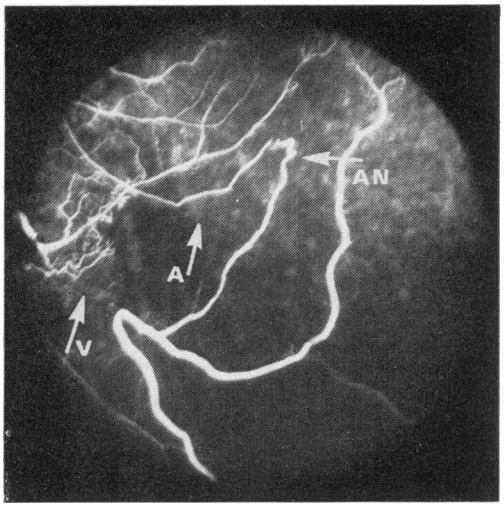

Fig 7 *Fluorescein photograph five months after occlusion showing secondary arterial occlusion* (A), *venous occlusion* (V) *and arteriovenous anastomosis* (AN)

Within a few weeks of the second venous occlusion secondary arterial changes of sheathing and narrowing were seen. After five months fluorescein angiography revealed secondary venous and arterial occlusion and an arteriovenous anastomosis had developed adjacent to the macula (Fig 7).

Comment

The experimental models of retinal vein occlusion which we have explored separate definitively the arterial and venous components. The arterial supply to the damaged retinal sectors was meticulously spared. The resultant lesion could therefore be attributed to venous obstruction alone. Clear-cut capillary occlusion, as well as secondary arteriolar and venular obstruction resulted. Additionally, revascularization of infarcted retina with similarities to human retinal neovascularization ensued. The experimental procedure described did not, however, lead to the two salient sequelæ of human vein occlusion, namely: neovascularization out of the plane of the retina with fluorescein leakage and persistent œdema of the macula. The possibility that antecedent arterial disease is required for the development of these phenomena cannot be excluded.

Summary

Using the monkey as an experimental model with a single venous occlusion but with no arterial damage, the features of human branch vein occlusion can be reproduced.

With double venous occlusion, widespread areas of vessel closure occur and these areas are gradually revascularized. The new vessels are seemingly dissimilar to those originally present but do not leak fluorescein on angiography. Secondary arterial and venous changes develop shortly after occlusion.

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Mr J M Cappin and Mr Rodger Whitelocke
(*Moorfields Eye Hospital, City Road, London EC1 and The Institute of Ophthalmology, Judd Street, London WC1*)

The Iris in Central Retinal Vein Thrombosis

Iris neovascularization in eyes with central retinal vein thrombosis was first reported in detail by Coats in 1906, but its pathogenesis has remained an enigma. Since then, iris new vessels have been observed in a wide variety of conditions including carotid-cavernous fistula, carotid stenosis, central retinal artery thrombosis, Coats' and Eales' diseases, diabetic and sickle cell retinopathies, retinal detachment, and tumours of the retina, choroid, and iris (Schulze 1967). Iris neovascularization has also been produced experimentally by occluding the long posterior or anterior ciliary arteries (Schulze 1967, Anderson & Morin 1971). Anterior segment fluorescein angiography has recently been performed in many conditions including studies of central retinal vein thrombosis (CRVT) (Raitta 1968, Vannas & Raitta 1972) and retinal artery thrombosis (Karjalainin 1971).

The observations presented in this study are derived from a personal study of 78 cases referred from the Casualty Departments of Moorfields Eye Hospital and King's College Hospital during the last three years (J M C). Also some data derived from several cases of Dr E Kohner examined by one of the authors (J M C) is included.

Rubeosis is defined here as the progressive development of new vessels on the iris observed clinically. Three topics will be briefly discussed in this paper: the vascular changes in the iris following CRVT (demonstrated by fluorescein angiography); the natural history of these changes; and the ocular and systemic abnormalities associated with rubeosis.

Iris Fluorescein Angiography

Twenty-one patients were suitable for iris angiography, having relatively unpigmented irides. This was performed by R W (assisted by J M C) employing a beam-splitting device of his design which permits simultaneous bilateral iris angiography and therefore a direct comparison of changes in the affected eye with the normal control (Whitelocke 1974, in preparation). Digital counters recorded the injection time and the time after the injection of fluorescein, and these readings were incorporated on the film.

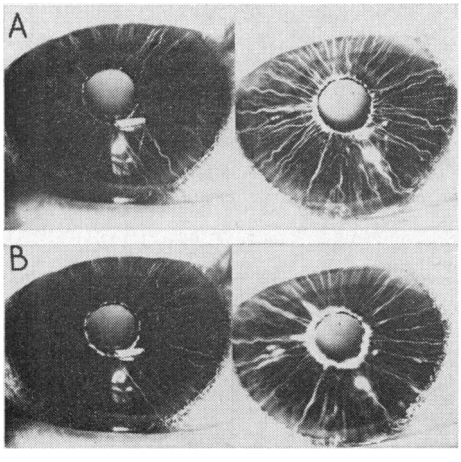
After an intravenous injection of 2 ml sodium fluorescein (20%) exposures were made every 2 seconds up to 1 minute, and at later intervals. The procedure was repeated subsequently, up to nine months after the venous occlusion.

When the intra-ocular pressure of the affected eye was at least 4 mmHg less than that of the other eye, the iris vessels of the affected eye were relatively dilated and the fluorescein arrival time was 2–4 seconds earlier. This was observed in 7 cases examined within one month of the occlusion, irrespective of the subsequent iris vascular changes, and persisted up to nine months in some.

The 3 patients whose angiograms are presented here all had right-sided CRVT.

Case 9

The affected eye of this patient was hypotonic, tensions to applanation being 9 mmHg and 17 mmHg right and left eyes respectively. By 22 seconds after injection (Fig 1A), the radial vessels of the affected eye had filled more completely with fluorescein and were more dilated than those of the normal eye. In a later film (Fig 1B), fluorescein leakage from both radial vessels and peripupillary capillaries was evident, but was not associated with flare and cells in the anterior chamber. Nine months after the occlusion, neither fluorescein leakage nor new vessels were observed but the radial vessels were still dilated.



LEFT RIGHT

Fig 1 **Case 9** *Iris angiography 22 seconds* (A) *and 27 seconds* (B) *after fluorescein injection.* A, *shows radial vessel dilatation in right eye.* B, *radial vessel and peripupillary leakage*

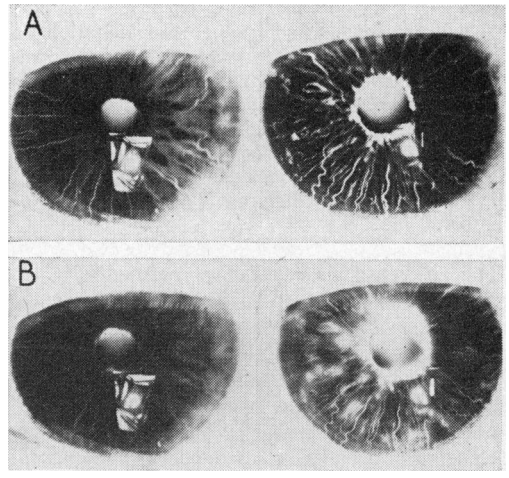


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Fig 2 **Case 13** *Iris angiography 24 seconds* (A) *and 76 seconds* (B) *after injection of fluorescein.* A, *shows vascular dilatation and new vessels in the right eye.* B, *leakage from new and radial vessels*

Case 13

This patient's angiogram revealed early new vessels four weeks after the occlusion, and these were only visible on slit lamp examination at eight weeks. At 24 seconds after injection (Fig 2A), the radial vessels were again more dilated than in the opposite iris, and new vessels formed small clusters at the iris periphery and around the pupil. After 76 seconds (Fig 2B), there was marked fluorescein leakage from both new and radial vessels. Leakage could also be seen at sites where groups of other new vessels were seen six weeks later on slit lamp examination and angiography. On the occasion of the first angiogram (Fig 2), there were no inflammatory signs in the anterior chamber, and the intra-ocular pressures were 23 mmHg and 21 mmHg right and left eyes respectively.

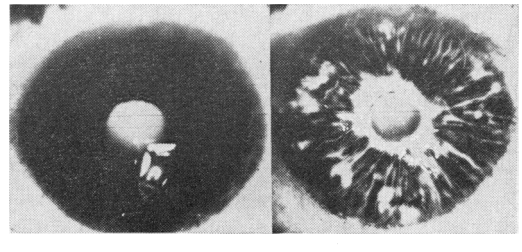

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Fig 3 **Case 2** *Iris angiography showing dilatation and leakage from new and radial vessels. Left iris has minimal residual fluorescence at this stage*

Case 2
This patient also showed iris neovascularization on angiography (Fig 3) three weeks before this was clinically observed. The circulation in the affected iris appeared slower than that of the normal eye, whose iris vessels show little residual fluorescence in this film. Subsequent angiograms showed increasing tortuosity of the new vessels and leakage over the whole iris. This was associated with flare and cells in the anterior chamber.

The increase in vascular permeability in hypotonic eyes and in irides with early new vessels, as evidenced by leakage from radial iris vessels, may be a reaction to either anterior segment ischæmia, or to a vaso-active substance. Leakage did not occur in eyes with tensions of more than 10 mmHg in the absense of iris new vessels, nor was there evidence of segmental defects of iris perfusion in any of the cases examined.

Natural History of Vascular Changes
Iris vascular changes can be grouped into three categories: transient, slowly progressive, and accelerated; according to their natural history. The first group was characterized by the transient appearance of dilated iris vessels. These were observed around the pupil in 4 cases at three and six months after the occlusion, without anterior chamber activity or hypotony, and in 2 other cases after an angle-closure attack precipitated by the CRVT. In all cases, the vessels were not visible four to five months later. Angiography demonstrated only capillary dilatation without fluorescein leakage.

True rubeosis occurred in 32 patients. In the prospective series 14 cases (25%) developed rubeosis. This group may be subdivided into two categories according to whether or not there is a sudden increase in intra-ocular pressure at about 8 to 15 weeks after the occlusion.

The 'slowly progressive' category comprised 6 cases. Iris new vessels first appeared at 13 to 20 weeks after occlusion in 5 patients and at 6 weeks in one. In 3 cases, no sudden tension rise occurred until 9, 11, and 13 months after the occlusion, and in 3 other cases this has not yet been observed after 10, 12 and 20 months. In 5 out of 6 cases, the opposite eye had a raised tension and 3 had cupped discs. Characteristically, peripheral anterior synechiæ (PAS) developed slowly in the early stages without inflammatory signs. Deep anterior chambers (depth more than 2.5 mm) were present in all cases. The depth increased by an average of 0.3 mm when the intra-ocular pressure began to rise.

The mechanism behind the sudden rise in tension seen in the 'accelerated' group is related to the angle width, the presence of preexisting chronic simple glaucoma, the amount of PAS, inflammation, and hæmorrhage. The causes of initial tension rise in eyes with narrow angles are: (1) Rubeosis first, then PAS. (2) Closed angle attack with minimal rubeosis initially. The causes in eyes with wide angles are: (1) Slight rubeosis and marked PAS. (2) Equal rubeosis and PAS. (3) Slight rubeosis and PAS with marked inflammation. (4) Slight rubeosis and PAS. Hyphæma is the cause of IOP rise. This tentative classification analyses the interaction of these factors as observed in this series but indicates only an early stage in a process terminating inevitably with extensive PAS and rubeosis.

In eyes with narrow angles, rubeosis may appear first and PAS develop rapidly over the next 2–3 weeks. Alternatively, a closed-angle attack associated with minimal rubeosis may be the presenting picture, initially responding to miotics and carbonic anhydrase inhibitors, with a subsequent further rise in tension during the next 2–6 weeks as PAS and rubeosis progress.

In only 3 cases of the wide angle group did the degree of visible rubeosis appear to correlate with the extent of PAS, and in most cases the initial pressure rise occurred before florid rubeosis was observed. In one case, the initial tension rise could be attributed to hyphæma alone, since the tension fell with subsidence of the hyphæma, later to rise again as PAS developed. Only 4 out of the 32 cases with rubeosis developed hyphæmas over a three-year period.

Relationship of Rubeosis to Coexisting Ocular and Systemic Abnormalities
This series confirms the well-known correlation between primary glaucoma in the opposite eye and the development of rubeosis (Table 1), occurring in 70% of cases with rubeosis and 31.8% of patients without rubeosis. Also, cotton-wool spots were observed more often in eyes which developed rubeosis, and corresponding areas of capillary closure were seen in trypsin-digests of the retinæ of 3 enucleated eyes. No correlation with the degree of retinal hæmorrhage or

Table 1
Ocular correlations

	No. of patients	
	Rubeotic	*Nonrubeotic*
Primary glaucoma in opposite eye ●		
Chronic simple	16	7
Narrow angle	2	5
Ocular hypertension	3	2
Total	21 (70%)	14 (31.8%)
Cotton-wool spots ■		
Present	17	26
Absent	6	34

● $\chi = 10.04, P < 0.005$ ■ $\chi^2 = 5.02, P < 0.02$

Table 2
Blood biochemistry (mg/100 ml)

	Uric acid ●			*Urea* ■			*Cholesterol* ▲		
	Mean	*s.d.*	*n*	*Mean*	*s.d.*	*n*	*Mean*	*s.d.*	*n*
Rubeotic	6,69	1.64	22	42.4	16.54	22	255.2	45.3	22
Nonrubeotic	5.59	1.38	66	36.3	13.04	66	224.7	54.0	66

●$t=2.73, P<0.01$ ■$t=1.73, P<0.05$ ▲$t=2.19,\ 0.02<P<0.05$

papillœdema was possible because of the difficulty in quantitating these signs. Optic disc new vessels were noted in at least 8 cases and demonstrated by angiography before the corneæ became œdematous, although previously their rarity in rubeotic eyes has been the subject of comment (Smith 1954). The majority of eyes in which rubeosis developed initially had poor vision (92% had an acuity of counting fingers or less). There was no association between rubeosis and the degree of relative hypotony in the affected eye or the difference in ophthalmic artery pressure.

Seventy-eight per cent of patients with rubeosis were over 60 years of age compared with 62% of those without, and therefore cases in each group had to be matched for age (and sex) before comparisons of the incidence of systemic disease could be made. When this was done, a higher incidence of electrocardiographic evidence of ischæmic heart disease was found in patients with rubeosis; in 12 cases out of 22 with rubeosis, and 16 out of 66 without ($\chi^2=5.5$, $P<0.02$). Blood pressure readings showed much variation, but radiology or ECG findings suggested cardiac enlargement in 21 out of 30 cases with rubeosis compared with 17 out of 60 without, a highly significant difference ($\chi^2=10.2$, $P<0.005$).

Serum uric acid levels were significantly higher in the rubeotic group and did not correlate with urea levels (Table 2). However, the mean values fall within the limits of normal, though there is still a significantly higher incidence of uric acid levels of 7.0 mg/100 ml and more amongst those patients with rubeosis. The differences of mean blood urea and cholesterol are not significant, and the incidence of clinical diabetes was similar in both groups.

Discussion

It is evident that a state of ocular ischæmia is present in those conditions in which iris neovascularization occurs. Whether anterior or posterior segment ischæmia or both predispose to rubeosis is the problem in CRVT. Hypotony during the early months after the occlusion may well be due to anterior segment ischæmia, but it is no more common or severe in those cases which develop rubeosis. As already noted, the changes observed in early rubeotic irides on angiography, especially the slowing of circulation, could be due to either anterior segment ischæmia or a vaso-active substance, but there were no areas of defective iris perfusion. In a series of 50 eyes with venous thrombosis and iris neovascularization, the author (J M C) was unable to find evidence of ciliary artery occlusion (unpublished observations) nor have other pathological studies revealed this, though this does not exclude the possibility of transient anterior segment ischæmia.

A greater degree of posterior segment ischæmia appears to be more common in cases with rubeosis as suggested by the increased incidence of cotton-wool spots. Poor cardiac function may be either a contributory factor or just an associated condition.

It is interesting to compare the occurrence of rubeosis in CRVT (10–25% of cases) with retinal artery thrombosis (3% of cases) since both conditions have ischæmic retinæ. Primary glaucoma, which increases retinal venous pressure and may interfere with choriocapillaris flow (Blumenthal *et al.* 1971), is common in venous occlusion but rare in retinal artery thrombosis. Pathological studies of arterial thrombosis with iris neovascularization have frequently demonstrated obstruction of the posterior ciliary arteries and also the retinal vein on occasions (Karjalainin 1971).

These differences might be explained by modifying a current hypothesis (Smith 1954). If an ischæmic retina produces a vaso-active substance, it would diffuse forward into the eye if not removed via the retinal veins or choroidal circulation. In CRVT, the retinal venous outflow is obstructed and the choroidal circulation possibly defective, resulting in a high incidence of rubeosis. In most cases of retinal artery thrombosis, these outlet pathways for vasoactive factor are patent, but the rare occasions that they become obstructed are associated with iris neovascularization.

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