

Foundation,⁹ and the Manchester Regional Hospital Board has recently contracted for patients from regional hospitals to work in this unit, which has specialized in certain products.

Many regional hospital boards are considering setting up schemes of industrial work therapy, and an encouraging prospect of collaboration with local health authorities exists. Further provision of hostels by the latter will, it is hoped, progress in parallel. In Birmingham the industrial therapy association works in close liaison with the Association for Mental Health, and this body has recently opened a hostel close to the factory. Through these occupational organizations community care may become more effective and acceptable.¹⁰ Employers have contact with patients in their working conditions within the hospitals. And the general public have points of contact (though so far in restricted numbers) with the patients through car-washing services, which produce immediate results—among them a satisfied customer. Increased acceptance of industrial therapy will help to banish the old institutional neurosis for ever.¹¹

Cotton-wool Spots

Some few years after von Helmholtz had devised the ophthalmoscope Richard Liebreich, chief assistant to A. von Graefe, described "rounded, bright, milk-white, slightly raised spots" which he had observed with the ophthalmoscope in patients with Bright's disease.¹

Because of their fluffy appearance, the retinal spots which Liebreich had described became known as cotton-wool spots. They are usually restricted to the posterior segment of the fundus, they rarely exceed one-third of the size of the optic disc, and disappear without trace in six to twelve weeks. They are found in diseases associated with arterial hypertension and also in a number of diseases of arterioles such as polyarteritis nodosa and systemic lupus erythematosus, as a result of blocking of these vessels in fat embolism and subacute bacterial endocarditis, and also in severe anaemias such as pernicious anaemia and anaemia after haemorrhage. Histological study of cotton-wool spots shows them to contain characteristic clusters of "cytoid bodies" in the nerve fibre layer. These are round or spindle-shaped cell-like structures with granular pseudocyttoplasm and eosinophilic nucleus-like globules.

When J. S. Friedenwald found it possible to visualize the retinal vascular network by staining the retina with Schiff's reagent he discovered that the cytoid bodies also contained material which stained intensely by this technique. The cotton-wool spots were regularly located within the terminal bifurcation of the precapillary arterioles, and Friedenwald therefore concluded that these lesions were ischaemic infarcts.²

Two technical developments since 1949 have made it easier to study cotton-wool spots. In 1960 T. Kuwabara and D. G. Cogan discovered that the entire retinal vasculature

could be detached from the retina after it was incubated in a solution of trypsin. Because conventional stains can be used to stain the vascular network free from non-vascular components which also take up the dyes, a much better visualization of retinal vessels became possible.³

The second technical advance was the almost simultaneous discovery in two laboratories of a method of experimental production of cotton-wool spots by intracarotid injection of microspheres of known size. Ranging from 7 to 40 microns in size, these microspheres can be either of latex⁴ or of glass.⁵

In 1963 N. Ashton and J. Harry⁶ used trypsin digestion of a retina from a hypertensive subject to show hyaline fatty changes typical of fibrinoid necrosis in the terminal and precapillary arterioles supplying the cotton-wool-spot-bearing area of the retina. They also showed that the capillaries at the site of the cotton-wool spot, though obliterated, were not destroyed and that the capillary bed reopens as the lesion resolves. They ascribed the arteriolar changes to endothelial injury caused by hypertension.

When studied by fluorescence angiography cotton-wool spots show two constant features: there is failure of capillary filling during the angiographic phase, and profuse fluorescein leakage for a long period afterwards. This last phenomenon led J. V. Hodge and C. T. Dollery⁷ to postulate that cotton-wool spots were caused by an exudative reaction to arteriolar injury. The pathogenesis of cotton-wool spots was recently re-examined by Dollery and his colleagues⁸ by means of experimental occlusion of retinal arterioles in the pig by the intracarotid injection of a suspension of glass microspheres. Within a few minutes of embolization a grey patch could be observed in the ischaemic region of the retina. This lesion then underwent morphological changes which resulted within one to two days in the development of a cotton-wool spot resembling that of man in both colour and texture. The period of ischaemia necessary to produce a cotton-wool spot need only be short. Thus when within 24 hours the microsphere had moved to a more distal position the whole of the area initially poorly perfused developed a cotton-wool spot.

Since 1950, in a series of papers issued from his laboratory at the Institute of Ophthalmology, Ashton and his collaborators have made important contributions to our basic knowledge of the pathology of the retinal circulation. In a recent paper M. Shakib and Ashton⁹ have given an account of their study of the ultra-structural changes resulting in the formation of the cotton-wool spot. Within one hour of embolization examination by electron microscopy showed that at the centre of the lesion there was swelling of the nerve fibres and of cells of the plexiform and outer nuclear layers. After 24 hours, when dense white areas indistinguishable from cotton-wool spots appeared in the ischaemic region, there was within the swollen segments of the axons a striking accumulation of mitochondria, neurofilaments, dense bodies, and inclusion membranous whorls. Such a proliferation of axonal organelles could take place only if the ganglion cells of the injured axons had survived. No such changes in the axons were observed in experimental total retinal ischaemia. The cotton-wool spot therefore represents a focal reaction of injured axons of living nerve cells.

The pseudonucleus of the cytoid body almost certainly consists of the conglomeration of these proliferating and degenerating intracellular ultra-structures. Either the swollen axons, or the cytoplasm of the macrophage which has ingested them, account for the pseudocyttoplasm of the cytoid body. These observations should therefore put an end to the century-old controversy on the nature of the cytoid body.

¹ Liebreich, R. L., *Ophthalmoskopischer Befund bei Morbus Brightii*. *Arch. f. Ophthalmologie*, 5 (part 2), p. 265, 1859.

² Friedenwald, J. S., *Amer. J. Ophthalm.*, 1949, 32, 487.

³ Kuwabara, T., and Cogan, D. G., *Arch. Ophthalm.*, 1960, 64, 904.

⁴ Gay, A. J., Goldor, H., and Smith, M., *Invest. Ophthalm.*, 1964, 3, 647.

⁵ Ashton, N., and Henkind, P., *Brit. J. Ophthalm.*, 1965, 49, 225.

⁶ — and Harry, J., *Trans. Ophthalm. Soc. U.K.*, 1963, 83, 91.

⁷ Hodge, J. V., and Dollery, C. T., *Quart. J. Med.*, 1964, 33, 117.

⁸ Dollery, C. T., Henkind, P., Paterson, J. W., Ramalho, P. S., and Hill, D. W., *Brit. J. Ophthalm.*, 1966, 50, 285.

⁹ Shakib, M., and Ashton, N., *ibid.*, 1966, 50, 325.