In addition to its direct effect upon the blood-coagulation mechanism, dextran sulphate relieved oedema in cases of thrombophlebitis and produced effects similar to those of heparin on the plasma lipoproteins and plasma cholesterol.

Our thanks are due to Professor A. P. Thomson for his interest in this study, to Drs. E. Bulmer, C. F. Hawkins, G. M. Holme, and Clifford Parsons for permission to treat and publish details of cases under their care at the General Hospital and Queen Elizabeth Hospital, Birmingham. We are indebted to Dr. M. J. Meynell for determination of the prothrombin time and other pathological investigations and to Dr. H. A. Ellis for clinical assistance. The dexulate used in this investigation was generously supplied by Messrs. Glaxo Ltd. This work was carried out while one of us (S. M. J.) was in receipt of a grant from the Medical Research Committee, United Birmingham Hospitals Endowment Fund.

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"Whatever the cause, it has been remarked at post-natal clinics how women at this stage [the early post-natal months] may indulge in very acrimonious comments about their husbands, especially in relation to their sexual demands. But this hostility, though virulent, is transient. Surely at this stage there is much conflict in the wives' minds, and they and their husbands need both support and comfort from society, rather than a demand that they should evince a bliss which theory and tradition expect. 'She's got everything she wants . . . a husband, a baby, a new home. She must be in her seventh heaven. What more can she want?' This style of comment only adds to the burden of guilt, when discontent arises. It may also induce the girl to wonder if she is abnormal, in that she cannot throw off anxiety and tension, and assume the glow which is the *sine qua non* of young mothers in magazines! Possibly now the first bitterness is sown. Certainly by the time the first child is 3 or so, it is quite common for the parents to need matrimonial guidance."—Mrs. HEIGER writing in the October issue of *Marriage Guidance*.

DEXTRAN SULPHATE: USE AS AN ANTICOAGULANT, AND ACTION IN LOWERING SERUM CHOLESTEROL

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The sulphuric esters of several polysaccharides of high molecular weight possess an anticoagulant action similar to that of heparin (Chargaff *et al.*, 1936; Astrup *et al.*, 1944). Many of these compounds cause precipitation of fibrinogen (Astrup and Piper, 1946) and agglutination of platelets (Piper, 1945), and when injected into animals lead to intractable bleeding (Astrup *et al.*, 1944). Walton (1951, 1952, 1953, 1954) showed that dextran sulphates of high molecular weight had similar biological actions but that compounds of smaller molecular weight (about 7,500) caused no such toxic effects. Ricketts (1952) prepared and studied the properties of a series of sulphuric esters of dextran which differed in molecular weight and sulphur content. Dextran sulphate of molecular weight of about 7,500 was non-toxic, but toxicity developed with increasing molecular weight. Anticoagulant activity was independent of molecular weight but depended on the number of sulphate groups for each glucose unit. Ricketts and Walton (1953) prepared a dextran sulphate which had anticoagulant action but was not toxic.

A clinical trial of dextran sulphate of optimum molecular weight and sulphur content showed that this substance was an effective anticoagulant and had an action similar to but more prolonged than that of heparin (Ricketts *et al.*, 1953).

We report the effect on the clotting-time of single and repeated intravenous injections of dextran sulphate sodium ("dexulate") and describe the use of this drug in the treatment of thrombotic disease. The change in serum total cholesterol during prolonged treatment with dextran sulphate is also described.

Methods

Measurement of Clotting-time.—By venepuncture 2 ml. of blood was withdrawn, using a sterile dry syringe, and approximately 0.5 ml. of blood was added to each of three clean, dry test-tubes, 0.75 cm. internal diameter. The test was timed from the entry of blood into the syringe. The tubes were at once placed in a water-bath at 37° C., and at intervals of one minute each tube was lifted and tilted through 90 degrees. When the blood did not flow on tilting, the tube was inverted and gently shaken, to break the film of clot on the surface of the blood. The end-point was reached when no blood flow occurred with this manœuvre. The average of the results from the three tubes was taken as the clotting-time. In the control of dextran sulphate therapy this method of estimating clotting-time was more satisfactory than determining the end-point of clotting by tilting to 90 degrees only. By the latter method lower values were obtained, which did not give a reliable guide to the control of dosage. In two patients an attempt was made to control therapy by clotting-times measured without inversion

and shaking of the tubes, but this led to overdosage with the development of toxic effects.

Estimation of Serum Total Cholesterol.—To 24 ml. of a mixture of equal parts of acetone and ethyl alcohol was added 1 ml. of serum and the mixture allowed to stand for 18 hours. It was then centrifuged and 5 ml. of the supernatant was evaporated to dryness. The residue was dissolved in 5 ml. of chloroform, and 3 ml. of a reagent prepared by mixing one part concentrated H_2SO_4 and 10 parts acetic anhydride was added to the solution. The mixture was placed in the dark at 20° C. for 20 minutes, and then the intensity of green colour was measured in a colorimeter (EEL), using Ilford 204 tricolor red filter. A standard solution of cholesterol in chloroform was estimated with each batch of sera. To exclude physico-chemical interference with the estimation, samples of blood from untreated patients were divided into two portions. To one portion was added dextran sulphate to produce a concentration of 1% (three samples) and 0.1% (one sample), and to the other an equal volume of saline. The serum total cholesterol was then estimated. On no occasion was there a difference greater than 5 mg./100 ml. between the serum total cholesterol of each pair. Thus dextran sulphate in concentrations of 0.1 and 1% did not interfere with the method by which serum total cholesterol was estimated.

Standardization of Dextran Sulphate.—The anticoagulant activity of dextran sulphate was at first assayed in terms of international standard heparin units. This was unsatisfactory, and a new unit of dextran sulphate has been defined as the activity of 0.04 mg. of a standard preparation of dextran sulphate kept in the Department of Biological Standards, National Institute for Medical Research, London (Mussett and Perry, 1956). One dextran sulphate unit is approximately equivalent in anticoagulant activity to one international unit of heparin. We have expressed all doses of dextran sulphate in terms of standard dextran sulphate units.

Effect on Clotting-time of a Single Intravenous Injection of Dextran Sulphate

A single intravenous injection of 7,500 units of dextran sulphate was given to each of six volunteers, and the clotting-time was measured during the following eight hours. The initial clotting-time before the injection was the average of three separate estimations.

Table I shows that in four of the six cases the clotting-time was prolonged to more than twice the initial level for six hours. In the other two cases the corresponding periods of prolongation were about three and five hours respectively.

TABLE I.—*Effect on Clotting-time of Single Intravenous Injection of 7,500 Units of Dextran Sulphate*

Patient	Patient's Weight (Kg.)	Initial Clotting-Time (Min.) (Mean of Three)	Clotting-time (Min.) at Intervals After Dextran Sulphate				
			30 min.	2 hr.	4 hr.	6 hr.	8 hr.
1	43·2	5	23	22	16	14	10
2	67·8	8	64	25	21	20	14
3	67·6	5	20	12	12	10	8
4	61·0	6	22	13	7	7	—
5	72·2	6	26	29	20	12	10
6	81·2	8	77	33	24	8	—

Effect on Clotting-time of Repeated Intravenous Injections of Dextran Sulphate

Repeated intravenous injections of dextran sulphate were given to 11 patients, of whom seven had acute myocardial infarction, three had persistent angina following a previous myocardial infarction, and one had thrombosis of the inferior vena cava. In each case the clotting-time before starting treatment was the average of three separate estimations. An attempt was made to prevent the clotting-time falling below twice the level before treatment. The dose of dextran sulphate was kept constant at 5,000 units, and the frequency of dose was varied, depending on the clotting-time, which was measured at intervals during each day.

It was found that injections were required eight-hourly during the first 24 hours. Thereafter the frequency could be reduced, and after 48 hours the clotting-time could be maintained at a minimum of twice the pre-treatment level with injections every 12 hours. In all patients who continued treatment long enough, one injection every 24 hours was sufficient from the eleventh day onwards, and in most patients this dosage was sufficient much earlier. In nine courses of treatment with dextran sulphate lasting 14 days or longer the average dose on each day is shown in Fig. 1. Illustrative cases showing the control of the clotting-time by repeated doses of dextran sulphate are shown in Figs. 2 and 3. The clotting-times recorded were measured immediately before the next injection was given—that is, they are minimum values.

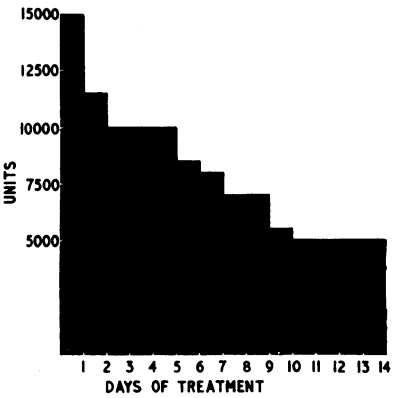

FIG. 1.—Average dose of dextran sulphate on each day of treatment in nine cases.

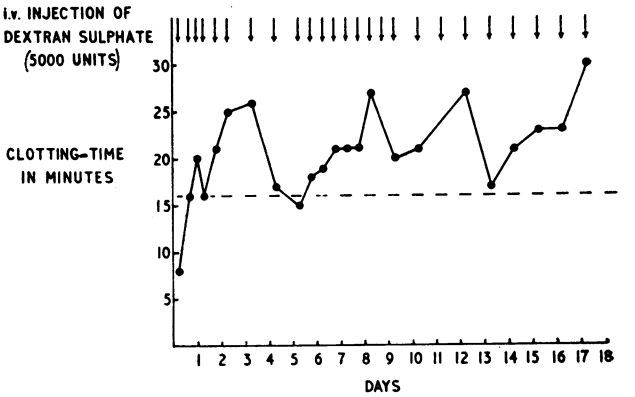

FIG. 2.—Control of clotting-time during treatment with dextran sulphate in a patient with persistent angina following myocardial infarction. Twice the clotting-time before treatment is indicated by the broken line.

At the end of treatment the return of the clotting-time to normal was gradual, taking three to four days.

The variation in clotting-time during 24 hours after an injection of 5,000 units of dextran sulphate was studied in one patient on the first and fourteenth days of treatment. On the first day, when the clotting-time was prolonged to about two and a half times the normal value as a result of an injection of dextran sulphate, a second injection was given. Following this there was an abrupt initial rise followed by a steady fall, to reach twice the patient's normal value in five hours (Fig. 4). In the second series of observations, made when the patient had been stabilized on one injection of dextran sulphate daily, there was a similar initial rise, but the fall was much more gradual, and a satisfactory

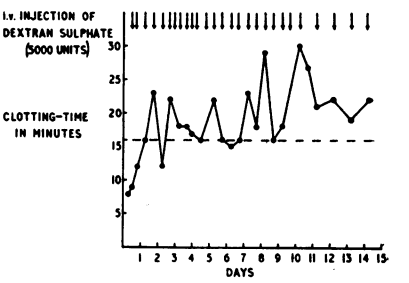

FIG. 3.—Control of clotting-time during treatment with dextran sulphate in a patient with acute myocardial infarction. Twice the clotting-time before treatment is indicated by the broken line.

anticoagulant effect persisted for over 24 hours (Fig. 4). It should be noted that in both series of observations the clotting-time immediately before the injection was prolonged to approximately the same extent.

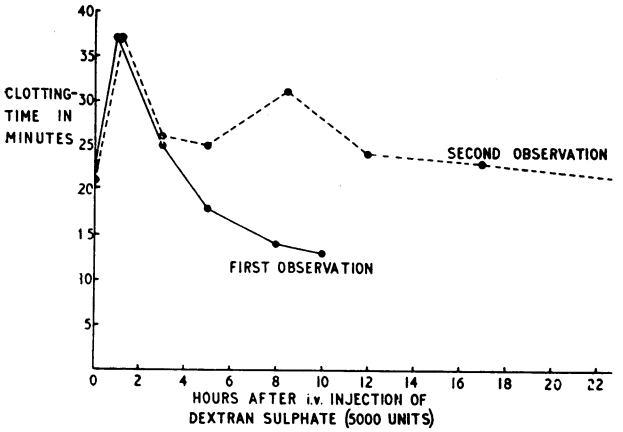

FIG. 4.—Change in clotting-time following an intravenous injection of 5,000 units of dextran sulphate on the first day of treatment (first observation) and the fourteenth day of treatment (second observation) in the same patient.

Effect of Dextran Sulphate on Serum Total Cholesterol

In nine cases the serum total cholesterol was measured before and at intervals during treatment with dextran sulphate; the results are shown in Fig. 5. The value for serum cholesterol before treatment is the average of at least two separate estimations, and in each case not less than four subsequent values were obtained and expressed as percentages of the initial value. There was a marked fall in serum total cholesterol in all cases, reaching 50–60% of the initial level after 6–12 days of continuous treatment. The average value of serum total cholesterol before treatment, the lowest level recorded, and the day of treatment on which this occurred are shown in Table II.

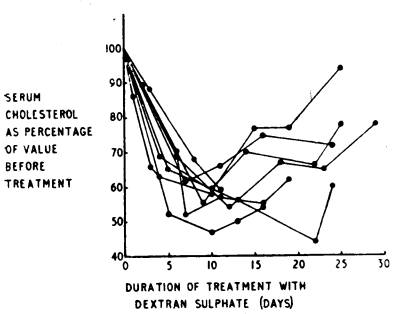

FIG. 5.—Change in serum total cholesterol during treatment with dextran sulphate in nine cases.

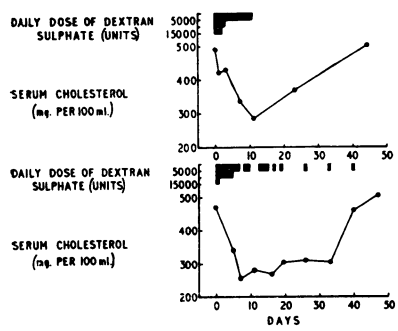

FIG. 6.—Change in serum total cholesterol in a patient with familial hypercholesterolaemia (1) during and after continuous treatment with dextran sulphate (upper curve), and (2) during a second course of continuous treatment followed by weekly injections (lower curve).

However, this fall was not sustained, and in seven patients whose treatment was continued for more than 14 days the value of serum total cholesterol began to revert towards the original level. In six of these patients it was noted that the rise corresponded with the reduction in dosage from 10,000 to 5,000 units daily.

A patient with familial hypercholesterolaemia was given two courses of dextran sulphate, and a profound fall in serum total cholesterol occurred on both occasions (Fig. 6). Thirteen days after the first course of treatment had been stopped the serum total cholesterol was still only 76% of the original value. After the second course of treatment weekly intravenous injections of 5,000 units of dextran sulphate were given, and at first the reduction in serum cholesterol appeared to be maintained; but these weekly injections did not prevent the return of serum total cholesterol to its original level within 28 days (Fig. 6).

TABLE II.—*Maximum Fall in Serum Total Cholesterol During Dextran Sulphate Treatment*

Patient	Average Serum Total Cholesterol Before Treatment (mg./100 ml.)	Lowest Serum Total Cholesterol (mg./100 ml.)	Day of Treatment on which Serum Total Cholesterol was Lowest
1 {	486	287	11
1 {	486	254	7
2	258	115	22
3	320	190	10
4	230	125	12
5	207	115	9
6	180	105	9
7	292	180	7
8	435	205	10

Patient 1 received two separate courses of treatment.

One patient, whose serum total cholesterol at the end of continuous treatment was approximately 60% of the original level, was given weekly intravenous injections of 5,000 units of dextran sulphate. With this dosage the reduction in serum total cholesterol persisted for only seven days. Another patient, whose serum total cholesterol at the end of continuous treatment was 78% of the value before treatment, was given weekly injections of 10,000 units of dextran sulphate. In this case the cholesterol had returned to its original level in nine days and thereafter did not fall.

Toxic Effects

A mild degree of alopecia was observed in three male patients, occurring after 14–21 days of continuous treatment. No other toxic effects were noted in this series of patients when the dosage of dextran sulphate was controlled as described above. Two additional patients, not included in the present study, developed diarrhoea, with the passage of blood in the stools after 14 days of treatment. The dosage in these two cases was controlled by clotting-times measured by simply tilting the tubes, without inverting and shaking, with the result that lower values of clotting-time were recorded. In an attempt to maintain prolongation of the clotting-time, a higher dosage of dextran sulphate was given to these two patients than to any of the other patients. There was a profound fall in serum total cholesterol in both these cases, from 230 to 65 mg. and from 340 to 130 mg. per 100 ml. respectively.

Discussion

At present the regime of anticoagulant therapy most frequently employed is intravenous injections of heparin, usually given at six-hourly intervals for two days, followed by oral administration of ethyl biscoumacetate or phenindione. A serious drawback to the use of heparin is that frequent intravenous injections are required to maintain an adequate prolongation of the clotting-time.

We have shown that following a single intravenous injection of 7,500 units of dextran sulphate, the clotting-time was prolonged to more than twice the normal for four to six hours. Duff *et al.* (1951) reported that an intravenous injection of 7,500 units of heparin resulted in lengthening of the clotting-time to twice normal for only three to four hours. The response of different subjects to a single dose of dextran sulphate was variable, as with heparin (de Takats, 1943).

A more important finding is the cumulative effect of dextran sulphate. Three injections, each of 5,000 units, were required in the first 24 hours, but thereafter the frequency of dosage decreased, so that with most patients injections at

12-hourly intervals were sufficient to maintain suitably prolonged clotting-times from the third or fourth day of treatment onwards. The frequency of dosage could be further reduced to once daily after 5 to 11 days of treatment.

We have tried to keep the clotting-time continuously greater than twice normal and have not allowed it to fall to an almost normal level between injections, as is often permitted during heparin treatment.

In all patients cumulation has proceeded until eventually one injection of 5,000 units every 24 hours was sufficient. Thereafter no further cumulation appeared to occur, although two patients were treated for a further period of over two weeks with 5,000 units every 24 hours. Ricketts *et al.* (1953) also obtained evidence of an additive effect after several injections of dextran sulphate.

Dextran sulphate appears to be a suitable substitute for heparin in initial anticoagulant treatment. Heparin is commonly used only for 48 hours until ethyl biscoumacetate or phenindione has become effective; for this purpose the present results suggest that 5,000 units of dextran sulphate given eight-hourly for 24 hours and then 12-hourly for a further 24 hours would be safe and effective in prolonging the clotting-time.

Continuous treatment over a period of several weeks is a practical procedure with dextran sulphate, as with many patients one injection daily sufficed after the first week. This has some advantages over the combination of heparin and oral anticoagulant. One venepuncture daily for the injection of dextran sulphate is not any more arduous than the daily venepuncture required to obtain blood for estimating the prothrombin time. Our results suggest that, once the period of maintenance treatment is reached, estimations of clotting-time are necessary only every two or three days. As with heparin, the anticoagulant effect of dextran sulphate can be quickly neutralized with protamine sulphate (Walton, 1951).

Reports have appeared of certain other sulphated polysaccharides—the polysulphuric esters of polyanhydromannuronic acid, polyhexuronic acid, and polygalacturonic acid—which have been found to have clinical value as anticoagulants (Seifter and Begany, 1948; Hirschboeck and Madison, 1950; Mangieri *et al.*, 1951; Scholz and Barker, 1952). There have been several reports of undesirable side-effects following the use of these compounds; the commonest toxic manifestations appear to have been alopecia and diarrhoea (Hirschboeck *et al.*, 1954), but generalized vasomotor collapse has also occurred (Sorenson and Wright, 1950).

Since Hahn (1943) showed that an injection of heparin cleared the turbidity of lipaemic plasma in dogs, many workers have confirmed this in man (Anderson and Fawcett, 1950; Block *et al.*, 1951; Utz *et al.*, 1953). There is evidence that the degree of clearing of turbidity of alimentary lipaemia by heparin is less in coronary artery disease than in normal persons (Block *et al.*, 1951; Oliver and Boyd, 1953). It has been shown that transient changes in the distribution of the lipoprotein fractions occur after the injection of heparin (Graham *et al.*, 1951; Rosenberg, 1952; Chandler *et al.*, 1953), but most workers have noted no effect on the total amount of cholesterol in the blood following a single injection of heparin (Anderson and Fawcett, 1950; Block *et al.*, 1951; Eder and Russ, 1952; Chandler *et al.*, 1953; Herzstein *et al.*, 1954; Soffer and Murray, 1954).

Repeated doses of heparin at intervals of 2 to 14 days kept the lipoprotein pattern altered in some patients but had little or no effect on the serum cholesterol (Graham *et al.*, 1951). However, Basu and Stewart (1950) reported that heparin in therapeutic doses produced a fall in the level of serum cholesterol after 24 hours, and Hollister and Kanter (1955) found that in two patients with essential hyperlipaemia intravenous injections of 100 mg. of heparin three times weekly produced a fall in all fractions of the blood lipids. Daily intramuscular injections of heparin in chicks produced a small decrease in total plasma cholesterol and other lipid fractions after four weeks (Opdyke *et al.*, 1955).

W. D. Brown (1952) reported that dextran sulphate had similar effects to heparin in clearing alimentary lipaemia, and single doses of other polysulphated esters of polysaccharides—"treburon" and "paritol"—have also been shown to clear alimentary lipaemia (Brown *et al.*, 1952; Ackerman and Zilversmit, 1953) without influencing serum cholesterol levels (Zinn *et al.*, 1952). On the other hand, Chandler *et al.* (1953) found that treburon given by buccal absorption produced a significant reduction in serum cholesterol and serum phospholipids five to seven hours after administration. Treburon given under these conditions had no effect on the clotting-time.

We have shown that intravenous injections of 5,000 units of dextran sulphate two or three times daily consistently produced a profound fall in serum total cholesterol. This reduction in cholesterol was not maintained when the dosage was reduced to 5,000 units daily in response to the lengthened clotting-time. With the methods of administration investigated so far, it has not been found possible to produce a sustained fall in the serum total cholesterol without an excessive prolongation of the clotting-time.

Summary

A single intravenous injection of 7,500 units of dextran sulphate produced an increase in the clotting-time to more than twice normal for four to six hours.

With repeated injections of dextran sulphate, cumulation occurred so that the clotting-time could be maintained at more than twice normal by a dosage of 15,000 units in the first 24 hours, 10,000 units daily for the next 4 to 10 days, and thereafter 5,000 units daily.

During treatment with dextran sulphate there was at first a profound fall in serum total cholesterol. This reduction persisted only while the dosage was 10,000–15,000 units daily.

It is suggested that dextran sulphate is an effective anticoagulant for clinical use and provides a possible alternative to the usual combination of heparin and oral anticoagulant. However, toxic effects may occur, particularly if the dose is not carefully controlled.

The development of a mild degree of alopecia was observed in three male patients. Overdosage in two cases resulted in diarrhoea, with the passage of blood in the stools.

We wish to express our thanks to Professor G. M. Wilson for much helpful advice and criticism; to Dr. A. Jordan and the staff of the Department of Chemical Pathology, Royal Infirmary, Sheffield, who performed all the estimations of serum total cholesterol; to Dr. H. Swan, for assistance with the early part of the work; and to Glaxo Laboratories Ltd., who supplied the dextran sulphate used in this work.

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PLACE OF DIRECT SURGERY IN TREATMENT OF OBLITERATIVE ARTERIAL DISEASE*

BY

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Obliterative arterial disease may be due to a variety of causes, including thrombosis after an injury, coarctation of the aorta, thromboangiitis obliterans, an embolus, or the condition of so-called primary arterial thrombosis. I shall not discuss the place of direct surgery in the treatment of these lesions beyond mentioning that it is the best treatment for coarctation of the aorta and for thrombosis of a major artery after an injury, a good treatment for primary thrombosis and some emboli, but only occasionally possible in patients with thromboangiitis obliterans. I am concerned mainly with atherosclerosis and the place of arterial reconstruction operations in the treatment of this all too common disease.

Atherosclerosis is a general disease which affects the arteries of the whole body, and it is an important principle that an arterial reconstruction operation can have only a local effect. Therefore this type of surgery is justified only when the local manifestations of this general disease predominate to an unusual extent. In many patients symptoms arise from the occlusion of several arteries, and it is obviously a mistake to reconstruct the femoral artery of a patient who suffers from both angina pectoris and intermittent claudication. On the other hand, it is justifiable to reconstruct the femoral artery of a patient who suffers from angina pectoris and gangrene of a toe; from the patient's point of view an arterial reconstruction operation is a smaller procedure than a major amputation (Rob, Eastcott, and Owen, 1956). Fortunately, in a fair proportion of patients atherosclerosis remains relatively localized. This is particularly so in patients with occlusion of the abdominal aorta or iliac arteries, and sometimes so in those with thrombosis of the popliteal, femoral, carotid, mesenteric, renal, and subclavian vessels. In my view, at least 50% of patients with occlusion of the abdominal aorta and iliac arteries are suitable for a reconstruction operation, about 25% of those with femoro-popliteal thromboses, and probably about 5% of those with an internal carotid thrombosis, although this latter figure is merely a rough estimate.

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Thrombosis of Abdominal Aorta and Iliac Arteries

The symptoms produced by this lesion are variable. One patient may be able to walk slowly for half a mile before the onset of the pain of intermittent claudication, and another with an almost identical thrombosis may have gangrene; the symptoms depend upon the efficiency of the collateral circulation. From a surgical point of view this lesion may be divided into two types—the extensive occlusion extending from the iliac arteries below to the renal arteries above (Fig. 1), and the localized occlusion usually confined to the region of the bifurcation of the abdominal aorta (Fig. 2).

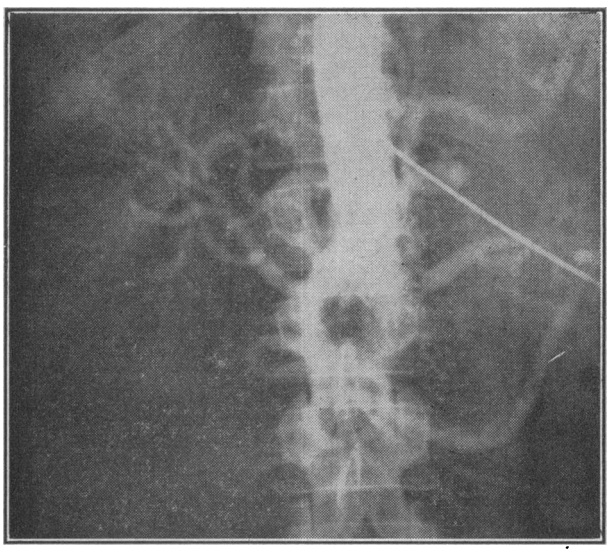

FIG. 1.—Thrombosis of the abdominal aorta in a man aged 36. The occlusion has reached the renal arteries and there is a partial occlusion of the left renal artery. The patient had grade IV hypertension with a blood pressure of 210/110.

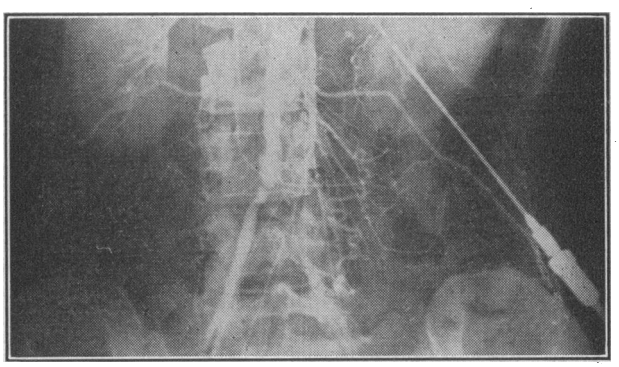

FIG. 2.—Thrombosis localized to the region of the aortic bifurcation. This patient, a woman aged 34, had gangrene of her right foot. An arterial reconstruction was successful.

It is a relatively simple matter to restore the blood flow in most of the patients with the localized type of occlusion. We have had only one death out of 28 such operations and only two recurrent thromboses, and each of these affected only one iliac artery. On the other hand, those with high occlusions present a major problem and require a major operation. For these patients it is necessary to clamp the aorta above the renal arteries and insert a plastic prosthesis or homologous arterial transplant from this level to the iliac arteries. Two of our seven patients with this lesion have died as a result of the operation, both from renal failure, but the risk of this has been reduced by using hypothermia. Because of the good results obtained with surgery in those patients with localized occlusions and the high mortality of conservative care in those with an occlusion which has