The post-operative course was uneventful except for the development of a hyperdynamic hypertensive state on the third day. This was not fully explained as due to acidosis from retained bronchial secretions, but the blood-pressure fell after bronchoscopic aspiration and the administration of Arfonad (trimetaphan camphorsulphonate) intravenously. The patient was discharged on the 28th post-operative day and was symptom-free when he returned to work 10 weeks after the injury.

Discussion

Traumatic aortic rupture is to be suspected in a patient who complains of chest pain and shortness of breath after a deceleration injury. Physical examination and chest *x*-ray examination confirm the diagnosis; a penetrating chest *x*-ray film defines the aorta and the shadow due to the mediastinal haematoma more clearly (Fig. 2). The extravasation of blood into the mediastinal tissues in cases of leaking dissecting aortic aneurysms has been described as "arcuate excrescences" (Wood *et al.*, 1932) and as "knobbly irregularities" (Levene *et al.*, 1954). Logue (1943) described the wide smooth mediastinal shadow of haemorrhage occurring together with pleural effusion as being characteristic of aortic rupture. The localized paraortic knuckle is demonstrated in Fig. 2, and typical widening of the mediastinal shadow, a constant finding on chest *x*-ray films, is shown in Fig. 1; the left-sided pleural effusion is most pronounced in the third chest *x*-ray film (Fig. 3), taken three hours after injury.

Although the clinical findings in traumatic aortic rupture may be insignificant because there is no evidence of external chest injury, the lesion must be recognized because most victims will soon die unless early operation is undertaken.

Thus the diagnosis should be made as early as possible because of the progressive nature of the lesion and the need for organizing emergency operative repair, by means of partial left heart bypass or, if this is not available, by a temporary shunt between the left subclavian artery and the femoral artery. The by-pass should be established before the false sac of the mediastinal haematoma is explored. In addition to saving more lives, surgical correction during the first 24 hours allows the aorta to be repaired by direct suture; the advantages of direct end-to-end suture of the aorta have been demonstrated by Alley *et al.* (1961). In the cases reported by Jahnke *et al.* (1964), in which surgery was delayed for several days, it was necessary to use a graft of foreign material because the vessel ends were too firmly fixed by organizing haematoma. McKnight *et al.* (1964), in two cases repaired at 12 and 24 hours respectively, chose to use Teflon grafts so as to avoid the possible occurrence of medial dissection; however, this is not seen as a complication when coarctation of the aorta is excised and continuity restored by direct end-to-end suture.

Although some authors have suggested aortography where aortic rupture is suspected, it is felt that this is indicated more for the late aneurysm, as valuable time may be lost during initial treatment: the developing clinical picture as illustrated by this patient made a diagnosis possible without using special radiological techniques.

Summary

A 17-year-old boy was admitted to hospital after a road accident in which he sustained a severe blow on the chest. Traumatic rupture of the thoracic aorta was diagnosed on clinical and radiological signs. Operative repair was undertaken four hours after the injury; this early surgical repair resulted in a successful outcome, the patient returning to work 10 weeks after the accident.

References

Alley, R. D., Van Meirop, L. H. S., Li, E. Y., Kausel, H. W., and Stranahan, A. (1961). *Arch. Surg.*, **83**, 300.
Bowen, D. A. L., and Teare, R. D. (1962). *Thorax*, **17**, 150.
Dobell, A. R. C., MacNaughton, E. A., and Crutchlow, E. F. (1964). *New Engl. J. Med.*, **270**, 410.
Eiseman, B., and Rainer, W. G. (1958). *J. thorac. Surg.*, **35**, 347.
Fleischaker, R. J., Mazur, J. H., and Baisch, B. F. (1964). *J. thorac. cardiovasc. Surg.*, **47**, 289.
Jahnke, E. J., Fisher, G. W., and Jones, R. C. (1964). Ibid., **48**, 63.
Levene, G., Burke, E. N., and Arnois, D. C. (1954). *Amer. J. Roentgenol.*, **72**, 1004.
Logue, R. B. (1943). *Amer. J. med. Sci.*, **206**, 54.
McBurney, R. P., and Vaughan, R. H. (1961). *Ann. Surg.*, **153**, 670.
McKnight, J. T., Meyer, J. A., and Neville, J. F. (1964). Ibid., **160**, 1069.
Parmley, L. F., Mattingly, T. W., Manion, W. C., and Jahnke, E. J., jun. (1958). *Circulation*, **17**, 1086.
Passaro, E., and Pace, W. G. (1959). *Surgery*, **46**, 787.
Spencer, F. C., Guerin, P. F., Blake, H. A., and Bahnson, H. T. (1961). *J. thorac. cardiovasc. Surg.*, **41**, 1.
Stoney, R. J., Roe, B. B., and Redington, J. V. (1964). *Arch. Surg.*, **89**, 840.
Strassmann, G. (1947). *Amer. Heart J.*, **33**, 508.
Wood, F. C., Pendergrass, E. P., and Ostrum, H. W. (1932). *Amer. J. Roentgenol.*, **28**, 437.

Peripheral Vascular Lesion in Diabetes Mellitus

JAMES M. MOORE,* F.R.C.S.ED., F.R.C.S.GLASG.; IAIN D. O. FREW,† M.B., CH.B.

[WITH SPECIAL PLATE]

Brit. med. J., 1965, **2**, 19–23

This report gives the results of a histological study of the blood-vessels of the skin of the leg; amputated limbs and skin biopsies were examined and the findings were then correlated with the results of previous clinical assessment.

Lesions of the feet occur much more commonly in diabetics than in non-diabetics. Bell (1957), in a necropsy series of 52,062 cases, found that the incidence of gangrene was increased 53 times in male diabetics and 71 times in females.

It used to be assumed that the cause was a greater liability to develop atherosclerosis plus a lowered resistance to infection. However, Oakley, Catterall, and Martin (1956) emphasized the importance of neuropathy; they felt that most lesions of the feet in diabetics could be explained by a superimposition of neuropathy on the degree of arterial disease common to non-diabetics of the same age and sex.

Nevertheless, occasionally one sees diabetics with gangrene who show little clinical evidence of neuropathy or widespread sepsis, and who have a good blood supply as judged by the presence of a palpable pulse at ankle level. The question arises whether in diabetes there is a specific obliterative lesion of small distal blood-vessels.

* Senior Registrar, Department of Surgery, Victoria Infirmary, Glasgow (presently Consultant Surgeon, Southern Ayrshire Hospitals).
† Registrar, Department of Pathology, Victoria Infirmary, Glasgow.

Goldenberg, Alex, Joshi, and Blumenthal (1959), in a very detailed histological study of amputation material, described a lesion of small arteries and arterioles which was present in 92% of 92 diabetic specimens. The characteristic feature was endothelial proliferation and deposition of a periodic-acid-Schiff-*positive* material in the wall. The lesion was present in vasa vasorum, vasa nervorum, and vessels of muscle and skin; dermal vessels were examined in 51 diabetics, with positive findings in 63%.

Material and Methods

Since 1959 39 amputations have been performed in cases carefully examined clinically and fully documented beforehand. In the diabetic group there were 21 limbs from 20 patients and five amputated toes and partial amputations of the foot. In the non-diabetic group there were 12 limbs from 11 patients and one amputated toe.

More recently skin biopsies from the leg have been taken from 78 patients also fully examined clinically; there were 16 diabetics with foot lesions, 18 diabetics without foot lesions, 19 non-diabetic patients with atherosclerosis, 22 other controls with miscellaneous diseases, and three subjects both of whose parents were diabetic. The site chosen for skin biopsy was the antero-lateral surface at mid-leg; it was felt that this was the most distal site that would be safe with regard to good healing. The specimens were removed by a knife and measured 5 by 2.5 mm. approximately. Most were taken while the patient was undergoing operation under general anaesthesia, but in other cases 1% plain lignocaine was used (a preliminary study having revealed no histological difference between specimens removed by the two methods).

Eleven patients had both skin biopsies and amputations. In all, skin was examined from 104 patients (52 diabetics and 52 non-diabetics).

Clinical Examination.—The femoral, popliteal, posterior tibial, and dorsalis pedis pulses were palpated, and the blood-pressure was recorded. The peripheral nervous system was then examined, tests including ankle- and knee-jerks, plantar responses, touch, pain from pinprick, sharp–blunt differentiation, and vibration sense. Inquiry was made regarding pain and paraesthesiae in the legs and sweating of the feet. Note was taken of the state of the nails and skin. In most of the later cases the reaction to an intradermal injection at mid-leg of 0.1 ml. of histamine acid phosphate was assessed by noting the extent of the weal and flare at five and ten minutes. In these cases the capillary fragility was also estimated by a modified Hess test with a cuff at a pressure of 80 mm. Hg for four minutes (Barnes, 1950). Petechiae in a 6-cm. circle on the flexor aspect of the forearm were counted, using a hand lens in a bright light.

Histological Technique.—Amputation specimens were received at the laboratory unfixed, and blocks were taken routinely from the following sites, where applicable: (1) the side of unaffected toes, (2) dorsum of foot over second metatarsal, (3) medial and lateral aspects of ankle 1 in. (2.5 cm.) below malleoli, (4) anterior aspect of leg to correspond with the small skin biopsies, (5) large vessels and nerves in the proximal part of the specimen. The small skin biopsies were received in formal acetate and were handled as one block. All blocks were embedded in paraffin after a process of double fixation in formal acetate (18 hours) and formal corrosive (24 hours). Sections, 6 μ thick, were stained by the following methods:—(1) To demonstrate the general structure of the tissues: (*a*) haemalum and eosin, (*b*) Masson–Goldner. (2) To demonstrate details of the basement membrane of small blood-vessels: (*a*) alcoholic periodic-acid-Schiff (P.A.S.), (*b*) alcian green (modification of Putt and Hukill, 1962), (*c*) orange G and aniline blue (Dunn, 1940). (3) To demonstrate elastic tissue: elastica (Lawson, 1936).

Results

Microscopical examination of the skin from both the biopsy and the amputation specimens showed that in most diabetic cases there was a patchy proliferative lesion affecting principally arterioles and capillaries. This angiopathy consisted of two parts: (1) proliferation of the lining endothelium (see Special Plate, Fig. 1) and (2) thickening, with sometimes splitting, of the basement membrane (Special Plate, see Fig. 2); it was most marked in arterioles and the larger capillaries, shading off on the one side into small arteries and on the other into the smaller capillaries. Similar changes were noted in the vasa vasorum and vasa nervorum in amputated limbs of diabetics.

The changes in the basement membrane were of particular interest. As reported by Goldenberg *et al.* (1959), and others since, the basement membrane of affected vessels was markedly positive with the P.A.S. reaction. In some of the present cases, however, this reaction was rather weak and indefinite, and, therefore, the basically similar alcian green reaction was used with more consistent results; vessels with diabetic angiopathy all showed a dark blue-green colour, in contrast to the much paler colour of normal basement membranes and the almost colourless background tissue. Dunn's classical method was also used, but this did not seem to be so specific and gave much less delicate results. Staining for elastic tissue showed no specific abnormality in the internal elastic lamina of the small arteries where angiopathy was present.

This angiopathy was found in the vessels of the skin of the leg in 46 of the 52 diabetic cases; only 3 of the 52 non-diabetics showed such a lesion (Table I).

TABLE I.—*Incidence of Angiopathy of Small Vessels in* 104 *Patients*

	Average Age	Total No.	No. with Angiopathy
Diabetics	62 years	52	46 (88%)
Non-diabetics	58 years	52	3 (6%)

Blind assessment of the 78 skin biopsies was undertaken. The pathologist attempted to allocate the cases to the diabetic or non-diabetic groups merely on the basis of the histological appearance of the small vessels; the allocation was correct in 90% (Table II).

TABLE II.—*Results of Blind Histological Assessment of* 78 *Skin Biopsies*

	No. of Cases	No. Correctly Allocated
Diabetics	34	29 (85%)
Non-diabetics	44	41 (93%)
Total	78	70 (90%)

Considerable variation was noted in the degree of the angiopathy, and cases were therefore placed in one of four arbitrary grades; in practice, however, there was a gradual transition from the mildest cases to the most severe.

The changes typical of each grade are:

Grade I (+).—The only change is slight thickening of the basement membrane in arterioles (diameter 20–40 μ).

Grade II (++).—Arterioles and capillaries show moderate thickening of the basement membrane and slight endothelial proliferation.

Grade III (+++).—Changes are most pronounced in arterioles. The basement membrane is thickened and is split into two or three concentric rings; endothelial proliferation is moderate and plump cells bulge into the lumen. Changes of lesser degree are seen in minute arteries (up to 120 μ diameter), while in capillaries they are limited to simple thickening of the basement membrane with slight endothelial proliferation.

Grade IV (++++).—The appearances are similar to those in grade III but are greater in degree. Splitting of the base-

J. M. MOORE AND I. D. O. FREW: PERIPHERAL VASCULAR LESION IN DIABETES MELLITUS

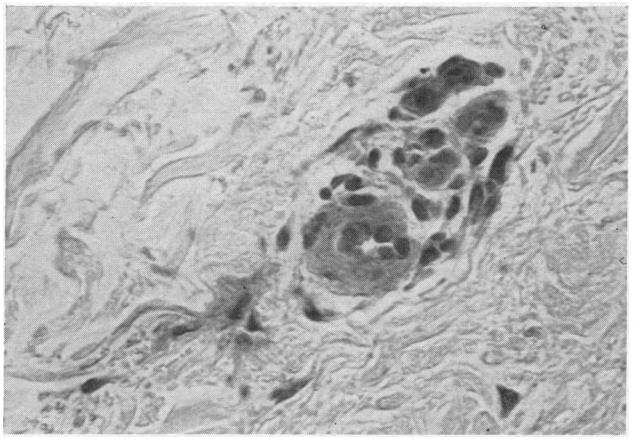

FIG. 1.—Endothelial proliferation and thickening of vessel wall (grade III). (Haematoxylin and eosin. ×120.)

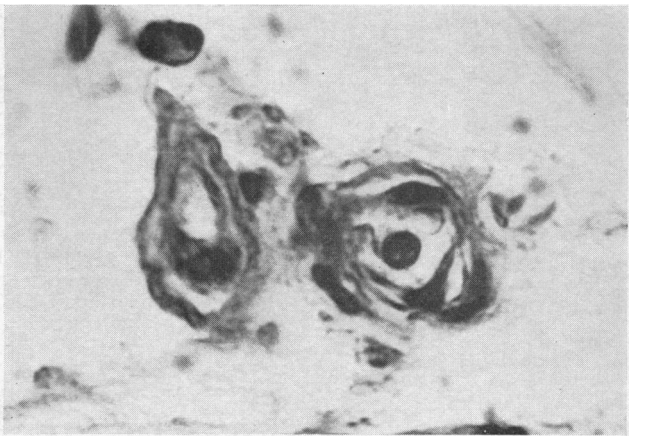

FIG. 2.—Splitting of basement membrane (grade III). (P.A.S. reaction, green filter. ×240.)

KINSEY SMITH: ACUTE RENAL FAILURE IN PHENINDIONE SENSITIVITY

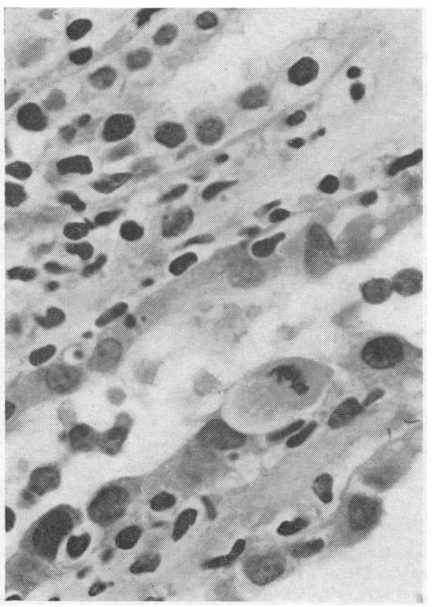

FIG. 1.—Case 1.

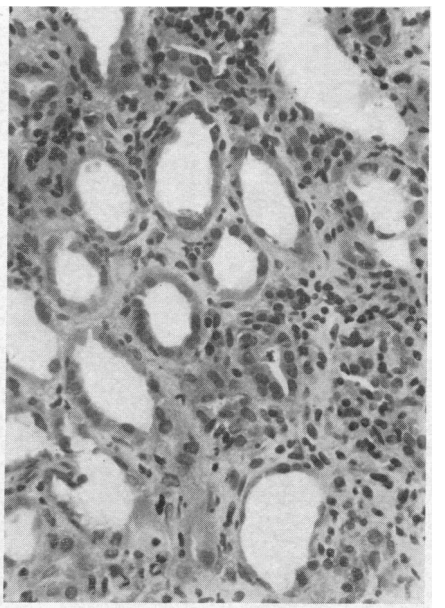

FIG. 2.—Case 1.

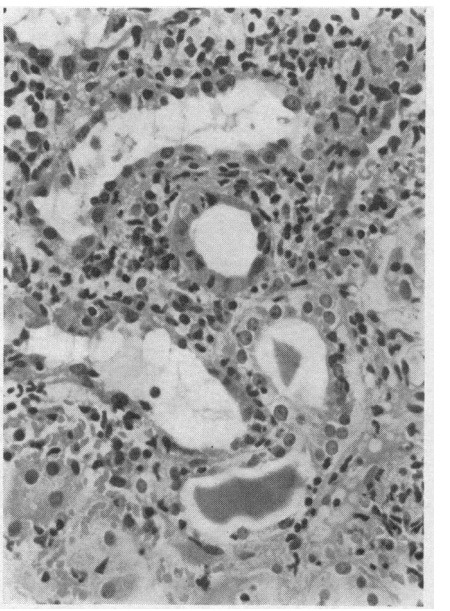

FIG. 2.—Case 5.

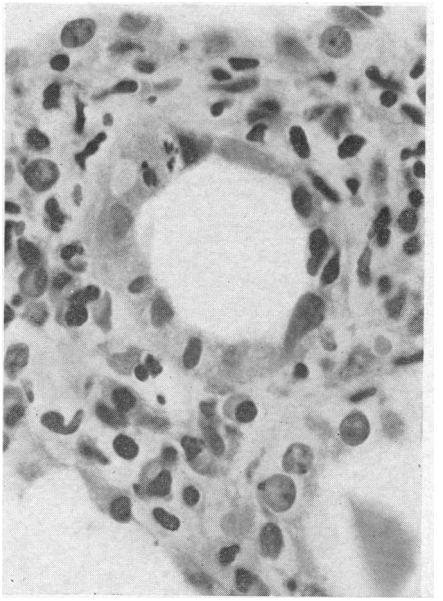

FIG. 1.—Case 5.

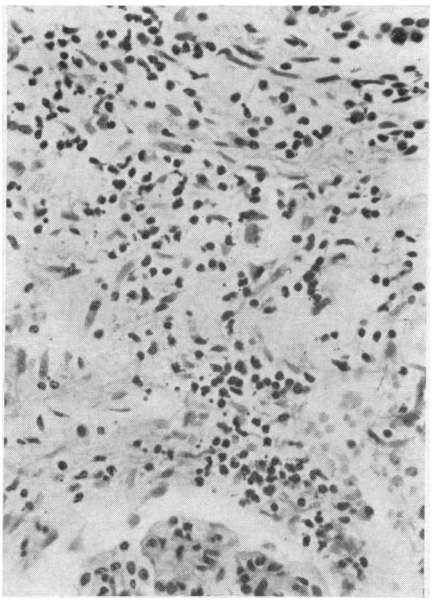

FIG. 2.—Case 4.

FIG. 1.—Showing mitotic figures in tubular epithelial cells in Cases 1 and 5. The interstitial infiltrate can also be seen, and contains plasma cells. (Haematoxylin and eosin. ×680.)

FIG. 2.—Lower-power view showing intense interstitial infiltrate in Cases 1 and 5 and some patchy round-cell infiltration in Case 4. (Haematoxylin and eosin. ×260.)

ment membrane in vessels of 20–100 μ diameter is sometimes so pronounced that rings of basement membrane material extend far out into the surrounding stroma.

Diabetic Cases with Foot Lesions

The gradings for the severity of the other factors, apart from the angiopathy, were as follows:

Severity of Diabetes.—Because of the considerable variation in patients' requirements at different times, an arbitrary classification was adopted.

Mild: those normally controlled by diet with or without chlorpropamide.

Moderate: those normally requiring chlorpropamide or small doses of insulin, not exceeding 20 units daily.

Severe: insulin-dependent diabetics usually requiring over 20 units daily.

Atherosclerosis

+ If neither dorsalis pedis nor posterior tibial pulse were palpable.

+ + If no pulses were present below the femoral.

+ + + If no pulses were present below the femoral (or the femoral pulse also was absent) and there were marked ischaemic foot changes such as coldness, pallor, or rubor.

Neuropathy

± If the only neurological abnormality was an absent ankle-jerk.

+ If other signs were present.

+ + If there were gross objective and subjective changes.

Of the 34 diabetic patients with foot lesions, 25 were female and nine male. The average age was 66 years, with a range from 50 to 82. Ten were hypertensive (diastolic blood-pressure of 100 mm. Hg or over). The duration of the diabetes was nine years on average, ranging from the newly diagnosed to 30 years; in seven cases the diagnosis of diabetes was made when the patient presented with a foot lesion. Nineteen cases were mild diabetics, 11 were moderate, and only four were severe.

In the majority of the 34 cases with foot lesions the three factors—atherosclerosis, neuropathy, and angiopathy—were all present together. The incidence of the various combinations of these is given in Table III (for this purpose cases with absence of ankle-jerk only have been included under Neuropathy).

TABLE III.—*Association of Atherosclerosis, Neuropathy, and Angiopathy in 34 Diabetics with Foot Lesions*

	No. of Cases
Atherosclerosis, neuropathy, and angiopathy ..	21
Neuropathy and angiopathy	7
Atherosclerosis and neuropathy	4
Atherosclerosis and angiopathy	2

A finding of note was that atherosclerosis, involving large vessels in a severe form, was absent in 21 of the 34 diabetics with foot lesions—nine had good pulsation down to ankle level and 12 had pulsation down to the popliteal artery.

Neuropathy in an obvious form occurred in 20 of the 34 cases. Only two of the 34 had ankle-jerk present, against nine out of the 16 atherosclerotics with foot lesions. Table IV indicates the severity of the atherosclerosis and neuropathy found in the diabetics with foot lesions.

TABLE IV.—*Severity of Atherosclerosis and Neuropathy in 34 Diabetic Cases with Foot Lesions*

	Severity	No. of Cases
Atherosclerosis	−	9
	+	12
	+ +	5
	+ + +	8
Neuropathy	−	2
	±	12
	+	18
	+ +	2

Sepsis and ulceration, rather than gangrene, were present in 9 of the 34 cases, and, as might be expected, all of these had neuropathy (+ or + + in degree) and 5 showed no sign of atherosclerosis.

Angiopathy was noted in all but 4 of the 34 diabetics with foot lesions. The incidence of the various degrees of angiopathy is compared with that in the group of 18 diabetics without foot lesions (Table V). Admittedly the average age in the latter group was rather lower at 55 years (range 15 to 84), but this was not thought to be of importance (see below). The sex incidence was similar to the other group, with 14 females to 4 males. The difference in the incidence of the degrees of angiopathy in the two groups, noted in Table V, is statistically significant, and this suggests there may be a positive correlation between the degree of angiopathy and the development of diabetic foot lesions.

TABLE V.—*Degree of Angiopathy Related to Incidence of Diabetic Foot Lesions*

	Angiopathy					
	−	+	+ +	+ + +	+ + + +	Total
Diabetics with foot lesions ..	4	9	7	11	3	34
Diabetics without foot lesions	2	9	6	1	0	18

Negative Diabetic Cases

In the whole diabetic group, with and without foot lesions, 6 out of 52 cases showed no evidence of angiopathy; in five a skin biopsy only was available, but in one a limb was examined. Four had foot lesions and two had none. The absence of angiopathy could not be ascribed to the mildness and short duration of the diabetes; one was severe (15 years' duration), two were moderate (11 and 13 years' duration), and three were mild (12 years', 12 years', and >1 year's duration).

Angiopathy and Various Other Factors

No correlation was obvious between the degree of angiopathy and age. The average age of those diabetics without angiopathy was 65 (53–81), with + angiopathy 54 (15–74), with + + angiopathy 71 (53–84), with + + + angiopathy 62 (50–76), and with + + + + angiopathy 71 (62–82). It is significant that angiopathy was found in the two youngest diabetics in the series, aged 15 and 24.

As regards the duration of diabetes, the incidence of the degrees of angiopathy in those of a known duration of under one year, one to five years, and over five years, respectively, was calculated. No correlation could be established between the duration of the diabetes and the degree of angiopathy. In fact there were eight diabetics with a known duration of under one year, and four of these showed + + + or + + + + angiopathy.

Similarly, with regard to severity of the diabetes, no difference in the incidence of the various degrees of angiopathy was apparent between the mild, moderate, and severe groups. Of the 10 severe diabetics seven showed only + angiopathy and one was negative.

The presence of hypertension (a diastolic blood-pressure of 100 mm. Hg or over) also failed to show a correlation with the degree of angiopathy. The three cases which were the most pronounced examples of severe angiopathy in the whole series were not hypertensive.

Non-diabetic Group

Only 3 of the 52 patients were found to have angiopathy, and this was only + in degree; one patient was a man of 50

suffering from atherosclerosis with an occlusion of the popliteal artery. The second was a man of 62 with an atherosclerotic occlusion of the femoral artery; he had also suffered from Parkinson's disease for many years. The third, a man of 60, was considered to be a healthy control; he was having a hernia repaired and there was no evidence of any vascular disease. In all three cases urine tests on several occasions failed to reveal any sugar and their glucose-tolerance tests were negative. Table VI gives the composition of the non-diabetic group.

TABLE VI.—*Details of Non-diabetic Group of 52 Patients*

Disease	No. of Patients	No. with Angiopathy
Atherosclerosis	25	2
Controls with normal arterial circulation and no evidence of systemic disease (varicose veins, herniae, etc.)	14	1
Buerger's disease	2	
Temporal (giant-cell) arteritis	1	
Embolic gangrene	1	
Scleroderma	1	
Rheumatoid arthritis	2	0
Myelomatosis with amyloid disease	1	
Myxoedema (12 years' duration, treated with thyroid)	1	
Cirrhosis of liver and regional ileitis	1	
Two sons, one daughter (adult siblings), both of whose parents were diabetic	3	
	52	3

Reaction to Intradermal Histamine

The results are given in Table VII. An abnormal reaction was taken to be one in which, even after 10 minutes, there was not both weal and flare; merely delayed reactions not obvious until 10 minutes have not been counted abnormal. The histamine-reaction result was considered in relation to the patient's blood-pressure, neuropathy, atherosclerosis, and angiopathy.

TABLE VII.—*Reaction to Intradermal Histamine*

Group	No. of Cases Tested	No. Abnormal
Diabetics with foot lesions	13	7
Diabetics without foot lesions	8	0
Non-diabetic atherosclerotics with foot lesions	6	4
Miscellaneous	17	2
Total	44	13

On analysis of the seven diabetic cases with abnormal responses, in only one did the angiopathy seem a probable explanation; in two severe atherosclerosis seemed an adequate cause; in three neuropathy appeared to be the explanation; and in one, with a good flare but no weal, the reason was not clear.

In the 21 diabetic cases tested it was not possible to demonstrate a correlation between the severity of the angiopathy and abnormal histamine reactions.

Capillary Fragility Estimations

With the technique mentioned previously a count of over 20 petechiae in the 6-cm. circle was regarded as a positive result.

Twenty of the cases tested were diabetic (average age 59) and the results were positive in six; 25 were non-diabetic (average age 55) and three of these were positive. In the diabetic cases the incidence of capillary fragility in the various grades of angiopathy was compared, but there was no evidence that it was any higher in those with more severe angiopathy.

Previous Published Work

Over the years evidence has accumulated from a number of authors, using different methods, suggesting that there might be an abnormality of very small blood-vessels in diabetics. For example, Starr (1930) studied such vessels by means of the skin response to histamine and by calorimetry; Megibow, Pollack, Megibow, Bookman, and Osserman (1949) used microplethysmography following tetraethylammonium bromide blockade; Handelsman, Levitt, and Conrad (1952) measured the skin temperature response to Priscol (tolazoline hydrochloride); and Mendlowitz, Grossman, and Alpert (1953) made use of indirect heating and tetraethylammonium chloride for a calorimetric method. (It must be mentioned that Martin (1953), using indirect heating and Priscol in patients with diabetic neuropathy, found no evidence of occlusive vascular disease.)

Studying the capillaries of the conjunctiva in living diabetic subjects by means of a stereoscopic microscope, Ditzel (1954) and Ditzel and Sagild (1954) found changes, mainly on the venous side, which were not present in controls. Following Goldenberg's paper in 1959, a number of other workers, mainly from the United States and Scandinavia, have described histological changes of a rather similar pattern: Aagenaes and Moe (1961) studied necropsy specimens from the pulp of fingers and toes and also used electron microscopy for a few biopsies; Pedersen and Olsen (1962) used skin and muscle biopsies from the legs of a small series of patients; Handelsman, Morrione, and Ghitman (1962) took punch skin biopsies from the forearms of patients; Zacks, Pegues, and Elliot (1962) studied interstitial muscle capillaries; Weber and Wicht (1962) used punch biopsies of skin and subcutaneous tissue from the ball of the great toe and correlated the findings with the results of plethysmographic studies; Bloodworth (1963) investigated mainly kidney and eye vessels but also included capillaries of muscle and subcutaneous tissue; and Bojsen-Møller (1963) examined gastro-intestinal and skin capillaries but found no specific changes in the former.

A most interesting paper has come from the Joslin Clinic (Camerini-Dávalos, Caulfield, Rees, Lozano-Castaneda, Naldjian, and Marble, 1963). Using electron microscopy, they examined skin from the lobe of the ear in subjects thought likely to develop diabetes in the future—for example, children whose parents were both diabetic. They found changes in the dermal capillaries.

British workers appear to have shown little interest in this field.

Discussion

The present findings certainly confirm the work of Goldenberg *et al.* (1959) on amputated limbs, as we have noted a lesion affecting the small vessels of diabetics characterized by proliferation of the endothelium and thickening of the basement membrane; in addition, evidence of angiopathy was found in the small vessels in skin biopsies from diabetics with healthy lower limbs and in those with less serious foot lesions in which amputation was not required.

Goldenberg *et al.* found the changes in the vessels in 2 out of 25 specimens with "arteriosclerosis obliterans" and in one out of five with thromboangiitis obliterans. Weber and Wicht (1962) observed the changes in 5 out of 29 controls. In our series the characteristic angiopathy was noted in only 3 out of 52 non-diabetics; and in the majority of our cases (the 78 skin biopsies) a strictly blind assessment was made. It has been suggested that similar angiopathy might be found in other conditions, such as autoimmune diseases or myxoedema. Of our three non-diabetics with positive findings two had atherosclerosis and one appeared healthy; no examples were found in other diseases. The angiopathy clearly cannot be considered to be a completely specific diabetic lesion, but it is very nearly so, as the 90% accuracy of our blind assessment emphasizes.

As well as in skin from the leg and in the vasa vasorum and vasa nervorum, we have noted the angiopathy in skin from the abdominal wall of diabetics and in the afferent arteriole of

the glomerulus in cases of diabetic renal disease. It has been suggested that angiopathy might play a part in the development of neuropathy, atherosclerosis, and renal and retinal lesions; and, indeed, that it should be looked on as an integral part of the diabetic state rather than as a complication.

The six diabetics who were negative are of interest: five of them had skin biopsies only, and as the small-vessel lesion may be of patchy distribution it could have been missed—for example, in one case in which the skin biopsy was negative the amputation tissue later was + + + +.

In view of the work of Camerini-Dávalos *et al.* (1963) we were very interested in the state of the vessels in two sons and a daughter of a diabetic father and mother, but none showed any sign of angiopathy.

The case of a man aged 48 was also of note; he had suffered several attacks of pancreatitis over the preceding three years and was found to have a little sugar in the urine on occasions. Glucose-tolerance tests suggested mild diabetes and the skin biopsy showed angiopathy. It would be tempting to regard such a patient as an example of "pancreatic" diabetes, but the pancreatitis might well have been merely coincidental in the course of the ordinary type of mild diabetes. In contrast, a case of haemochromatosis (bronze diabetes) examined at necropsy, and therefore not included in this series, showed no evidence of angiopathy in the skin.

Clinically there is no doubt that the diabetic and the atherosclerotic tend to suffer from different types of lower-limb lesion. The atherosclerotic usually presents with intermittent claudication and the popliteal and ankle pulses are absent; many diabetics present with gangrene of a toe despite a palpable popliteal pulse (although, of course, the diabetic may also suffer from the typical atherosclerotic lesion of large vessels).

Of our 34 diabetics with foot lesions, nine had good pulsation down to ankle level and 12 others had pulsation down to the popliteal artery. As it is unusual to have a foot lesion due to atherosclerosis if a popliteal pulse is present, it seems reasonable to blame some element peculiar to the diabetic state for the lesions in 21 out of our 34 cases.

It now appears that we must accept an occlusive angiopathy of arterioles and capillaries as another factor, in addition to neuropathy and sepsis, which probably contributes to the characteristic nature of the foot lesions suffered by the diabetic patient.

Reaction to Intradermal Histamine

Following the work of Lewis (1927) on the "triple response," Starr (1930) used the skin reaction to histamine as a means of estimating roughly the state of the circulation. Atherosclerosis diminished the reaction, but when the large arteries were healthy he thought that changes in the minute vessels might be thus detected; he found evidence of such changes in the majority of the 100 diabetics tested.

In our series 7 of the 21 diabetics tested gave abnormal results. However, despite Starr's work, in only one of these was it felt that angiopathy was likely to be the main factor responsible.

Again, Lewis (1927) noted that histamine did not produce the normal reaction in cases with degeneration of peripheral nerves; there would be a good weal, but, because of the defective axon reflex, no flare of arteriolar dilatation. Thus, as Learmonth (1953) emphasized, there would be interference with the body's response to trauma, and even if the blood supply was intact there would be a relative ischaemia so far as defence and repair were concerned.

In three of our cases with abnormal histamine reactions neuropathy seemed to explain the absence of flare. Seven cases showed a flare, in one very marked, despite + neuropathy, but it should be pointed out that these reactions were done at mid-leg, and at a more distal site the result might well have been different.

Capillary Fragility

A number of investigators have found increased capillary fragility in diabetics. Barnes (1950) studied 220 diabetics and found increased fragility in 85% of those with retinitis and in 48.5% of those without retinitis. Handelsman *et al.* (1962) suggested that there might be some relation between the increased capillary fragility and diabetic angiopathy. In our cases there was no suggestion that those with marked angiopathy had a higher incidence of capillary fragility; admittedly the numbers were small and the skin biopsies were not taken from the area used for estimating capillary fragility. From the thickening of the wall seen histologically in those capillaries with angiopathy one would not have expected them to be unduly fragile.

Summary

A characteristic angiopathy was found in the blood-vessels of the skin of the leg in 46 out of 52 diabetic cases; only 3 out of 52 non-diabetic controls showed such a lesion.

This angiopathy affected arterioles and capillaries principally and consisted of proliferation of the endothelium, together with thickening of the basement membrane.

The incidence of the severe degrees of angiopathy was significantly higher in diabetics with foot lesions than in those without; it was believed that such an occlusive lesion of small vessels could play an important part in the causation of the foot lesions commonly suffered by the diabetic patient.

We wish to thank the patients who volunteered to have a skin biopsy performed and the physicians and surgeons of the Victoria Infirmary who have co-operated in this work by allowing us to study patients under their care. In particular, thanks are due to Mr. J. P. Galloway for his encouragement, and to Dr. W. B. Davis for his advice and helpful criticism. We also thank Mr. A. Swanson, who prepared the large number of sections examined, and Mr. H. C. Gray, who provided the photomicrographs.

References

Aagenaes, Ö., and Moe, H. (1961). *Diabetes*, **10**, 253.
Barnes, R. H. (1950). *Amer. J. med. Sci.*, **219**, 368.
Bell, E. T. (1957). *Amer. J. clin. Path.*, **28**, 27.
Bloodworth, J. M. B., jun. (1963). *Diabetes*, **12**, 99.
Bojsen-Møller, F. (1963). Ibid., **12**, 429.
Camerini-Dávalos, R. A., Caulfield, J. B., Rees, S. B., Lozano-Castaneda, O., Naldjian, S., and Marble, A. (1963). Ibid., **12**, 508.
Ditzel, J. (1954). *New Engl. J. Med.*, **250**, 541.
—— and Sagild, U. (1954). Ibid., **250**, 587.
Dunn, J. S. (1940). *J. Path. Bact.*, **51**, 169.
Goldenberg, S., Alex, M., Joshi, R. A., and Blumenthal, H. T. (1959). *Diabetes*, **8**, 261.
Handelsman, M. B., Levitt, L. M., and Conrad, H., jun. (1952). *Amer. J. med. Sci.*, **224**, 34.
—— Morrione, T. G., and Ghitman, B. (1962). *Arch. intern. Med.*, **110**, 70.
Lawson, W. H. (1936). *J. techn. Meth.*, **16**, 42.
Learmonth, J. (1953). *Brit. med. J.*, **1**, 743.
Lewis, T. (1927). *The Blood Vessels of the Human Skin and Their Responses*. Shaw, London.
Martin, M. M. (1953). *Lancet*, **1**, 560.
Megibow, R. S., Pollack, H., Megibow, S. J., Bookman, J. J., and Osserman, K. (1949). *Amer. Heart J.*, **38**, 468.
Mendlowitz, M., Grossman, E. B., and Alpert, S. (1953). *Amer. J. Med.*, **15**, 316.
Oakley, W., Catterall, R. C. F., and Martin, M. M. (1956). *Brit. med. J.*, **2**, 953.
Pedersen, J., and Olsen, S. (1962). *Acta med. scand.*, **171**, 551.
Putt, F. A., and Hukill, P. B. (1962). *Arch. Path.*, **74**, 169.
Starr, I., jun. (1930). *Amer. J. med. Sci.*, **180**, 149.
Weber, H. W., and Wicht, C. L. (1962). *S. Afr. J. Lab. clin. Med.*, **8**, 83.
Zacks, S. I., Pegues, J. J., and Elliot, F. A. (1962). *Metabolism*, **11**, 381.