

The present investigation has confirmed that a deficiency of folic acid is very common in late pregnancy, and can readily be prevented by prophylactic administration of this vitamin. The risk of inducing neurological changes in an unrecognized case of Addisonian anaemia, in this age-group and with such a short course of treatment, is exceedingly slight. We therefore have not thought it necessary to add vitamin B₁₂ to our prophylactic regimen. Over the age of 30, however, patients with megaloblastic anaemia of pregnancy should be investigated with Addisonian anaemia in mind. In the two hospitals concerned no case has been found in association with pregnancy during the last three years. Francis and Scott (1959) appear to have reached similar conclusions.

Summary

In order to study the routine administration of folic acid during the last trimester of pregnancy, the haemoglobin levels at term of 758 women treated with folic acid and iron have been compared with 721 controls treated with iron alone. The mean haemoglobin in the group treated with folic acid was 82.2%, as against 79.82% in the controls. The difference of 2.38% is statistically significant ($P < 0.01$). Folic acid appeared to raise the haemoglobin not only of anaemic patients but also of normal women, resulting in a higher haemoglobin value at all levels.

A comparison of the 721 controls with 983 pregnant women who attended the antenatal clinic before routine iron prophylaxis in hospital was begun has shown a rise in the haemoglobin at term from 73.4 to 79.82%.

66% of women had haemoglobins of less than 80% when they first attended hospital, but in the majority the anaemia responded to treatment even in the control group. In at least 20% of patients who remained anaemic despite treatment there was a sharp rise in the haemoglobin after delivery.

A further 66 cases of megaloblastic anaemia of pregnancy have been reported, 45 of which were diagnosed during the period of the folic-acid trial. There were no cases of the disease in the group treated with folic acid, but the incidence in the control group was also somewhat lower than in the past. The overall incidence was 1.2% of all hospital confinements. In 14 out of 41 cases of megaloblastic anaemia there was evidence of diminished fat-absorption.

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NATURAL HISTORY OF STREPTOCOCCUS FAECALIS ENDOCARDITIS

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Bacterial endocarditis due to *Streptococcus faecalis* has certain distinct features. These must be recognized so that an early diagnosis can be made and effective treatment given. Andrewes and Horder (1906) and Horder (1909) were the first in this country to draw attention to bacterial endocarditis due to this organism. In recent years the importance of this condition has grown because of its resistance to antibiotic therapy. Geraci and Martin (1954) reviewed 33 cases and noted that in 15 there was no underlying heart lesion and that many followed operations on the genito-urinary and gastrointestinal tracts. They emphasized the high mortality with inadequate treatment. Rantz and Kirby (1943) found that the human infections usually caused by this organism were acute suppurative otitis media, infections of the urinary tract, terminal peritonitis in association with coliform bacillus, and subacute bacterial endocarditis. The incidence of this infection in bacterial endocarditis is variously reported as 3.2% (Sirota *et al.*, 1947), 3.8% (Loewe *et al.*, 1951), and 5-10% (Robbins and Tompsett, 1951). Geraci and Martin (1954) thought that there might have been a relative rise in incidence in the past ten years.

Present Investigation

We here give a review of eight patients with bacterial endocarditis due to *Str. faecalis* (or enterococcus) out of a total of 49 proved cases of bacterial endocarditis admitted to this hospital in the past nine years. In addition, there was one patient with bacterial endarteritis due to this organism. The course of the disease and the problems of treatment are discussed.

Only bacteriologically proved cases are included. Table I gives a list of the various organisms identified. The three cases with a non-haemolytic streptococcus are considered separately because of the different bacteriological properties of that organism and because it is less resistant to penicillin and streptomycin than the average *Str. faecalis*.

TABLE I.—Organisms Identified in 49 Cases

Organism	No.	Percentage of Total
<i>Str. viridans</i>	28	57
" <i>faecalis</i>	8	16
<i>Staphylococcus pyogenes</i> .. .	5	10
Non-haemolytic streptococcus .. .	3	6
<i>Pneumococcus</i>	2	4
<i>Bacillus aerogenes</i>	1	2
<i>Str. pyogenes</i>	1	2
" <i>agalactiae</i>	1	2

Bacteriology.—The organism belongs to group 1 of Lancefield's classification. It is usually non-haemolytic. It grows freely in ordinary laboratory media and is heat-resistant. It is usually resistant to penicillin, and may readily develop resistance to other antibiotics. It is a saprophyte in the mouth, intestine, and vagina. In this study each of the strains of *Str. faecalis* conformed to the following characteristics. Morphologically they were Gram-positive oval-shaped cocci, arranged in pairs or short chains. On blood agar their colonies were grey, shiny, and circular. On MacConkey's bile-salt-neutral-red-lactose agar their colonies were small and red, with deep-red centres. The sensitivities of the strains to antibiotics in Cases 2, 3, 4, 7, and 9 were tested *in vitro* by "sentest." The strains in Cases 4 and 7

were apparently sensitive to penicillin and those in Cases 4, 7, and 9 apparently sensitive to streptomycin. These results, based as they are on sentest alone, are not thought sufficient to exclude these strains from the present study. The strains in Cases 1, 5, 6, and 8 were determined by sentest and also by the tube-dilution method. The pattern of their sensitivities to the different antibiotics is therefore much more accurately determined.

Clinical Features.—Table II summarizes the histories of the eight cases of subacute bacterial endocarditis and the only case of *Str. faecalis* endarteritis superimposed upon a traumatic arteriovenous aneurysm. The age incidence varied from 20 to 77. Six of the nine patients were 60 or over, and five of the nine were men. The duration of symptoms varied from 10 days to 24 weeks, the average being 9 weeks.

The source of infection in three patients (Cases 3, 6, and 7) appeared to be in the renal tract, in three patients (Cases 1, 4, and 8) in septic teeth, and in one (Case 2) in a liver abscess. In Cases 5 and 9 no focus of infection was found.

Results of Treatment.—Two patients (Cases 1 and 8) were effectively treated with massive doses of penicillin

TABLE II

Case	Sex and Age	Duration of Symptoms in Weeks	Evidence of Underlying Heart Lesion	Focus of Infection and Portal of Entry	<i>Str. faecalis</i> Antibiotic Sensitivity					Antibiotic Therapy	Comment		
					P.	St.	T.	C.	E.				
1	M 68	4	None	Periapical abscess	Slightly Inhibited by Abscess	S. 0	R. 1	S. 50	<3	<3	—	P. 2-8 mega units daily—5 weeks	Cured
2	M 66	78	None	Stone in common duct. Cholecystitis liver abscess	Wound Blood	R. R. R. R.	R. R. R. R.	S. S. S. S.	S. S. S. S.	—	—	Short courses of i.v. T., C., oral T. P. 1 mega unit and St. 1 g. daily last 3 wks.	Apical systolic murmur developed in hospital. Blood cultures negative while on P. and St. Died of cerebral haemorrhage. Necropsy showed vegetations in mitral valve. No stenosis or thickening of chordae tendineae
3	F 64	12	Chorea at 12	Repair of cystocele three months previously. "Edentulous"	1st admission	R. R. R.	R. R. R.	S. S. S.	S. S. S.	—	—	P. 2 mega units and St. 2 g. daily 1 week. T. 1.5 g. daily for 8 wks. P. 8 mega units, St. 2 g.→1 g., and probenecid 2 g. daily for 8 wks.	No response initially. Blood sterile while on tetracycline. Clinical improvement. Relapse 1 month later. Cured with P. and St. Moderate deafness and dizziness
4	M 77	12	Harsh apical systolic murmur 6 months previously	Dental sepsis		S. S. S.	S. S. S.	S. S. S.	—	—	—	P. 8 mega units, St. 2 g., and probenecid 1.5 g. daily for 7 wks	Cured. Heart signs unchanged
5	F 34	712	Mitral stenosis. Aortic stenosis and incompetence	Teeth healthy. No focus found	Resistant to Inhibited by Urine Blood	—	>50	—	—	—	—	P. 4-8 mega units, St. 2-1 g., and probenecid 2 g. daily for 8 wks	Infection apparently cured. Slight vestibular damage. Died of congestive cardiac failure 5 wks later. No necropsy
6	M 60	4	None	Removal of ureteric calculus 4 months previously	Inhibited by	6	—	<3	6	—	—	P. 4-16 mega units and St. 4 g., daily for 5 wks. Chlor-tetracycline 2 g. for 2 wks	Developed gross aortic incompetence. Infection apparently cured. Died 5 months later of congestive cardiac failure. No necropsy
7	F 53	3	Previous mitral valvotomy. Mitral stenosis. Aortic stenosis and incompetence	Pyelonephritis 3 wks previously. "Edentulous"		S. S. S.	S. S. S.	S. S. S.	—	—	—	P. 4 mega units St. 2 g., and probenecid 2 g. daily for 6 wks	Infection apparently cured. Slight vestibular damage. Aortic incompetence worsened. Died 6 wks later. Necropsy showed small vegetation on anterior aortic cusp (? sterile) and perforation of cusp
8	M 20	1½	Aortic incompetence. Mild mitral stenosis. Previous subacute bacterial endocarditis due to <i>Str. viridans</i>	Erupting tooth with infection	Inhibited by	S. 0.05	R. 50	S. <3	S. 3	—	—	P. 4 mega units daily for 6 wks	Cured. Aortic incompetence worsened
9	F 60	24	Normal heart. Traumatic arteriovenous aneurysm of right common carotid artery after mastoidectomy	No focus found. "Edentulous"		R. S. S.	S. S. S.	S. S. S.	—	—	—	St. 2-1 g. daily for 4 wks. Oral P. V 3 g. daily 4 wks after	Cured. Slight vestibular damage, recovering subsequently

P.=Penicillin. St.=Streptomycin. T.=Tetracycline. C.=Chloramphenicol. E.=Erythromycin. R.=Resistant. S.=Sensitive. The sensitivity tests were performed by either the Evans sentest technique or the tube-dilution method. The "edentulous" state was purely a clinical observation. Penicillin concentrations are expressed in units per ml. Streptomycin, tetracycline, and chloramphenicol concentrations are expressed in µg. per ml.

alone, and two (Cases 3 and 4) with the combined regime of penicillin and streptomycin. The case of bacterial endarteritis was cured by streptomycin and oral penicillin. Case 3 responded to oral tetracycline clinically, and bacteraemia was suppressed during therapy, but she relapsed a month after treatment. She was subsequently cured with combined penicillin and streptomycin.

Deaths.—Four of the nine patients died. Three deaths occurred 5, 6, and 20 weeks after the end of apparently successful treatment, and were from congestive heart failure. The fourth died from cerebral haemorrhage while being treated.

Illustrative Cases

The following case summaries illustrate a number of interesting points.

Case 2.—A man of 66 had no significant past history apart from a minor stroke 12 months previously. He was admitted to hospital with typical biliary colic and was treated conservatively. Two months later he was readmitted with obstructive jaundice. At laparotomy a stone was found in the common bile-duct. The gall-bladder was inflamed. An abscess found in the right lobe of the liver was drained and *Str. faecalis* isolated. He was treated with intravenous tetracycline for two weeks and oral neomycin for two days. The jaundice subsided. He remained anaemic and unwell, and developed a bed sore from which *Str. faecalis* was isolated. A low-grade pyrexia persisted. Transfusion and a course of chloramphenicol were given with temporary improvement. At this stage, some three months after admission, *Str. faecalis* was isolated from a number of blood cultures. It was resistant to penicillin and streptomycin and sensitive to the broad-spectrum antibiotics *in vitro*. An apical systolic murmur was heard for the first time. Tetracycline was given for two weeks, but bacteraemia persisted. Combined therapy with penicillin and streptomycin sterilized the blood-stream, but the patient died suddenly of a cerebrovascular accident three weeks after the beginning of treatment. At necropsy vegetations were found on the mitral valve, which showed no evidence of previous rheumatic disease.

Comment.—Clearly the focus of infection here was the biliary tract and liver. The bacterial endocarditis appeared to have developed on a normal valve. Blood cultures remained positive while the patient was receiving tetracycline.

Case 6.—A dental surgeon of 60 had previously had regular medical examinations, which revealed no evidence of valvular disease. Four months previously a ureteric calculus had been removed in another hospital, to which he was later readmitted with malaise, vague pains, and transient loss of vision. On examination, an apical systolic murmur was noted; E.S.R. was 40 mm. per hour (Westergren). Coliform bacilli and *Str. faecalis* were isolated from his urine, and the latter organism was also cultured from his blood. A course of streptomycin, 2 g. daily, was given for a week, the treatment being continued at home with chlortetracycline for two weeks. He remained unwell. On admission to this hospital he was found to have aortic incompetence, splenomegaly, and anaemia. *Str. faecalis* was again isolated from the blood-stream. It was resistant to penicillin and streptomycin, and sensitive to tetracycline and chloramphenicol *in vitro*. Massive doses of penicillin, increasing from 4 to 16 mega units daily, with 4 g. of streptomycin, reducing to 2 g. daily, appeared to control the infection. Repeated blood cultures were sterile. However, he developed mild vertigo and died from congestive cardiac failure five months after the cessation of antibiotic therapy.

Comment.—In this case the subacute bacterial endocarditis followed a urological operation. Delay in diagnosis with inadequate initial antibiotic treatment had

unfortunate results. Mitral and aortic incompetence were apparently caused by infection superimposed on normal valves. Although the infection was successfully controlled, the heart failure progressed and was the cause of death.

Case 3.—A housewife aged 64 had chorea as a child and repair of cystocele three months prior to admission. No heart murmur was recorded then. Ever since the operation she had felt unwell, with vague pains and a low-grade fever. On admission she was found to have mild pyrexia, mitral incompetence, splenomegaly, raised E.S.R., and a mild normochromic anaemia. Urine culture was sterile. *Str. faecalis* was isolated from the blood-stream in repeated cultures. It was resistant to penicillin and streptomycin and sensitive to all broad-spectrum antibiotics. Two mega units of penicillin and 2 g. of streptomycin given daily for a week had no effect. Bacteraemia persisted. She was given 1.5 g. of oral tetracycline daily for eight weeks with clinical improvement and suppression of bacteraemia, but the infection relapsed a month later. This time she was given 8 mega units of penicillin intramuscularly with 2 g. of probenecid orally and 2 g. of streptomycin daily for two months with complete cure. She was well four months later and blood cultures remained sterile, though a moderate degree of eighth-nerve damage persisted.

Comment.—This case underlines our opinion that broad-spectrum antibiotics should not be used by themselves in this condition, even though the organism is sensitive to these drugs. Moreover, failure to respond to relatively normal doses of penicillin and streptomycin should not tempt one to abandon this regime, but emphasizes the need for much higher doses of these antibiotics until response is achieved.

Discussion

The recorded incidence of this form of bacterial endocarditis varies from 3% to 10%. It occurred in 16% of 49 cases in the present series. The peak incidence in men has been said to occur at about 60 years and in women at about 30. This corresponds with the age when men suffer from urological disorders and with the peak incidence of abortions in women.

The precipitating factors are many and varied. The association of this form of endocarditis with oral infection, such as a periapical abscess, though uncommon, has been recorded (James, 1952; Geraci and Martin, 1954). The urinary tract is by far the commonest focus of infection in most cases. This is not surprising in view of the high frequency of positive cultures of *Str. faecalis* from the urine of patients with infections of the urinary tract. It is interesting to note that transient bacteraemia has been said to occur in 45% of patients who have had transurethral resections (Creevy and Feeney, 1949). Merritt (1951) reported a rather high incidence of 8% of bacterial endocarditis after transurethral resection in 7,000 cases. The precipitating factors in the four cases of *Str. faecalis* endocarditis reported by Finn and Kane (1952) were prostatectomy, urethral dilatation, and removal of a renal calculus. In two of the three cases recorded by Cates *et al.* (1951) the endocarditis followed abortion and prostatectomy respectively. Beattie (1954) reported two cases—one after forceps delivery and one after prostatectomy.

In Cases 3, 6, and 7 in our series the infection followed repair of cystocele, removal of renal calculus, and pyelonephritis respectively. The gastro-intestinal tract seems to have been less frequently incriminated. McCoy and Mason (1951) described a case associated with carcinoma of the sigmoid colon. They postulated

that the malignant ulcers might have been the sites of entry of the organism. The infection has also been known to follow haemorrhoidectomy (Geraci and Martin, 1954). In Case 2 in this series it followed ascending cholangitis and liver abscess. Our observations bear out the experience of others that this form of bacterial endocarditis may follow gynaecological and urological procedures, gastro-intestinal infections, and dental sepsis. An edentulous state is therefore no bar to the diagnosis of subacute bacterial endocarditis, because the focus of infection may be at any of the other sites mentioned and because there may be infected buried roots.

Bacterial endarteritis superimposed on an arteriovenous aneurysm is well known. Parmley *et al.* (1954) described the only case of endarteritis and endocarditis due to *Str. faecalis* complicating a traumatic femoral arteriovenous aneurysm. Our Case 9 had apparently had the infection for six months without evidence of endocarditis.

The percentage of patients with previously normal hearts is varying reported as between zero (Sirota *et al.*, 1947) and 55 (Geraci and Martin, 1954). Three of our eight cases had apparently normal hearts. The ability of this organism to settle on normal endocardium is difficult to explain.

It has been stated (Geraci and Martin, 1954) that suppurative lesions are not uncommon in this condition. Horder (1909) described a case complicated by a splenic abscess which ruptured, causing general peritonitis. Rantz and Kirby (1943) had a similar case and two others, one with an abscess in the myocardium and one with ulceration of the interventricular septum. None of our cases had evidence of peripheral suppurative lesions.

The sensitivity of the organism to antibiotics should be tested in every case. Table III (modified from

TABLE III

Organism	Inhibitory Concentration of Penicillin
<i>Str. faecalis</i>	Usually greater than 1 unit/ml.
„ <i>viridans</i>	0.02 to 0.03 unit/ml.
„ <i>pyogenes</i>	0.02 or less ..

Robbins and Tompsett, 1951) compares the sensitivity of *Str. faecalis* to penicillin with that of the other common streptococci.

Sirota *et al.* (1947) stated that the average *Str. faecalis* was about 36 times as resistant to streptomycin compared with the standard organism. There is, however, no direct correlation between the sensitivity results and the outcome of antibiotic therapy, as illustrated by Case 3. Occasionally the organism may turn out to be relatively sensitive to penicillin (see Cases 1, 4, 7, and 8); though unusual, it has been recorded (Mathews, 1948; McCoy and Mason, 1951).

Combined penicillin and streptomycin therapy was first advocated by Hunter (1947), and its value was subsequently confirmed by Robbins and Tompsett (1951), Cates *et al.* (1951), and Geraci and Martin (1954). Cates *et al.* (1951) further demonstrated in the laboratory that the effect of the combination was not purely additive, but synergistic. Our results agree with those of these authors. The dosage of antibiotics recommended by Hunter is 10 mega units of penicillin and

2 g. of streptomycin daily for a minimum period of six weeks. In certain instances, 4 g. of streptomycin daily may be necessary initially to achieve response. 2 g. of probenecid daily by mouth should be added if the organism is extremely insensitive to penicillin.

Hager *et al.* (1951) successfully treated a case with 5 mega units of penicillin and 24 g. of caronamide daily. The serum level of penicillin was found to be increased twentyfold. In Geraci and Martin's series seven of the treated patients (22%) were cured by penicillin alone. Our Cases 1 and 8 were successfully treated with large doses of penicillin alone. Chlorotetracycline has proved disappointing (Brainerd *et al.*, 1949; Harvey *et al.*, 1949). There have been very few reported cures from its use. Waisbren (1954) recorded a case cured by the combination of erythromycin, chlortetracycline, and streptomycin, and suggested this regime as an alternative when penicillin and streptomycin had failed. Havard *et al.* (1959) reported a case in which the organism was extremely resistant to streptomycin and to the combination of penicillin and streptomycin tested *in vitro*. Cure was achieved by the use of systemic penicillin and neomycin, though transient renal damage was produced and the patient became totally deaf.

Prolonged treatment with streptomycin often causes eighth-nerve damage. In such a lethal disease it is a calculated risk which must be taken. Renal function should always be determined, and, if impaired, streptomycin should be used with greater care.

The recorded results of treatment are difficult to evaluate, since the outcome depends not only on the cure of the infection, but also on an early diagnosis and on the presence or absence of heart failure. Using penicillin and streptomycin in early cases, Geraci and Martin had a mortality of only 14%.

Antibiotic cover should be given to patients with rheumatic or congenital heart lesions when undergoing gastro-intestinal, gynaecological, urological, or dental operations. There is no evidence to suggest that in the case of dental operations the usual regime of penicillin cover is inadequate. For the other procedures we recommend 2 mega units of penicillin and 1 g. of streptomycin daily, given immediately before the operation and for three days subsequently. Although the risk of bacterial endocarditis developing after dental operations is well recognized, the risk after other types of surgery is rarely appreciated.

Summary

Eight cases of subacute bacterial endocarditis and one case of bacterial endarteritis due to *Str. faecalis* are analysed. The ability of this organism to settle on a normal heart is stressed and the various precipitating factors are discussed. Combined therapy with large doses of penicillin and streptomycin, with or without probenecid, is recommended. Experience to date suggests that the broad-spectrum antibiotics should rarely be used by themselves in this condition. A regime of prophylaxis is recommended for patients with rheumatic or congenital heart lesions undergoing certain operations.

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AORTIC OCCLUSION (LERICHE'S SYNDROME) IN MITRAL STENOSIS

REPORT OF SIX CASES

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Sudden occlusion of the aortic bifurcation by a "saddle" embolus is an uncommon, but well-recognized, complication of mitral stenosis. It usually presents as an acute surgical emergency (Lodin *et al.*, 1955). Peripheral emboli are a more frequent hazard to the patient with mitral stenosis and auricular fibrillation. Gradual occlusion of the abdominal aorta leading to a typical Leriche syndrome does not seem to have been described as a complication of mitral stenosis. This syndrome is characterized by bilateral intermittent claudication, wasting and weakness of the muscles in the lower limbs, and, in the male, loss of sexual potency. Mild nutritional disturbances of the skin may also be noted. Gangrene is a late and surprisingly uncommon complication. Before our previous paper (Starer and Sutton, 1958) none of the recent larger series on insidious aortic thrombosis mentioned mitral stenosis as an aetiological factor (Milanés *et al.*, 1952; Beaconsfield and Kunlin, 1953; DeBakey *et al.*, 1954; Pataro *et al.*, 1954).

In the diagnostic radiological department at St. Mary's Hospital six patients have been seen during the last few years in whom a typical Leriche syndrome developed during the course of mitral stenosis with auricular fibrillation. These cases have occurred among some 60 patients with aortic thrombosis, 32 of which

were reported in some detail in our previous communication (Starer and Sutton, 1958). However, only passing reference was made in that article to the aetiological significance of mitral stenosis, and the evidence is now presented in more detail.

Case 1

This patient had rheumatic fever in 1931, when aged 23. During 1941 she became short of breath and developed swelling of the ankles. From 1947 onwards she had several episodes of left submammary pain with cough and frothy sputum. In 1948 her right arm suddenly became white and cold. She felt pain in the arm when she used it vigorously; this pain was relieved by rest. Gradually the symptoms abated. During 1953 she was confined to bed for a few days with a mild gastro-intestinal upset. On rising she noticed coldness of both legs, gradually creeping up to the knees. This gave way to pain and later to numbness, and her toes became blue. On admission to her local hospital both femoral arteries were found to be pulsate. Her condition improved, but two weeks later the femoral pulses could no longer be felt and walking was limited to 50 yards (45.7 metres) because of bilateral claudication.

On admission to St. Mary's Hospital on December 31, 1953, signs of mitral stenosis and auricular fibrillation were observed. No pulses could be felt in the right brachial artery or at the wrist, and no pulses were palpable in the lower limbs. B.P. was 150/100 mm. Hg. No nutritional changes were present in the legs.

Aortography showed complete occlusion of the lower abdominal aorta (Fig. 1).

On February 3, 1954, valvotomy was performed. The aortic was moderately enlarged and contained a single clot. The degree of stenosis was slight, the valve easily admitting an index finger.

Comment.—From the present point of view this case is of particular interest. After undoubted peripheral emboli in both legs the femoral pulses disappeared during observation in hospital without, apparently, any further embolic episodes.

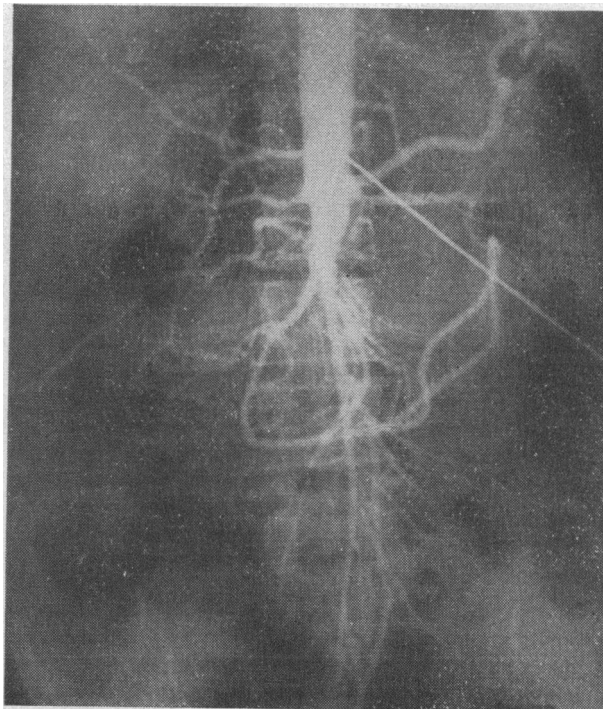


FIG. 1.—Case 1. Complete occlusion of the lower abdominal aorta opposite L3.