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Studies of cerebral circulation time in man[1]

1 Normal values and alterations with cerebral vascular disease and tumour in arm-to-retina circulation times

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During an extensive arteriographic investigation of subjects with arteriosclerotic, atherosclerotic, and thrombotic cerebral vascular disease, considerable delay has often been observed in opacification of the small cerebral arteries (Meyer, Sheehan, and Bauer, 1960; Sheehan, Bauer, and Meyer, 1960; Bauer, Sheehan, and Meyer, 1961; Bauer, Sheehan, Wechsler, and Meyer, 1962). The delay in filling is probably due to slowing of the cerebral circulation and in some cases it has been necessary to delay exposure of radiographs for one to five seconds in order to obtain satisfactory visualization of the intracranial vessels. Such prolongation of the circulation time, demonstrated arteriographically, has now been confirmed in some of our cases of cerebral vascular disease by the use of the Sanchez-Perez serial casette changer and a timing device. Slowing of the cerebral circulation time has also been shown following experimental cerebral embolism or occlusion of the middle cerebral artery (Meyer, 1958; Meyer, Gotoh, and Tazaki, 1962).

Such observations led us to the hypothesis that simple bedside measurement of the arm-to-retina circulation times might be a valuable, although indirect, method of evaluating slowed cerebral circulation in embolic, thrombotic, arteriosclerotic, and atherosclerotic cerebral vascular disease. The arm-to-retina circulation time has been evaluated previously in the diagnosis of carotid artery occlusion by comparison of the circulation times of the two sides (David, Saito, and Heyman, 1961; Hollenhorst and Kearns, 1961; Heyman, 1961) but not in other forms of cerebral vascular disease.

Theoretically, arm-to-retina circulation times should vary with cardiac output, systemic vascular resistance, cerebral vascular resistance, vascular resistance of the external carotid circulation, retinal vascular resistance, and the length of the vascular circuit from arm to retina. Preliminary observations have indicated that these theoretical assumptions are correct and the test is a useful one for measuring effective circulation time from arm vein to retina and (indirectly) to brain. In most cases, the physical examination, including evaluation of the heart, lungs, and blood pressure, and ophthalmoscopic examination permits one to assume that cardiac output, systemic vascular resistance, vascular resistance of the external carotid circulation, and retinal vascular resistance are normal. In such cases changes in the arm-to-retina circulation times may be assumed to indicate an alteration of cerebral vascular resistance or possibly in the length of the arm-to-retina vascular circuit.

Stated another way, the retinal vessels are in many ways comparable to the smaller intracerebral vessels, and since both systems arise from the internal carotid artery, presumably they would be affected in a comparable manner by haemodynamic changes such as decreased cardiac output, changes in viscosity of the blood, variations in blood pressure, and any abnormality in the carotid system proximal to the origin of the ophthalmic artery. Furthermore, it is possible that large changes in cerebral vascular resistance would also be reflected by a change in arm-to-retina circulation time since the ophthalmic artery represents only a small part of the peripheral vascular bed of the internal carotid artery. Large changes in the cerebrovascular resistance might therefore affect the arm-to-retina circulation time. The hypothesis that the arm-to-retina circulation time may be used as an indirect index of cerebral circulation time would, of course, be rendered invalid in the presence of local changes of the ophthalmic circulation such as occurs in glaucoma, central retinal artery occlusion, retinal venous thrombosis, or diffuse retinal vascular disease.

Measurement of the arm-to-retina circulation

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time is a relatively simple and innocuous procedure. The technique used in the present study is a modification of the method described by Novotny and Alvis (1959). In experiments with the test in over 100 patients the only complication so far encountered has been nausea or vomiting in 8% of patients. The present communication confirms that the arm-to-retina circulation time may be prolonged on the side of an occluded carotid artery but also shows that the test is by no means specific for that condition. Actually the test has a much wider application in the diagnosis of disease of both proximal and distal cerebral vessels and for demonstrating delayed effective cerebral circulation from a number of systemic causes. The present report presents the results of the arm-to-retina fluorescein circulation time in a total of 78 subjects. In the 53 experimental cases cerebral arteriography was performed in all except two a few hours (12 to 24) after the circulation times were measured. Cerebral arteriography consisted of bilateral carotid arteriograms and bilateral retrograde vertebral arteriograms when indicated.

METHODS AND CASE MATERIAL

The experimental series comprised 51 patients admitted to the Neurology Service at Detroit Receiving Hospital who were scheduled for cerebral arteriography. These were all suspected of cerebral vascular disease with the exception of two cases of cerebral tumour, nine cases of idiopathic epilepsy, and one case of presenile dementia. Two cases with diabetes mellitus with diabetic neuropathy were also studied. Cases with systemic causes of prolonged circulation time, such as congestive heart failure and dehydration, were excluded from the study. The arm-to-retina fluorescein circulation time was determined in each eye. Twenty-five patients were selected for testing from the Neurological and Medical Services who were believed to be free from any form of cerebral vascular disease. These 25 patients comprised the control group. The control group was comparable in every way with the experimental group except that the patients in the control group were younger. The mean age of the control group was 38 years and that of the experimental group was 56 years.

In order to obtain a satisfactory view of the retinal vessels two or three drops of a rapidly acting mydriatic (10% neosynephrine) were instilled into each eye 10 minutes before the test. The use of the mydriatic should be noted on the hospital chart as a routine since dilatation of the pupils may be mistaken as evidence of brain-stem compression. Five millilitres of 5% fluorescein solution were then rapidly injected into an antecubital vein. This was normally followed by the sudden appearance of the dye in the retinal arteries within a period of eight to 14 seconds. The end-point is definite and unmistakable. The observations reported here were made using the American Optical Company Giantscope model 144P, which was found to be a most satisfactory instrument for this particular study. The appearance of the fluorescein in the retinal arteries produces a vivid, greenish-yellow fluorescence when viewed through the Giantscope using the deep blue filter provided with the instrument. A satisfactory end-point may be obtained using a standard ophthalmoscope and a Kodak Wratten 44 or 45A filter. The blue filter that is attached to the portable Welch-Allyn ophthalmoscope is adequate for determination of the end-point.

Measurement of the circulation time from arm to retina was made by the use of a stop watch which was started as soon as the rapid dye injection was completed. At the start of this investigation two observers viewed both retinae simultaneously, but it soon became apparent that unless the patient was particularly cooperative, the method was awkward and at times impossible. Since many of our patients were obtunded, semicomatose, or comatose, the practice was adopted of viewing each eye separately with two separate injections. The two injections required that a syringe filled with 10 ml. of 5% fluorescein be left attached to a hypodermic needle inserted in an antecubital vein. The needle was left in the vein after the first injection of 5 ml. The second injection was made two minutes after the first. In this manner a definite end-point was obtained in the second eye although some traces of fluorescein persisted in the retinal veins. When a satisfactory end-point was not obtained with the first two injections, the test was repeated at intervals of two minutes until satisfactory. This was occasionally necessary in stuporous or uncooperative subjects who made frequent movements of the eyes and in patients with cataracts.

The only untoward effects noted following the injection of fluorescein was a short attack of vomiting in four patients. A few others complained of nausea. The majority, however, did not experience any sensation during the injection of the dye. In all patients the dye was noted in the urine during the 24-hour interval following the test. Many developed a yellow hue to the skin and conjunctiva which lasted up to 12 hours. This condition can easily be mistaken for jaundice and may cause concern to those attending the patient unless they are aware that the test has been performed.

RESULTS

In the control group of 25 patients, the mean arm-to-retina circulation time was found to be 10·3 seconds, the limits were 8·2 to 14·0 seconds and the standard deviation was 1·51 (Table I).

Thirty-three of the 53 experimental cases had abnormal arm-to-retina circulation times. They were prolonged (beyond 14 seconds) or there was a significant difference in the circulation time of the two sides, one side being longer or shorter than the other by more than one second (Table II). Twenty patients in the experimental group were considered to have normal arm-to-retina circulation times (Table III).

Analysis of the arteriograms in the patients with abnormal arm-to-retina circulation times showed

TABLE I

ARM-TO-RETINA FLUORESCEIN CIRCULATION TIMES IN A CONTROL SERIES WITHOUT CEREBROVASCULAR DISEASE

Sex	*Age*	*Arm-retina Time (sec.)*		*Clinical Diagnosis*
M	37	R14·0	L14·0	Myasthenia gravis
F	20	R 9·0	L 8·4	Glioma of brain-stem
F	41	R 9·4	L 9·6	Tabes dorsalis
F	10	R12·4	L13·0	Treated anaemia, post-intestinal haemorrhage
M	48	R11·6	L11·4	Syringomyelia
M	45	R10·8	L11·0	Cerebellar degeneration
F	60	R11·0	L11·4	Peripheral neuropathy
F	33	R12·0	L11·2	Devic's disease
F	58	R10·0	L 9·2	Cervical spondylosis
F	50	R 9·0	L 9·0	Cervical spondylosis
M	29	R 9·6	L 9·6	Infectious polyneuritis
F	64	R10·8	L10·8	Multiple sclerosis
F	57	R14·0	L14·0	Amyotrophic lateral sclerosis
F	43	R 8·6	L 8·6	Cholecystitis
F	28	R 9·6	L 9·8	Treated carbon monoxide poisoning
M	18	R 9·2	L 9·0	Pericarditis
M	39	R 8·2	L 8·4	Pneumonia
F	18	R10·2	L10·2	Pulmonary tuberculosis
F	43	R 9·6	L 9·6	Thalassaemia (Hb 10·4 g/100 ml.)
F	38	R10·0	L10·0	Pneumonia
F	38	R10·2	L10·2	Pneumonia

that all had at least one and some more than one abnormality which might account for prolonged circulation times. For tabulation purposes, the single most important factor was selected in each case as the cause for arm-to-retina circulation times (Table II). The cases with abnormal arm-to-retina circulation times were thereby separated into the following groups:

INTERNAL CAROTID ARTERY OCCLUSION Four patients were shown to have unilateral occlusion of the internal carotid artery by arteriography. All of these cases showed prolongation of the arm-to-retina circulation times on the side of the occluded artery. In one patient both internal carotid arteries were occluded. The circulation times were greatly prolonged on both sides.

STENOSIS OF THE INTERNAL CAROTID ARTERY Nine patients were found to have stenosis of one internal carotid artery at arteriography without occlusion of the opposite side. One of these patients later suffered thrombotic occlusion of both internal carotid arteries. In eight cases there was significant prolongation of the arm-to-retina circulation times on the side of the stenosed vessel; in the remaining case with severe bilateral stenosis the arm-to-retina circulation times were normal (see Case 2).

DIFFUSE CEREBRAL ARTERIOSCLEROSIS Fifteen patients showed changes of diffuse cerebral arteriosclerosis by arteriography (dilatation, tortuosity, diffuse irregularity of vascular lumen). A number also showed atherosclerotic changes in the internal carotid arteries but diffuse changes of the cerebral vessels were considered to be the prominent abnormality.

Fourteen of the 15 cases showed prolongation of the arm-to-retina circulation times, usually on both sides. All of the patients with the most prolonged circulation times, *i.e.*, 39·6 seconds or up to four times normal circulation times, were found in this group. Presumably this is due to diffuse increase in cerebral vascular resistance since severe retinopathy was not present. Only one patient of this group considered to have diffuse mild arteriosclerotic changes proven by arteriography had normal arm-to-retina circulation times.

MULTIPLE VENOUS ANGIOMATA OF SCALP, FACE, PALATE, AND NECK There was one patient in this group. This patient had a normal carotid arteriogram bilaterally but an abnormally fast arm-to-retina circulation time which was reduced to six seconds on the right side compared with nine seconds on the left side. It was concluded that the arm-to-retina circulation time was decreased due to decreased peripheral vascular resistance in the distribution to the right common carotid artery secondary to multiple arteriovenous shunts.

HYPERTENSIVE INTRACEREBRAL HAEMORRHAGE Two patients with small intracerebral haemorrhages, both having normal arteriograms, were found to have abnormal arm-to-retina circulation times. In one case the increased circulation time occurred on the side of the haemorrhage, and in the second case, the circulation time was 16 seconds bilaterally. The slowed cerebral circulation time in these cases is believed to be due to increased cerebrovascular resistance, since the delay was limited to the side of the haemorrhage in one case.

CEREBRAL TUMOUR One case of massive, grade 3, astrocytoma of the left cerebral hemisphere with cerebrospinal fluid pressure of 420 mm. of water had prolonged arm-to-retina circulation times on the same side as the tumour. The circulation time of the opposite side was normal.

DIABETIC NEUROPATHY In two cases with diabetic neuropathy the arm-to-retina circulation times were prolonged. Although arteriography was not performed in these two cases the slowed circulation time is believed to be due to diffuse diabetic vascular disease which also involved the retinal vessels.

TABLE II

ABNORMAL ARM-TO-RETINA CIRCULATION TIME

Case No.	*Sex*	*Age*	*Arm-retina Time (sec.)*		*Arteriography*	*Clinical Diagnosis*
Carotid Artery Occlusion						
1	M	66	R14·4	L21·6	L. internal carotid occluded, 80% stenosis R. internal carotid, absent L. vertebral, R. vertebral does not enter skull	Cerebral arteriosclerosis
2	F	43	R23·0	L24·0	Both carotid arteries occluded	Diffuse arteritis
3	M	61	R15·0	L19·2	L. internal carotid artery occluded	L. carotid occlusion
4	F	60	R22·0	L19·2	R. internal carotid artery occluded Diffuse cerebral arteriosclerosis	Carotico-vertebral basilar insufficiency
5	M	58	R12·2	L15·0	L. internal carotid artery occluded	L. cerebral infarction
Carotid Artery Stenosis						
6	F	67	R19·6	L15·4	Marked carotid tortuosity with 50% stenosis and post-stenotic dilatation on right	Carotico-vertebral basilar insufficiency
7	F	60	R15·0	L13·0	Bilateral arteriosclerotic and atherosclerotic changes in carotids with 30% stenosis on right	Cerebral arteriosclerosis
8	F	60	R11·0	L14·0	40% stenosis origin L. internal carotid artery due to atherosclerotic plaque	Cerebral arteriosclerosis
9	M	44	R14·2	L11·2	50% stenosis origin R. internal carotid artery due to atherosclerotic plaque	R. cerebral infarction
10	M	40	R11·0	L16·0	50% stenosis L. internal carotid artery at bifurcation due to atherosclerotic plaque	L. carotid insufficiency
11	M	62	R16·2	L13·4	Atherosclerotic plaque in both carotid siphons	Carotico-vertebral basilar insufficiency
12	F	70	R16·4	L14·0	Atherosclerotic plaques at origin of both internal carotid arteries	R. intracerebral haemorrhage
13	M	66	R15·6	L13·0	80% stenosis of R. internal carotid artery due to recent thrombus	R. cerebral infarction
Cerebral Arteriosclerosis						
14	M	68	R22·2	L25·4	Small plaques origin both internal carotid arteries; diffuse cerebral arteriosclerosis	Cerebral arteriosclerosis
15	M	68	R16·2	L13·0	Diffuse cerebral arteriosclerosis bilaterally	Carotico-vertebral basilar insufficiency
16	F	70	R15·2	L17·6	Moderate degree cerebral arteriosclerosis bilaterally	Cerebral arteriosclerosis
17	M	58	R25·6	L27·8	Poor filling R. middle cerebral artery; diffuse cerebral arteriosclerosis bilaterally	L. cerebral infarction
18	M	56	R16·4	L18·2	Diffuse cerebral arteriosclerosis bilaterally	Fronto-cerebellar degeneration
19	M	78	R38·6	L36·4	30% stenosis L. internal carotid artery at origin; 30% stenosis R. internal carotid artery at origin; diffuse cerebral arteriosclerosis bilaterally	Carotico-vertebral basilar insufficiency
20	M	70	R19·4	L22·4	Diffuse cerebral arteriosclerosis bilaterally	Cerebral arteriosclerosis
21	F	60	R18·4	L18·4	Diffuse cerebral arteriosclerosis bilaterally: dilatation and tortuosity of both internal carotid arteries	Cerebral arteriosclerosis
22	F	64	R21·0	L23·2	Marked cerebral arteriosclerosis bilaterally	Cerebral arteriosclerosis
23	F	80	R23·8	L26·2	Marked cerebral arteriosclerosis bilaterally	Cerebral arteriosclerosis
24	M	42	R22·0	L23·0	Diffuse cerebral arteriosclerosis bilaterally; dilatation and tortuosity of both internal carotid arteries	L. carotid thrombosis
25	M	72	R28·0	L24·6	Diffuse cerebral arteriosclerosis bilaterally; 50% stenosis at origin R. internal carotid	Carotico-vertebral basilar insufficiency
26	M	78	R22·6	L17·8	Diffuse cerebral arteriosclerosis bilaterally	Pituitary tumour
27	M	86	R38·2	L39·6	Marked dilatation and tortuosity both internal carotid arteries; diffuse cerebral arteriosclerosis bilaterally	Carotico-vertebral basilar insufficiency
Multiple Venous Angiomata of Scalp, Face, Palate, and Neck						
28	F	21	R6·0	L9·0	Normal	Multiple venous angiomata
29	M	61	R11·0	L14·8	Normal	L. intracerebral haemorrhage
30	M	64	R16·0	L16·0	Normal	L. intracerebral haemorrhage
Cerebral Tumour						
31	M	65	R14·6	L16·2	L. frontal lobe tumour	L. frontal glioma
Diabetic Neuropathy						
32	M	58	R15·0	L15·2	Not performed	Diabetic neuropathy
33	M	70	R15·4	L15·2	Not performed	Diabetic neuropathy

TABLE III

NORMAL ARM-TO-RETINA CIRCULATION IN PATIENTS WITH ARTERIOGRAPHY

Case No.	Sex	Age	Arm-retina Time (sec.)		Arteriography	Clinical Diagnosis
34	M	34	R13·2	L14·0	Normal	Intracerebral haemorrhage
35	F	48	R12·0	L11·0	Normal	Epilepsy
36	M	40	R14·0	L13·6	Normal	Epilepsy
37	F	30	R 9·0	L 9·0	Normal	Epilepsy
38	M	60	R13·0	L12·6	Normal	Epilepsy
39	M	40	R14·0	L14·0	Normal	Epilepsy
40	M	68	R11·0	L10·2	Normal	Intracerebral haemorrhage
41	F	50	R13·2	L14·0	Normal	Epilepsy
42	M	50	R11·4	L12·4	Normal	Epilepsy
43	M	56	R11·8	L11·0	Normal	Epilepsy
44	M	44	R11·4	L11·4	Normal	Epilepsy
45	M	52	R10·1	L11·0	Normal	Pre senile dementia
46	F	58	R11·0	L10·0	Mild generalized arteriosclerotic changes in cerebral vessels	Dentato rubral tremor
47	M	44	R12·0	L11·6	Normal	L. cerebral infarction
48	M	50	R14·0	L14·0	Normal	L. intracerebral haemorrhage
49	M	68	R10·4	L11·2	Normal	Infarction L. cerebral hemisphere
50	M	19	R12·0	L12·0	Saccular aneurysm L. anterior cerebral artery	Meningo-cerebral haemorrhage
51	M	70	R10·0	L 9·0	Tumour L. frontal area	L. frontal glioma
52	F	30	R10·2	L10·2	Saccular aneurysm R. post communicating artery	Meningo-cerebral haemorrhage
53	M	58	R13·8	L13·8	Tumour L. frontal area	Brain tumour

ILLUSTRATIVE CASES

CASE 1 A 66-year-old white man was admitted to the Neurology Service, Detroit Receiving Hospital, in a severely confused state. On examination he was found to have a severe motor and sensory dysphasia, a marked apraxia, and a mild right hemiparesis. Carotid arteriograms (Fig. 1) showed occlusion of the left internal carotid artery and an 80% stenosis of the right internal carotid at its origin. In addition, retrograde brachial arteriography showed absence of the left vertebral artery and a developmentally anomalous right vertebral artery which failed to enter the skull.

The arm-to-retina circulation times were 14·4 seconds on the right and 21·6 seconds on the left. The patient's cerebral circulation depended almost entirely on the flow through the stenosed right internal carotid artery. Cerebrovascular resistance in the distribution of both diseased vessels was reduced, hence the relatively normal arm-to-retina circulation time on the side of the stenotic but only patent vessel. The delayed arm-to-retina circulation time on the left side was due to the left internal carotid artery occlusion. Retinal flow depended upon the rich collateral circulation through the left external carotid artery. This collateral circulation contributed to the cerebral circulation by retrograde flow through the left ophthalmic artery. Although collateral circulation was well developed, the route from arm to retina was prolonged and undoubtedly velocity of flow was reduced.

CASE 2 A 43-year-old negro woman was admitted to the Neurology Service with a mild right hemiparesis with complete recovery in 48 hours. Examination at the time of admission revealed mild right hemiparesis. There was a loud systolic murmur over both carotid arteries, over the origin of both vertebral arteries, in both axillae, over the abdominal aorta, and over both femoral arteries. The erythrocyte sedimentation rate was raised to 84 mm. per minute. Arteriography showed severe stenosis bilaterally at the carotid bifurcation. There was also stenosis of the right vertebral artery at its origin and arteriograms showed irregularities in the walls of the iliac arteries. The aortic arch and the origins of the innominate and subclavian arteries were not diseased. The arm-to-retina circulation time was 11 seconds on both sides which was surprising in view of the bilateral carotid stenosis, but, like the preceding case, demonstrates that flow through a stenotic vessel may be rapid if cerebral vascular resistance is low. A diagnosis of diffuse arteritis was made and confirmed when an attempt at surgical reconstruction of the left carotid artery was abandoned because the vessels were found to be surrounded by inflammatory tissues. Surgery was performed some weeks after arteriography and at operation the left carotid artery was found to be occluded. The patient was treated with steroid and anticoagulant therapy. She became confused, took an overdose of anticoagulants on her own initiative, and haemorrhaged severely into the gastro-intestinal tract. Anticoagulant therapy was discontinued and she developed a progressive right hemiparesis with dysphasia and dyspraxia and became severely demented. At this time, 12 weeks after the initial normal circulation times, the arm-to-retina circulation times were repeated and were now grossly prolonged, 24 seconds on the right side and 23 seconds on the left. Repeat arteriography now showed complete occlusion of the right internal carotid artery (Fig. 2). It will be recalled that the left carotid artery had become occluded in the interval between the two studies. She was at this stage dependent on the vertebral basilar circulation and a poorly developed, external carotid collateral circulation on the right. The delayed cerebral circulation was reflected in the grossly prolonged arm-to-retina circulation times bilaterally.

CASE 3 A 70-year-old white woman was admitted to the Neurology Service with a history of two episodes of

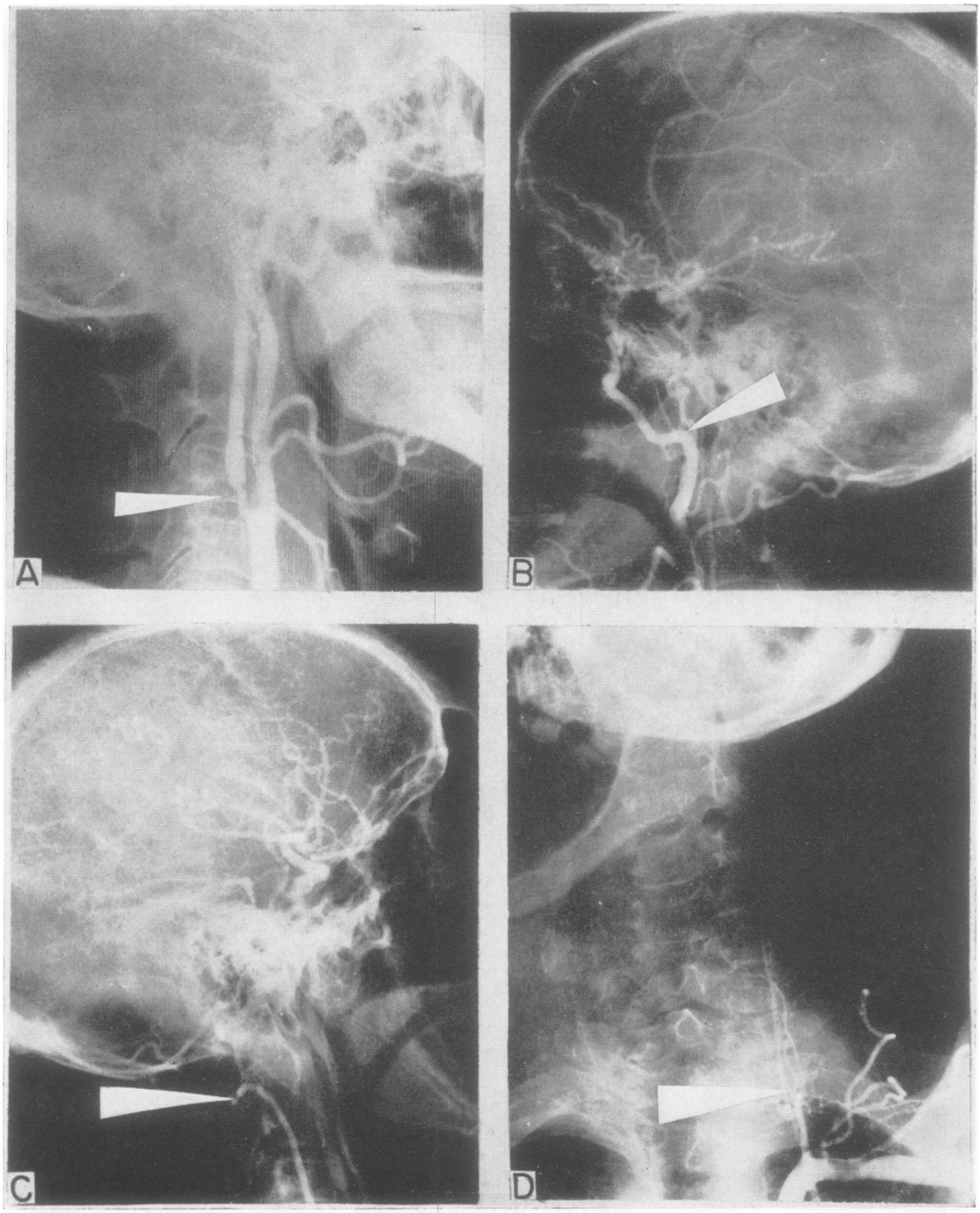

FIG. 1. *A 66-year-old white man with severe motor and sensory dysphasia, apraxia, and a mild right hemiparesis. Panarteriography demonstrated 80% occlusion at the origin of the right internal carotid* (A); *occlusion of the left internal carotid artery* (B); *a developmentally anomalous right vertebral artery which failed to enter the skull* (C); *and absence of the left vertebral artery* (D). *Arm-to-retina circulation times were 14·4 seconds on the right and 21·6 seconds on the left side.*

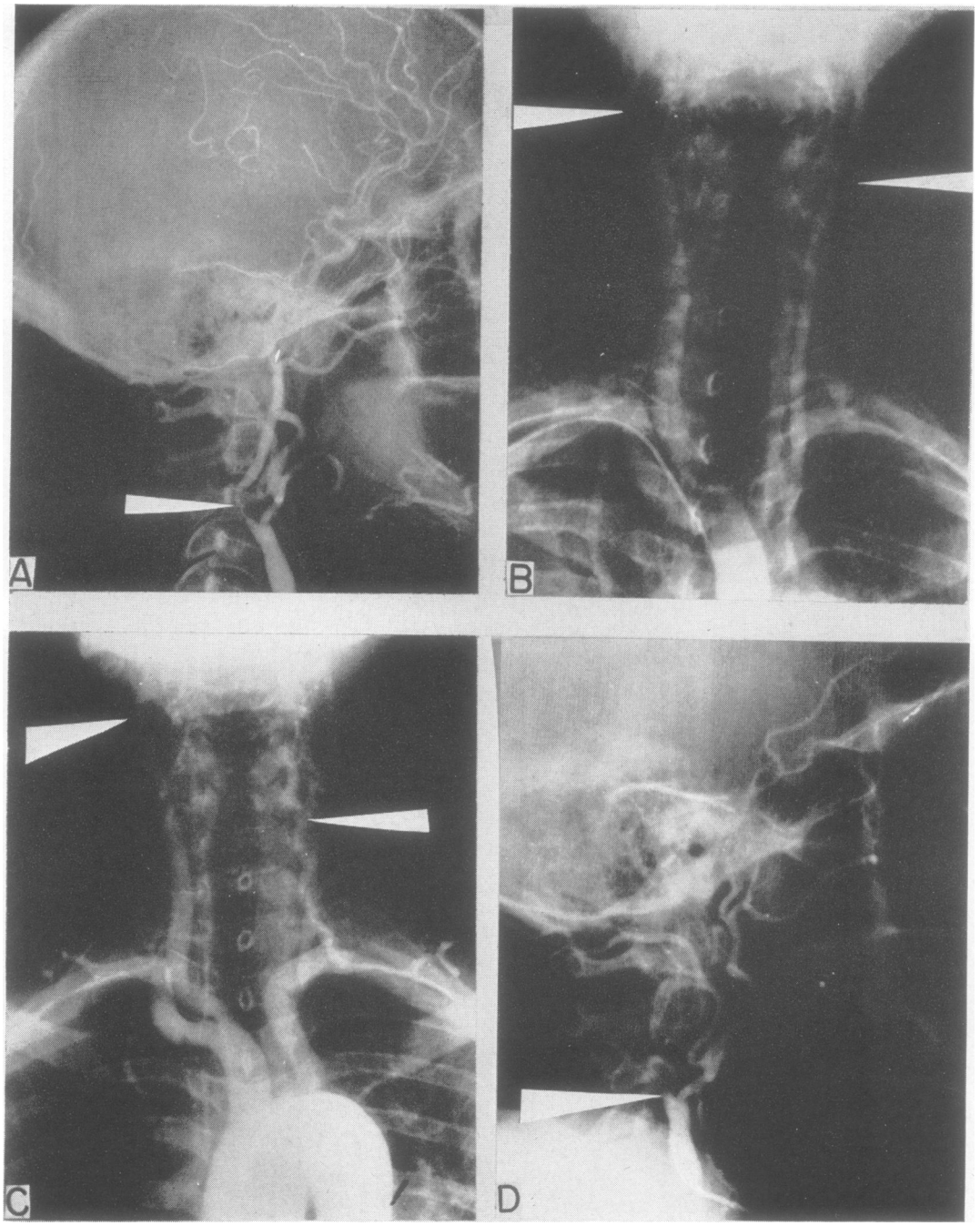

FIG. 2. *A 43-year-old negro woman admitted with a mild right hemiparesis with temporary complete recovery in a period of 48 hours. Arteriography shows severe stenosis bilaterally at the carotid bifurcation* (A, B, C). *Arm-to-retina circulation times were 11·0 seconds on both sides at this time. Repeat arteriography 12 weeks later showed complete occlusion of the right internal carotid artery* (D). *The arm-to-retina circulation times were now 24·0 seconds on the right side and 23·0 seconds on the left side and her neurological status had deteriorated.*

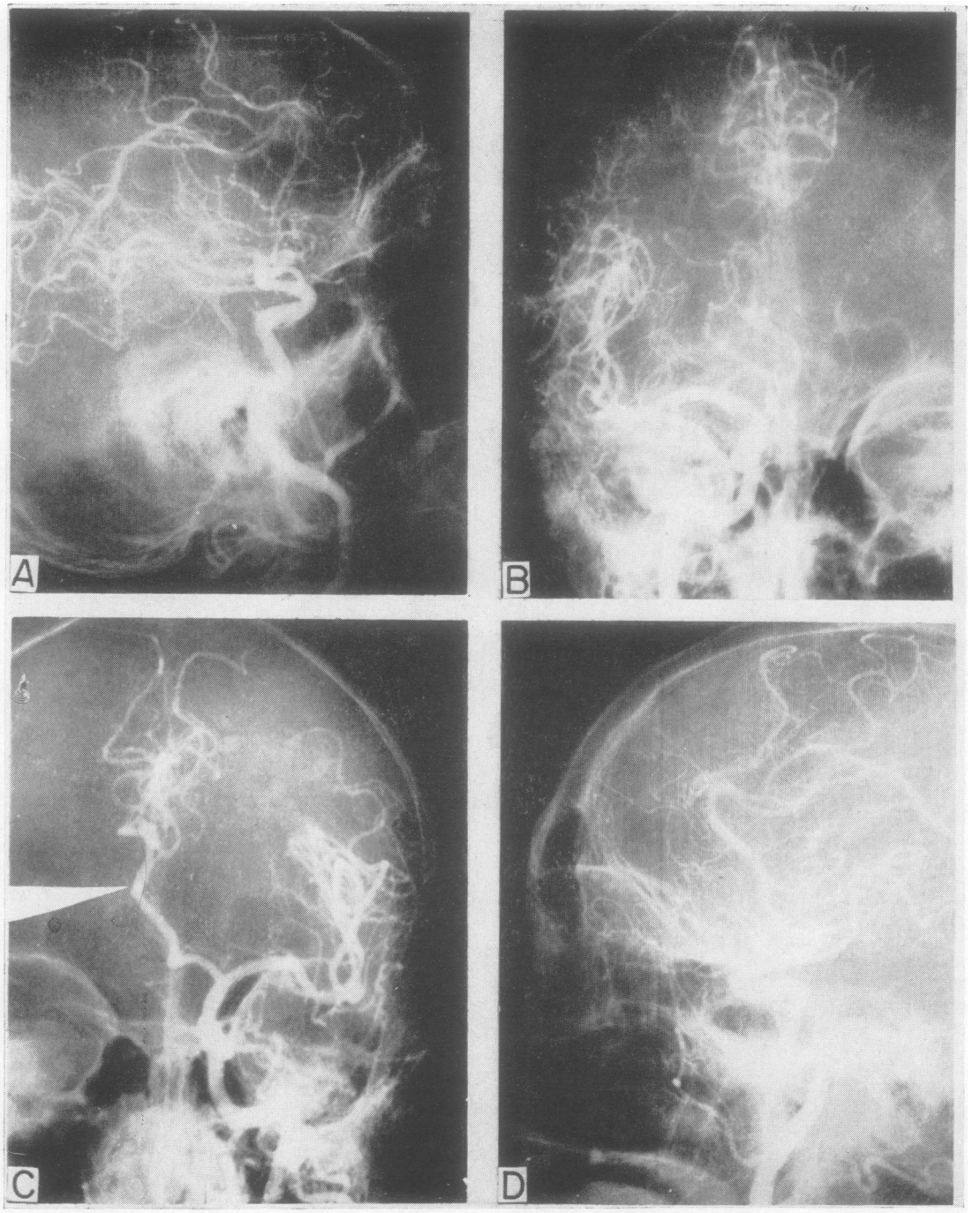

FIG. 3. *A 70-year-old white woman with a history of two episodes of right-sided hemiparesis followed by recovery and a progressive mental deterioration over a two-year interval. Carotid arteriography showed a marked diffuse bilateral cerebral arteriosclerosis. Arm-to-retina circulation times were 15·2 seconds on the right side and 17·6 seconds on the left side.*

weakness involving the right side of the body during the past two years. Both episodes were characterized by dysphasia with complete recovery after each attack. Progressive and persistent mental deterioration had occurred over the two-year interval. Two weeks before admission she gradually became bedridden and aphasic.

Examination revealed a poorly nourished, white woman with a pulse rate of 86/min. and blood pressure 135/80 mm. Hg in both arms. She was obtunded and showed a global aphasia but responded to stimuli and moved all four limbs. There was a residual right spastic hemiparesis with increased tendon reflexes on the right side and a right extensor plantar response. There was a bilateral grasp and a sucking reflex. On attempting to walk the patient an apraxia of gait was produced. A diagnosis of cerebral arteriosclerosis was made and she was treated conservatively. It was noted that she showed a worsening of symptoms during an episode of hypotension and again during a period when she was suffering from aspiration pneumonitis. Arm-to-retina fluorescein circulation times were 15·2 seconds on the right side and 17·6 seconds on the left side. Carotid arteriography (Fig. 3) revealed a marked, diffuse, bilateral cerebral arteriosclerosis. Presumably, the prolonged circulation times were due to increased cerebrovascular resistance due to severe cerebral arteriosclerosis.

CASES WITH NORMAL ARM-TO-RETINA CIRCULATION TIMES

Of the 20 patients who had normal arm-to-retina circulation times, 16 were considered to have normal carotid arteriograms and the remaining four had arteriographic abnormalities. The 20 cases are grouped according to clinical diagnosis.

Idiopathic epilepsy There were nine epileptic patients who had carotid arteriography for routine investigation of convulsive disorder. In none was any structural abnormality demonstrated. All of these nine patients had normal arm-to-retina circulation times and all had normal arteriograms.

Hypertensive intracerebral haemorrhage Three patients were admitted with the diagnosis of acute, small, intracerebral haemorrhage due to hypertension. All were found to have normal arm-to-retina circulation times performed a few hours after admission. Subsequent arteriograms were read as normal, although the cerebrospinal fluid was haemorrhagic and neurological defects were present.

Meningo-cerebral haemorrhage Two patients were admitted with acute subarachnoid haemorrhage and localized signs of cerebral damage. Both had normal arm-to-retina circulation times. Subsequent arteriography showed the presence of saccular aneurysm in both cases without vascular spasm.

Cerebral infarction secondary to arterial thrombosis of small cerebral vessels Two patients were considered to have had recent mild cerebral infarction due to thrombosis of small cerebral arteries. The arm-to-retina circulation time was normal in both patients and arteriography did not show any absence of filling of the anterior or middle cerebral systems. It is possible that these patients had thrombosis of small cerebral vessels which could not be recognized by arteriography.

Cerebral tumour The arm-to-retina circulation time was found to be normal in two patients subsequently shown to have brain tumours without gross increase in intracranial pressure. In both cases the tumours were intracerebral astrocytomas of the left frontal parasaggital area. The lesions were demonstrated by arteriography and confirmed by surgical exploration. Although both patients had early papilloedema, neither the intracranial pressure nor local compression of the vascular bed was apparently sufficient to cause slowing of the cerebral circulation time.

Pre-senile dementia One patient was diagnosed as presenile dementia of the Alzheimer type and was subsequently shown to have moderate bilateral cerebral atrophy by pneumoencephalography. Arm-to-retina circulation times were normal and carotid arteriograms were within normal limits.

Vertebral-basilar arteriosclerosis with dentato-rubral tremor This patient experienced the sudden onset of a coarse, proximal action tremor of both arms. Arm-to-retina circulation times were normal bilaterally. Carotid arteriography showed a mild degree of diffuse tortuosity and widening of the vessels. This was the only patient in the present series with cerebral arteriosclerosis who had normal circulation times.

DISCUSSION

The arm-to-retina fluorescein circulation time is a simple, reliable test that can easily be carried out at the bedside. Experience with the present series of cases reported here and that of others (Meyer *et al.*, 1960; 1962) indicates that it may be of considerable value in the diagnosis of suspected cerebral vascular disease. Unlike the measurement of the arm-to-tongue circulation time using decholin, which requires the cooperation and subjective report of the patient, it is an objective test and can be used in comatose patients. It provides information concerning the time of circulation from the peripheral veins to the retina. It can become prolonged if the cardiac output is diminished, if blood viscosity is increased, if systemic peripheral vascular resistance is decreased, if cerebral vascular resistance is altered, or if the carotid or retinal arterial flow is obstructed. The test is valuable because no matter what the cause of the delay it will indicate any decrease in velocity of venous return and flow of blood from the heart to the retina. If localized ophthalmic and retinal disease can be excluded, it will provide indirect evidence of delayed circulation time to the brain. Slowing may be unilateral or bilateral. Determination of the arm-to-retina circulation times in our control series of 25 cases agrees well with the normal circulation times reported by other authors (Meyer, 1958; Novotny and Alvis, 1959).

In the experimental group, 20 cases had normal arm-to-retina circulation times, and of these 15 had normal arteriograms, two had single saccular

aneurysms without arteriosclerosis, and two had brain tumours without cerebral arteriosclerosis or massive increase of intracranial pressure. Only one case with a normal arm-to-retina circulation time had mild diffuse cerebral arteriosclerosis. On the other hand, of the 33 patients with abnormal arm-to-retina circulation times, in only three patients were the arteriograms normal and each of these three had other factors that would contribute to an alteration in cerebral circulation time. One case had numerous arteriovenous shunts demonstrated by retrograde jugular venography through multiple venous angiomata in the external carotid circulation of the scalp and tongue. The remaining two cases had suffered from recent intracerebral haemorrhage, with probably increased cerebral vascular resistance.

Our results confirm that the arm-to-retina circulation time is prolonged in occlusion of the carotid artery and usually is prolonged when there is unilateral stenosis of the internal carotid artery (David *et al.*, 1961; Novotny and Alvis, 1959). In the present study the use of the test has been extended to other types of cerebral vascular disease and it has been shown that significant slowing of the arm-to-retina circulation time may occur due to diffuse cerebral arteriosclerosis without occlusion or stenosis of the carotid artery. Circulation times were prolonged as much as four times the normal value in some patients with diffuse cerebral arteriosclerosis, in the absence of heart failure, dehydration, and advanced arteriosclerotic retinopathy.

Two patients with brain tumour in this series did not show any abnormality in the arm-to-retina circulation time. One patient with a large tumour showed prolonged circulation on the side of the tumour. It therefore appears probable that slowing of the arm-to-retina circulation time only occurs in large tumours of the brain or in the presence of greatly increased intracranial pressure. The case with cerebral tumour is of unusual interest since the circulation time was only prolonged on the side of the tumour, indicating that the test can reflect lateralized changes in cerebrovascular resistance.

The decrease in the arm-to-retina circulation time to six seconds on one side compared with nine seconds on the opposite side in a case with multiple venous angiomata of the scalp, face, palate, and neck is clearly abnormal. This observation demonstrates that arteriovenous shunts may lead to increased cardiac output and decreased circulation time in the carotid circulation. This preliminary observation suggests that the arm-to-retina fluorescein test may prove of value in the diagnosis of vascular malformation of the brain provided that the arteriovenous shunt is of sufficient degree to produce a decreased cerebral circulation time on one or both sides. Studies of cerebral blood flow and circulation time using either nitrous oxide or radioactive techniques have shown that the cerebral circulation is increased and rapid in cerebral arteriovenous malformation (Shenkin, Spitz, Grant, and Kety, 1948; Greitz, 1956; Thompson, 1961; Nylin, 1961; Oldendorf and Crandall, 1961).

Only two cases of meningo-cerebral haemorrhage due to a ruptured saccular aneurysm have been included in this series. Both had normal arm-to-retina circulation times. In neither case was there a marked rise in intracranial pressure nor was there marked spasm of intracranial vessels at arteriography which is commonly seen in ruptured saccular aneurysm. It is probable that the arm-to-retina circulation time would be prolonged in the presence of vascular spasm or greatly increased intracranial pressure following rupture of a saccular aneurysm.

Preliminary results in the small series of patients with intracerebral haemorrhage reported here show that in this condition the arm-to-retina circulation time may be normal or prolonged. Of these five cases, two had abnormal arm-to-retina circulation times and in three cases the times were normal. All had normal arteriograms. In one patient the circulation times were equally prolonged on the two sides. It is believed that in the two cases where circulation was slowed, this was due to increased intracranial pressure with increased cerebrovascular resistance.

Two cases of cerebral infarction believed to be secondary to thrombosis of the small vessels in the distribution of the middle cerebral artery had normal arteriograms and normal circulation times. However, the fluorescein test was not performed on either within the first three days of the onset of symptoms. Observations in another group of patients with recent cerebral infarction indicate that there is a significant prolongation in fluorescein circulation times during the first three days of cerebral thrombosis with a subsequent decrease in later stages of the illness.

SUMMARY

The arm-to-retina fluorescein circulation time is a simple, safe, bedside procedure which provides valuable practical and theoretical information in the clinical investigation of patients with cerebral vascular disease. (The test is reliable in comatose and aphasic patients.)

In a series of 25 control cases we found the arm-to-retina circulation times to vary between 8·2 seconds and 14 seconds with a mean of 10·31 seconds.

Prolonged arm-to-retina circulation times may be due to carotid occlusion, carotid stenosis, or increased cerebrovascular resistance such as occurs in

diffuse cerebral arteriosclerosis. Other causes of prolongation of the arm-to-retina circulation times are discussed, including one case of cerebral tumour.

A shortened circulation time was demonstrated in one case of multiple venous angiomata in the distribution of the common carotid artery. The test may therefore be of value in the diagnosis of intracranial vascular lesions in which an arteriovenous shunt is present.

Normal arm-to-retina circulation times were found in patients with idiopathic epilepsy, in two cases of brain tumour without greatly increased intracranial pressure, and in two cases of meningocerebral haemorrhage.

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