COMMUNICATIONS

SICKLAEMIA RETINOPATHY*†

BY

K. RUBINSTEIN

Birmingham

THE retinopathy of sickle-cell anaemia is a striking feature of the disease. Retinal haemorrhage in a case complicated by subarachnoid bleeding was first reported by Cook (1930) and during the following 20 years a few sporadic reports referred to haemorrhage, venous congestion, and microaneurysms in the fundi. Within the past few years reports backed by electrophoretic diagnostic studies and based on careful clinical observation and follow-up have revealed the full extent of eye complications and brought the fundus picture up to date. Attempts have been made to correlate various features of this retinopathy with different allelic types of sicklaemia and to introduce a grading of fundus changes as has been done for diabetic or hypertensive retinopathies.

Symptoms and Signs

Sicklaemia retinopathy is a chronic, progressive, irreversible condition. The earliest fundus change is undoubtedly oedema of the retinal periphery, patchy, with perhaps a predilection for the temporal side. There is always—although it may be difficult to see—a fine meshwork of neovascularization with tortuous end-arterioles, dilated varicose venules, and arterio-venous anastomosis. All this occurs at the level of pre- and post-capillary vessels. The foci of this type may be at first uniocular but eventually they invariably affect both eyes. One may find only very minute changes in one eye of a patient presenting with gross retinopathy of the fellow eye. However, the foci soon become multiple peripherally, and careful examination of the post-equatorial fundus will often reveal small areas of corkscrew arterioles ending in a very fine nidus of neovascular meshwork.

These peripheral areas soon change their character. Neovascularization becomes systematized into brush-like vessels collecting towards larger venules; oedema becomes a patch of proliferation. The change comes on slowly (in weeks or months) but through stages of very thin filmy diaphragms and veils it progresses to thick, at first creamy, and then snowy-white bands, whorls, and banks. The pair of vessels (artery and vein) originally involved seems to come to an abrupt brushed T-junction termination at the edge of glial banking with venous dilatation and aneurysms, arteriolar tortuosity, and clustering anastomoses. As the gliosed area increases—usually along an eye meridian—it encroaches upon other retinal vessels but they may traverse the glia unchanged. Where the process progresses towards proliferative veil formation, there is a characteristic tendency for these

* Received for publication January 11, 1966.

† Address for reprints: Birmingham and Midland Eye Hospital, Church St., Birmingham 3.

veils jutting into the vitreous to form sharp, sickle-shaped edges. The extension of glia may involve very large areas of the fundus. The veils may extend along the blood vessels towards the optic disc (Fig. 1*a, b*).

FIG. 1 (*a, b*).—Right and left fundus of a 22-year-old Jamaican male nurse with haemoglobin S-C disease.

Over these areas of gliosis bright red patches often appear giving an impression of retinal tears. Most of them are not true retinal holes, and they may disappear after a time, while new ones form elsewhere. They are probably intraretinal haemorrhages (Goodman, von Sallman, and Holland, 1957), although there is a marked difference in appearance between these pseudo-holes and other retinal haemorrhages elsewhere in the fundus. Haemorrhages eventually become a prominent feature of the fundus. They are a presenting symptom in about half the cases of sicklaemia with ocular symptoms, and sickle-cell anaemia was put forward in the early literature as one of the possible causes of Eales's disease. The haemorrhages may be subchoroidal, choroidal, retinal, subhyaloid, or vitreal. They are thought to originate from areas of neovascularization. While glial and neovascular changes do not regress spontaneously, the haemorrhages, even when they are massive enough to obliterate the fundus reflex, may do so, often with dramatic

improvement of the visual acuity from, for instance, counting fingers to 6/6. Stretches of obliterated arteries are often seen, particularly in areas peripheral to glial foci. A unique picture of brilliant white appearance of the large portion of the arterial tree down to the smallest ramifications was described by Goodman and others (1957); their photographs look like a negative of a good fluorescein contrast picture. Other vascular changes described include congestion of the retinal veins, especially in sickling crises, and central retinal vein occlusion with retinopathy. Bilateral central retinal artery occlusion has also been reported (Kabakow, van Weimokly, and Lyons, 1955).

Angioid streaks were found in association with sicklaemia by Geeraets and Guerry (1960); areas of choroidal atrophy are seen in some cases—considered in the older literature to be patches of choroiditis; true retinal detachment is not uncommon; a case of glaucoma has been reported (Shapiro and Baum, 1964).

Incidence

I found it impossible to assess from the literature the incidence of retinopathy amongst sicklaemia cases, and equally impossible to assess the prominence of one or the other feature in relation to their allelic type. Until 1950 there were, of course, no electrophoretic studies and cases were diagnosed on speed of sickling and the overall clinical picture. Even after haemoglobin electrophoresis became a routine laboratory technique, extensive studies stimulated by it were retrospective, the selection of cases ruled by positive laboratory findings. For obvious reasons most of them were homozygous S-S cases, some S-C, and very few S-A. From these studies the following opinions were formed:

- (1) That the severity of the retinopathy is directly correlated to the severity of general disease;
- (2) That the incidence of severity of retinopathy is greater in homozygous S-S cases, less in S-C, and practically non-existent in S-A;
- (3) That there is a natural history of this retinopathy from venous congestion through peripheral vascular change to gliosis and then to massive haemorrhages.

Subsequent reports based on fewer patients with electrophoretic tests performed and presenting with eye symptoms proved to my satisfaction that all these assumptions were clearly untrue. A review of our own patients at the Birmingham Eye Hospital supports this view.

Present Clinical Material

Nine patients were studied during the past 3 years—not many amongst 50,000 new patients a year. Seven were West Indians, one Ghanaian, and one Nigerian. There were seven males and two females, and the average age was 31 years (range 22–42). There were no homozygotes, four were cases of S-C disease, and five of S-A (trait). None was anaemic. The average Hb was 98 per cent. (range 84 to 110). All had a very low erythrocyte sedimentation rate, average 1.6 mm./hr (range 0 to 5).

The presenting complaint was loss of vision in one eye: two noticed it on waking, six gave a history of gradual deterioration, and one was found accidentally on the occasion of an injury. The presenting signs in the affected eye were: vitreous haemorrhage (4), detached retina (2), retinal gliosis (3), retinal peripheral vascularization (1), glaucoma (1), aqueous flare and keratic precipitates (2). Only in one case (S-A) was a history of knee effusion obtained; otherwise, apart from one enlarged spleen, there was no history of past general episodes and no abnormal findings on physical examination. The retinopathies showed various degrees of severity, unrelated to the allelic type. The final visual acuity—to date—in the worse eye was: counting fingers (4), 6/24 (1), 6/12 (1), and

6/6 (3). All had changes in both eyes, but we did not see any venous congestion or thrombosis. Apart from peripheral oedema and neovascularization, which seem to be always the earliest of changes, I could not convince myself that there is a gradual transition from one feature of the retinopathy to another, *e.g.* that glial changes precede haemorrhages, and so on.

The most important conclusion from our studies is that the S-A type of heterozygote, while free from general symptoms, can nevertheless produce a fully-fledged retinopathy. Sickling tests in a number of our cases were at times negative, and proved positive only on repeated tests. A single negative sickling test should not be accepted as diagnostic in the presence of suggestive clinical signs.

Treatment

We have attempted to treat some of these patients. Four have been, for some time now, on a bicarbonate regime, as suggested by Lehmann (1963). They seem to tolerate the treatment well, and while we did not encounter dramatic turns for the worse, a slow deterioration of the fundi was the rule.

One case was treated with Rheomacrodex infusion before starting alkalizing therapy. The reports of Rheomacrodex helping to cut down the sicklaemia crises came from Watson-Williams (1963) and Garrett, Giles, and Sage (1963). In spite of a large dose of Rheomacrodex in my case (500 ml. 10 per cent. twice daily for 3 days), there was neither subjective nor objective change in the retinopathy.

Two retinal detachment cases were operated upon while negative sickling tests subsequently proved false were in hand. In one of them only a diathermy and drainage were done at first. The evacuated fluid was prompt, copious, and dark yellow, but this evacuation made no impression on the ballooning detachment; 5 days later I did a scleral resection, and this time the evacuated fluid was clear, after which the retina became flat, although the glial bands adjoining the detachment remained unchanged. A large area of choroidal atrophy was seen when the detachment flattened down.

The use of Diamox has been reported by Munro and Walker (1960) and others. Light coagulation has been tried but I have had no useful experience with it.

Pathogenesis

The mechanism of retinal changes revolves round the physical plugging of vessels with rigid sickled erythrocytes. Systemic symptoms are caused in the same way, and as any small arteriole may be involved there is hardly an anatomical site in the body which would not be described as being affected by this kind of infarct. Necrosis and bleeding may cause haematuria, subarachnoid haemorrhage, subperiosteal haemorrhages and exudates, joint effusions, leg ulcers, etc. Splenomegaly and coronary heart disease are common.

In the fundus the non-specific response of the retina makes the changes on the venous side of the circulation more prominent. However, ischaemia is bound to be caused by circulatory insufficiency on the arteriolar side of the capillary bed, and it is likely that the reason why a chronic retinopathy is seen rather in milder forms of sicklaemia, like the S-C and S-A groups, than in the S-S group is the very incompleteness and slowness of this obstruction. Progressive, gradual local hypoxia would allow and stimulate proliferative changes and neovascularization. What other specific factors operate to produce highly characteristic retinopathy, we do not know. A venous mechanism of retinal changes cannot, however, be accepted

while arteriolar occlusion is clearly involved in the general pathology of the disease (Chapman, Reeder, Friedman, and Baker, 1955). Even in the eye, the lesions of the choroid can only be ischaemic capillary infarcts of afferent and not efferent vessels.

If we accept the hypothesis of slow progressive ischaemia as the immediate cause of retinal vascular proliferation, we have to explain the pathognomonic and characteristic picture seen in this kind of retinopathy. It certainly is very different from, say, vein branch occlusion, in which a similar mechanism was recently suggested (Rubinstein, 1964). According to their findings of angioid streaks in sicklaemia patients and degenerative changes of Bruch's membrane and elastica of vessels, Geeraets and DuPont Guerry (1960) suggested that sickling alone might not be the only pathological feature of the disease which could involve changes in all elastic tissues of the body. This could—if proved—be the background of retinal reaction to ischaemia in these patients.

Summary

Nine cases of sickle-cell disease—designated for brevity sicklaemia—were studied. None was anaemic or had general symptoms. Four were of the S-C and five of the S-A type. All had marked retinopathy, progressive and gradually affecting visual acuity, in spite of attempts at treatment.

My thanks are due to Mr. P. Jameson Evans and Mr. M. J. Roper-Hall, who allowed me to report on their patients (one patient each), and particularly to Mr. S. J. Crews who has an interest in the problem, five patients out of the nine reported here being under his care.

REFERENCES

- CHAPMAN, A. Z., REEDER, P. S., FRIEDMAN, I. A., and BAKER, L. A. (1955). *Amer. J. Med.*, **19**, 773.
 COOK, W. C. (1930). *J. Med. (Cincinnati)*, **11**, 541.
 GARRETT, J. V., GILES, H. McC., and SAGE, R. H. (1963). *Lancet*, **1**, 431.
 GEERAETS, W. J., and GUERRY, DUPONT (1960). *Amer. J. Ophthal.*, **50**, 213.
 GOODMAN, G., VON SALLMANN, L., and HOLLAND, M. G. (1957). *A.M.A. Arch. Ophthal.*, **58**, 655.
 KABAKOW, B., VAN WEIMOKLY, S., and LYONS, H. A. (1955). *Ibid.*, **54**, 670.
 MUNRO, S., and WALKER, C. (1960). *Brit. J. Ophthal.*, **44**, 1.
 RUBINSTEIN, K. (1964). *Trans. ophthal. Soc. U.K.*, **84**, 564.
 SHAPIRO, A. L., and BAUM, J. L. (1964). *Amer. J. Ophthal.*, **58**, 292.
 WATSON-WILLIAMS, E. J. (1963). *Lancet*, **1**, 1053.