings are those of an inflammatory reaction; though they might at a pinch be held consistent with tubercle or with thromboangiitis obliterans they are by no means typical or frankly diagnostic of either state.

Loewenstein and his colleagues (1946) propose "retinal vasculitis" as the most accurate descriptive term for Eales's disease, since it conveys briefly the nature of the underlying pathology. It has also been suggested (Ballantyne and Michaelson, 1937) that this vasculitis may not be an expression of a single disease, but rather a phenomenon common to several, which are themselves of different aetiology. Benedict and Wagener (1940) are of similar opinion, holding that the lesion of the vessel walls is in all probability a non-specific one. Recently O'Malley (1944) has advanced the hypothesis that Eales's disease is an allergic syndrome, a retinal endophlebitis which may be set in motion by any one of a number of allergens. The histology of the lesions is quite in accord with such an interpretation, and the observations of Uyama (1936) may be taken to lend it some support from the experimental point of view. This writer was able to induce retinal venous lesions in four out of 26 rabbits by the injection of living tubercle bacilli into the bloodstream, after preliminary sensitization with tuberculous antigens.

Neurological complications of variegated pattern, pointing to mischief in either cerebral hemisphere or spinal cord, have been reported from time to time in Eales's disease (Ballantyne, 1909; Loewenstein, 1931; Marchesani and Stauder, 1935; Ballantyne and Michaelson, 1937; Silfverskiöld, 1947; Veirs, 1948). Through the courtesy of our ophthalmological colleagues at the Birmingham and Midland Eye Hospital we have lately had the opportunity of examining six patients suffering from recurrent intra-ocular haemorrhages, with a view to discovering whether they presented symptoms or signs of nervous ailment.

Case Reports

Case 1, Raymond M, aged 25, industrial chemist. Nothing of note in previous medical or family history.

In mid-July, 1950, discovered one morning when dressing that sight in right eye was

defective, "as though muddy water had been splashed in it". Came under the care of Mr. Douglas, who diagnosed Eales's disease. Treated by local x radiation (4,000r) of affected eye. No recurrence of intra-ocular bleeding. Only complaint now is that in bright sunlight he is aware of a peaked shadow in front of right eye.

Examination (May 16, 1951).

Right eye: well-marked retinitis proliferans extending from upper temporal margin of disk out into vitreous, and some small patches of chorio-retinal degeneration in lower temporal periphery of fundus. Vessels appear normal. Visual acuity J1 and 6/6.

Left eye: media clear, fundus normal, visual acuity J1 and 6/6.

No neurological signs. Heart normal. Blood pressure 125/80. Limb pulses all normal, no obvious abnormality of skin colour or temperature. Liver edge palpable 1-2 fingers on deep inspiration, and tender. Some small glands both axillæ.

Case 2, Leslie N, aged 31, gardener. Previous medical and family history not relevant.

In September, 1944, whilst serving with the army in Belgium, suddenly became aware of dark patches in front of right eye, and a week later lost the sight completely in this eye. Vision gradually recovered, but 2 months later again failed suddenly, to recover more slowly. Had further severe attacks in 1946 and 1949, both in the right eye. Came under the care of Mr. Jameson Evans in August, 1950, who made a diagnosis of Eales's disease and treated him with x ray (2,800r) to right eye.

At various times in the last 5 years he has had slight similar trouble with the left eye, but has never had a haemorrhage severe enough to worry him. For the same period has been subject to recurrent right frontal and retro-orbital headache. No other complaints.

Examination (May 21, 1951).

Right eye: visual acuity light perception only. Massive vitreous opacity which completely obscures fundus.

Left eye: visual acuity J1 and 6/6. No abnormality of media or fundus.

Heart healthy. Blood pressure 135/85. Peripheral pulses full, no alteration of skin temperature or colour apparent. No neurological signs. General examination negative.

Case 3, Nora F, aged 18. In Blind Institute from age 6 because of severe congenital myopia. Previous medical history otherwise irrelevant, and family history non-contributory.

In July, 1949, sight in left eye rapidly fogged over till she could see nothing but a white mist. She gradually recovered but a few weeks later, when lifting something heavy, her sight suddenly failed again. In October, 1949, Mr. Jameson Evans, having diagnosed Eales's disease, treated her with local x radiation (4,000r). A month or two later, the day after a fall, she woke to find that the sight had once more failed in the left eye; there has been no improvement since this time. In the last 18 months, sight in right eye has also worsened. Since July, 1949, she has complained of recurrent frontal headaches of throbbing character, brought on by stooping, heat, or exertion. No other symptoms.

Examination (May 22, 1951).

Left eye: perception of light only. Grey opacity throughout vitreous, which altogether obscures fundus.

Right eye: can just count fingers. There is a dark opacity in temporal half of vitreous, which masks part of fundus, and rest cannot be clearly distinguished because of very high grade myopia. The eyes are in constant wandering motion.

No neurological signs. Heart normal. Blood pressure 145/80. Peripheral pulses normal. General examination negative.

Case 4, Albert R, aged 28, furnaceman. Family history irrelevant, Previous medical history: occasional lumbago and left-sided sciatica for 2 years. Had right-sided epididymectomy in July, 1950, for low-grade chronic non-tuberculous infection of 12 months' duration.

Three years ago suddenly discovered sight in left eye defective, as if there were a grey smoke in front of it. Seen by Mr. Jameson Evans, who diagnosed Eales's disease, and later recommended x ray treatment, which was given in August, 1949 (4,000r). Sight recovered satisfactorily. No recurrence of haemorrhage in left eye, and never any trouble with right. No symptoms referable to other systems.

Examination (May 30, 1951).

Both eyes: no abnormality now detectable. Visual acuity J1 and 6/6 in the right eye; J4 and 6/12 in the left eye.

Heart normal. Blood pressure 145/80. Peripheral arteries healthy. No neurological signs. Slight restriction of forward flexion of lumbar spine, and of straight-leg raising on left. No other abnormal physical signs.

Case 5, Nugent McT, aged 28, stove assembler. Nothing relevant in previous medical or family history.

In October, 1947, first noticed something wrong with left eye, like a film over the sight. In April, 1948, vision in this eye suddenly failed. Seen by Mr. Weeden Butler, who diagnosed Eales's disease and treated him with deep x ray (4,000r). There has been no recovery of visual acuity in left eye. In last 3 years he has had occasional slight transitory disturbances of sight in right eye. No other symptoms at all.

Examination (June 13, 1951).

Left eye: perception of light only; complete vitreous opacity.

Right eye: media clear. No retinal haemorrhage or degenerative change. Arteries show some variation of calibre, and veins are a little swollen and constricted at arterio-venous crossings. Visual acuity 6/18 and J4.

Heart normal. Blood pressure raised (165/100). Peripheral vessels healthy, no skin colour or temperature change apparent in extremities. No neurological signs. Other systems negative.

Case 6, Edith S, aged 27, married. History of recurrent bilious attacks as a child, and of "growing pains" without joint swelling or recognized fever, with breathlessness on exertion from the age of 14 or 15. Between ages of 17 and 21 had occasional migraine, ushered in by dazzling flashes in front of eyes and gradually developing constriction of visual fields, followed by frontal and retro-orbital headache lasting several hours, with nausea and vomiting. Family history non-contributory.

In 1946 she first developed symptoms of intra-ocular bleeding in the right eye, and some months later, the left was also affected. She was seen by Mr. Jameson Evans who diagnosed Eales's disease. The right eye was treated with x rays (4,000r) in November, 1947, and the left eye (1,500r) in October, 1948. She has had several recurrences of haemorrhage in each eye since the radiation, but the sight has recovered fairly quickly and completely in each instance.

Examination (June 20, 1951).

Right eye: dark opacity in vitreous inferiorly and anteriorly. Fundal vessels and retina appear normal. Visual acuity J1 and 6/6.

Left eye: slight diffuse vitreous haze from recent haemorrhage, which interferes with detailed examination of fundus, but no gross abnormality present. Visual acuity J4 and 6/18.

Heart enlarged to left with mitral diastolic murmur; there is auricular fibrillation with a large pulse deficit. Blood pressure 140/90. Exercise tolerance poor. Limb vessels healthy, no peripheral colour change or temperature abnormality. No neurological signs. No other physical abnormalities.

CONCLUSIONS

In the six patients examined by us, the duration of whose ophthalmic symptoms ranged from 10 months to 6½ years, we discovered no manifest

evidence of nervous disease, a finding in conformity with the larger experience of Silfverskiöld (1947), who recorded the follow-up of 22 patients, diagnosed from 6 to 15 years earlier as suffering from Eales's disease. Headache was a symptom in three of our patients, but no other complaint of neurological bias was made spontaneously, or could be elicited by direct enquiry. In one patient (Case 6) the headache can confidently be dismissed as nosologically irrelevant to the ocular condition, since this was a woman who had suffered from paroxysmal vomiting since early childhood, which was replaced at the age of 17 by attacks of true migraine, a not unusual sequence of events to which Gowers (1907) drew attention many years ago. Her story is so typical that there is no good reason to believe that it is indicative of actual disease of the cephalic vessels; it is now generally accepted that the phenomena of migraine occur upon a physiological background of vasomotor instability in the carotid system. In the other two patients (Cases 2 and 3), where headache developed after the onset of eye trouble, the clinical evidence on which to base a decision is less clear-cut. Although it seems unlikely to us that there was spread of vascular pathology to the cerebral vessels, it is a possibility which cannot be absolutely denied without histological check.

With reference to the neurological complications of Eales's disease which have been reported in the literature, a word of caution about their too ready acceptance must be entered. It appears open to question how far any have really been the result of vasculitis of cerebral or spinal vessels comparable with that seen in the retina. Histological proof of characteristic lesions in the eye and of the presence of vascular lesions in the nervous system, with establishment of their essential identity, is a prime necessity. In the absence of such proof, so-called complications may in fact represent no more than the chance association of two aetiologically remote illnesses. Indeed it is our conviction that, to date, all the published cases with coincident neurological symptomatology either belong in such a category or else are not examples of Eales's disease at all. So far as we can discover, amongst reported cases with neurological disorder, *post-mortem* investigation of the nervous system has only been undertaken once, namely in Case 5 in the series described by Marchesani and Stauder (1935). This was a man of 45, who had no ocular symptoms other than occasional bright specks in front of his eyes, chiefly when reading. Four or five months before admission to hospital, he developed progressive weakness of his right arm and later of his right leg, together with headache and difficulty in finding his words. On examination he presented a mild dysphasia with right-sided pyramidal signs and sensory disturbance of cortical type. The fundi showed sheathing of arteries and veins on the surface of the disks, extending a short distance on to the surrounding retina, but the eyes were otherwise normal. He was suspected of harbouring a cerebral tumour, or (in view of certain peripheral vascular symptoms and signs) possibly of having cerebral Buerger's disease. He

shortly died of an intercurrent pneumonia, and at autopsy was proved to have thromboangiitis obliterans of the cerebral vasculature. The existence of cranial Buerger's disease has been recognized as an entity for nearly 20 years, since the pioneer studies of Foerster and Guttmann (1933), and there need be no hesitation in accepting the case as an example of that malady. However, reasons have already been given for doubting the validity of Marchesani's identification of Eales's disease as a localized form of thromboangiitis obliterans. We should be more than reluctant, therefore, to regard the case as an example of true retinal vasculitis with complicating neurological features.

Finally we should add that, in the cases under review, no symptoms suspicious of Buerger's disease could be unearthed in the anamnesis; pulsation was readily demonstrable in the peripheral vessels of both arms and legs in all cases, there was no trace of gangrene or cyanosis of the extremities, and skin temperatures (as judged simply by touch) were not in any way disturbed.

SUMMARY

(1) The history of Eales's disease is traced, and its symptomatology and pathology described. Neurological syndromes, indicative of cerebral or spinal dysfunction, have from time to time been asserted to appear as complications.

(2) Six cases of Eales's disease have been examined for signs or symptoms of nervous disorder, with negative results.

(3) It is pointed out that in cases of Eales's disease presenting a neurological semeiology, the latter can only be accepted as a complication in the strict sense, if backed by evidence of vascular lesions in the central nervous system histologically identical with those found in the retina. It appears that no case satisfying this criterion has yet been reported. In the absence of such pathological control, nervous disorders may be mistakenly regarded as complications, when in fact they represent a fortuitous superimposition of a second malady upon the original one. It seems likely that most of the published cases, with neurological signs purporting to be complications, are to be looked upon as examples of such a chance association of two diseases. In others, the primary diagnosis of Eales's disease is inadmissible; thus in one recorded case with autopsy findings, the ocular and nervous signs were due to thromboangiitis obliterans of retina and brain respectively.

(4) No symptoms or signs suggestive of Buerger's disease were noted in the cases under review.

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