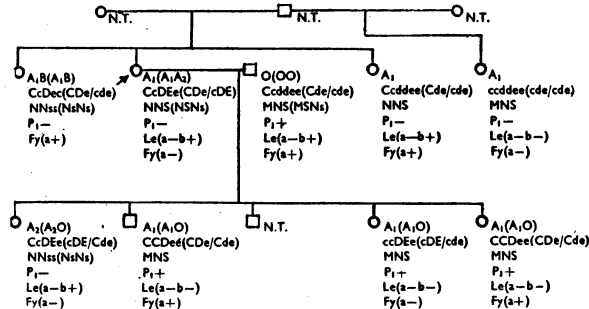


The possibility of her being a chimera appeared unlikely because of the variable reactions with anti-B sera and the apparent absence of signs of heterogeneity for any of the other blood-group systems. Investigations of the patient herself were cut short by her death a few weeks after they began.

Genetical Study

An investigation of the family put a completely different complexion upon the case. Fortunately a number of relatives were available and proved most co-operative. Their blood groups are shown in the pedigree. In the case of the ABO, Rh, and MNS



Pedigree of patients' family, showing blood groups. For the ABO, Rh, and MNS groups the phenotype is given first, followed by the genotype where known. The arrow indicates the propositus. She has a weak B-like antigen, apparently acquired. E antigen weak. N.T.=Not tested.

systems the phenotype is shown first, followed by the genotype where this can be deduced. The most unexpected and important finding was that the patient, whose husband was group O, had an A₂ daughter. This result was confirmed on a fresh specimen. The cells were tested with several anti-H as well as anti-A₁ sera on both occasions, and there is no doubt that this daughter is truly A₂. The patient's genotype must therefore be A₁A₂.

The finding that her sister was a normal A₁B revived the possibility that the patient might be a chimera, but the family were all certain that she had not had a twin brother or sister. The cells of her group A₁ daughter and son were used to absorb anti-A and anti-B sera. They behaved as ordinary A₁ cells, and did not remove anti-B, whereas those of the patient's group A₁B sister removed them completely: the patient's own cells removed very little indeed.

Discussion

The genetical investigation leaves virtually no doubt that the patient's genotype was A₁A₂ and hence that her B-like antigen was not the product of a gene at the ABO locus. The seven similar cases, all of group A₁, investigated by Cameron *et al.* (1959) and two, probably similar, which they quote from the literature, leave little doubt that the antigen in such cases is acquired as a result of old age or disease, though its first appearance has not yet been observed in any individual. Though five of the seven patients had cancer the authors do not consider that this association is proved to be specific: as they point out, cancer is a common reason for blood-grouping old people. However, the present case adds a further example of this phenomenon associated with cancer.

The present case, like all the others, is phenotypically of group A₁, but, being of genotype A₁A₂, differs from

the three others whose genotypes could be ascertained, and who were all A₁O.

Summary

The presence is described of a B-like antigen on the red cells of a patient of blood group genotype A₁A₂, suffering from carcinoma of the colon.

We thank the members of the family for their kind co-operation and their willingness to donate blood samples on more than one occasion. We also thank Dr. T. Cleghorn, Dr. J. W. Lacey, Dr. D. Lehan, and Surgeon Lieutenant K. J. McDonald, R.N., for obtaining blood samples from various members of the family.

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INTESTINAL DIVERTICULA

BY

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The majority of intestinal diverticula consist of hernial protrusions of the mucous membrane and submucous layers through the muscular coats of the bowel (primary type). In this inquiry, which is based on a study of patients encountered during a nine-year period, one case of acute diverticulitis of the caecum is reported; otherwise only propulsion diverticula are considered.

Diverticula of Duodenum

The total number of patients encountered with duodenal diverticula is unknown, but 10 in whom such diverticula have been demonstrated during routine abdominal investigations and without other demonstrable abnormality have been studied. Seven were female and three male, and the average age was 52 years. They all complained of flatulent dyspepsia, but the clinical findings did not permit differentiation from cholecystitis or chronic peptic ulcer. The disability was judged sufficient to warrant operation in only one of these patients, and pre-operative radiographs had appeared to show the diverticulum arising from the second part of the duodenum close to its junction with the first part. At operation it was traced behind the duodenum and pancreas to its origin from the postero-superior aspect of the third part close to its commencement. Five years after diverticulectomy this patient was found to have regained weight lost before operation, but still complained of occasional dyspepsia.

Two of these patients presented with haematemesis and melaena. One was a woman aged 60 who recovered without operation. Barium-meal x-ray examination revealed two diverticula arising from the fourth part of the duodenum (Fig. 1), and an associated colonic diverticulosis (Fig. 2). The second was a man aged 73 in whom colonic diverticula had been demonstrated three years previously. This patient died after repeated haematemeses and melaena over a period of 10 days. Post-mortem examination revealed four

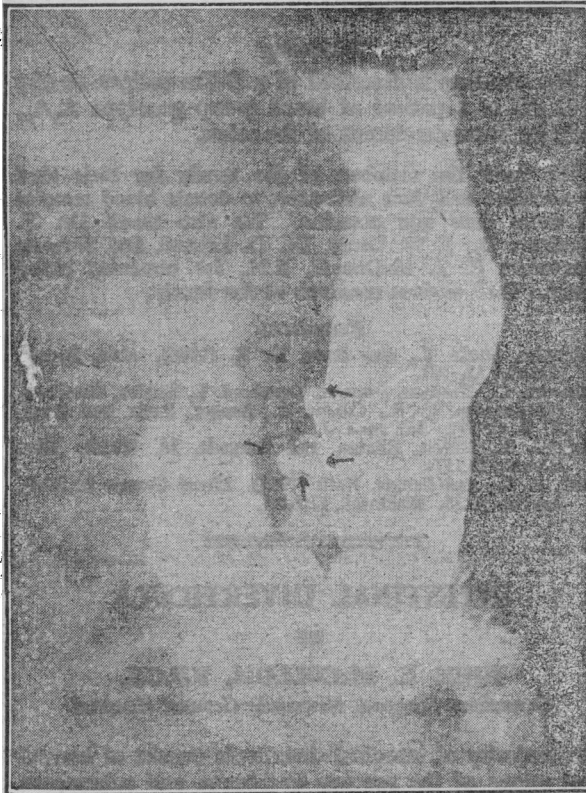


FIG. 1.—Barium-meal x-ray film. Arrows show two diverticula arising from fourth part of duodenum.

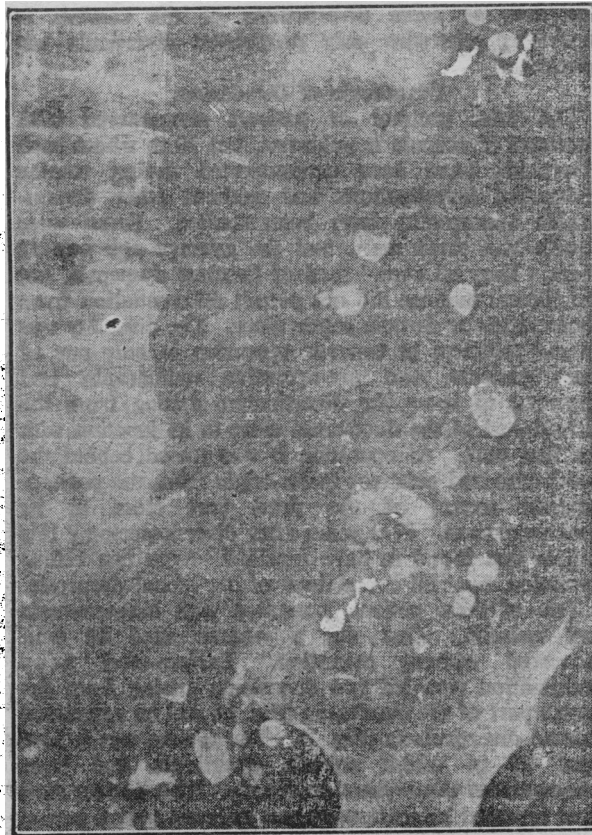


FIG. 2.—Same patient as in Fig. 1. X-ray film 18 days after barium meal, showing retention of barium in colonic diverticula.

diverticular openings in the third part of the duodenum—two on the antero-superior and two on the postero-superior aspect. The walls of the two posterior diverticula had become engulfed in the fibrotic reaction round about an aneurysmal dilatation of the abdominal aorta. A duodeno-aortic fistula had formed and caused the fatal bleeding.

Diverticula of the Jejunum-Ileum

No case of uncomplicated jejuno-ileal diverticulosis with disability sufficient to warrant surgical intervention has been encountered. Two patients presented with acute complications of the disease. A woman aged 65 died five days after admission to hospital with haematemesis and melaena. Post-mortem examination showed that the fatal bleeding was from a vessel which had erupted on to the surface of a shallow ulcer at the neck of a diverticulum situated close to the duodeno-jejunal junction. Three other diverticula were present in the upper jejunum, and whereas these were thin-walled and wide-mouthed, the wall of the ulcerated diverticulum was thickened by fibrosis and its neck was narrow. Another woman, aged 66, was admitted to hospital with acute diffuse peritonitis secondary to acute diverticulitis of the upper jejunum. Recovery followed resection of a segment of bowel bearing the acutely inflamed diverticulum and re-establishment of continuity by side-to-side anastomosis. Ten months after discharge this patient was readmitted to hospital with haematemesis which necessitated transfusion of 2 pints (1 litre) of blood. Barium-meal x-ray examination at this time showed multiple diverticula of the small bowel. Recovery took place without operation and the patient has remained well for four years.

Colonic Diverticula

Ninety patients investigated have been divided into six groups depending on the predominant clinical features when they were first referred for consultant opinion (see Table). The average interval between diagnosis and follow-up examination has been four years and two months.

Clinical Features in 90 Cases of Colonic Diverticula

Group	No. in Group	Clinical Features at First Examination	Immed. Mortality	Findings at Follow-up Examinations
1	45 (50%)	Recurrent abdominal pain and altered bowel habit	Nil	One death after rupture of diverticulum; otherwise no deterioration in any of them
2	9 (10%)	Painless diarrhoea		No deterioration
3	15 (17%)	Acute spreading peritonitis secondary to rupture of diverticulum	7 (47%)	One had severe melaena 3½ years after acute illness. Otherwise no important disability in surviving patients
4	13 (14%)	(a) Acute non-suppurative pericolicitis (6 cases) (b) Acute suppurative pericolicitis (4 cases) (c) Pericolicitis with fistula (3 cases)	(a) Nil (b) 4 (100%) (c) Nil	No deterioration in surviving patients
5	5 (5½%)	Intestinal obstruction Acute obstruction of small bowel (2 cases) Chronic obstruction of colon (3 cases)	Nil	Two of three patients who had proximal colostomy for chronic obstruction have deteriorated owing to advancing pericolicitis and pericolicitis. One has kept well for 9 years
6	3 (3½%)	Massive intestinal bleeding	1 (33%)	Two patients who recovered from severe melaena have had no recurrences

Diverticula of Caecum

Acute diverticulitis of the caecum has been encountered in one male patient aged 25. The pre-operative diagnosis was acute appendicitis, and at operation a mass of inflammatory tissue was found adherent to the medial wall of the caecum. The appendix was identified and removed. Further dissection revealed a diverticulum, similar in appearance to the appendix, projecting from the medial wall of the caecum; it was inverted into the caecum. Post-operative barium-enema x-ray examination showed one small diverticulum projecting from the medial wall of the ascending colon and no other abnormality.

Diverticula of the caecum occur in two distinct groups of patients. In the first the disease is limited to the caecum, acute diverticulitis is the only common complication, and the age of incidence is lower than that for diverticulosis of the intestine as a whole. In the second group multiple diverticula of caecum occur in association with a diffuse diverticulosis of the colon (Fig. 3). Operative experience has shown that this is not always revealed by radiological examination,

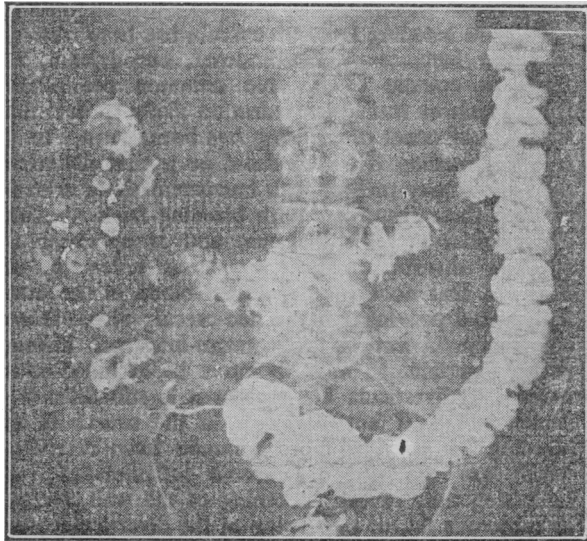


FIG. 3—barium enema Diverticulosis of whole colon, including caecum.

probably because the spasm and irritability of the left half of the colon, so frequently present, make it difficult for the radiologist to obtain a clear outline of the right half of the colon. Lloyd-Davies (1953) found that methanthelinium bromide given one hour before intestinal x-ray study overcame this spasm and facilitated pre-operative assessment of the extent of the disease. In the case of patients requiring operative treatment the final decision on the extent of the disease and the operative intervention necessary can be made only after careful inspection of the whole intestine at laparotomy.

Comment

The commonest presenting complaint in diverticulosis is of recurrent episodes of abdominal pain, accompanied in the case of duodenal and jejuno-ileal diverticulosis by flatulent dyspepsia, and in colonic cases by alteration in the bowel habit. The frequency with which diverticula are found simultaneously in several segments of the bowel denotes that it is a disease of the whole intestine, although the occurrence of a

complication may direct attention mainly to one segment. Surgical intervention, other than that necessary for relief of an existing complication, would be advisable only where it could be shown that a serious complication was likely to occur in an individual or a group of patients. Such intervention would not prevent progress of the disease or development of later complication at a different level in the bowel.

It is doubtful if uncomplicated duodenal diverticula ever require active surgical treatment. Operation may be necessary in uncomplicated jejunal cases, particularly if the dyspepsia is accompanied by obstructive features. The demonstration of duodenal or jejunal diverticula may be regarded as an adequate explanation for chronic or recurrent dyspepsia, provided precautions have been taken to exclude other active lesions. I was formerly taught that these diverticula could as a rule be disregarded and that another cause for the disability would be found. The reverse of this is equally true, and a concomitant diverticulosis may be responsible for the major disability in patients with chronic duodenal ulcer or disease of the biliary tract.

Of the 90 patients with colonic diverticula, 60 are contained in the three groups who presented with recurrent attacks of abdominal pain, painless diarrhoea, or signs of pericolicitis without frank pus formation, and follow-up examinations have shown that with one exception there has been no deterioration in any of them. The fact that a serious complication—perforation of a diverticulum—occurred in one patient, emphasizes the risks they are subject to but does not provide a mandate for prophylactic colon resection. The two most important complications of colonic diverticulosis encountered have been diffuse peritonitis secondary to acute perforation of a diverticulum, and acute suppurative pericolicitis. Review of the case histories of 19 patients with one or other of these complications has not revealed any feature by which individuals particularly liable to them might be recognized, and there is not likely to be any opportunity for prophylactic surgical treatment.

At operation on patients with perforation of colon, it has not been possible to identify that this was in a projecting diverticulum, and it has been found difficult to distinguish with certainty between diverticulitis, neoplasm, and ulcerative colitis. This is analogous to the similar difficulty of distinguishing between simple ulcer and neoplasm in cases of gastric perforation, and has influenced the management of these patients. Careful clinical assessment, sigmoidoscopy, and x-ray study are necessary after recovery from the acute illness and before a final decision is made. Hughes and Shaw (1952) concluded that proximal colostomy will not prevent further leakage from the sigmoid colon during the time it is most to be feared, and colostomy appears to be unnecessary if the perforation has been small and the local inflammatory reaction sufficient to rule out the possibility of further leakage from the bowel. I believe that a proximal colostomy should be performed in the majority of patients: experience has shown that this may be closed after recovery from the acute illness, and the later prognosis for patients who recover from perforated diverticulum is good.

The causes of death in the four patients with acute suppurative pericolicitis were toxæmia and exhaustion (one case), diffuse peritonitis (two cases), and suppurative pylephlebitis (one case). Pathological examination in all of them showed widespread



FIG. 4.—Barium enema. Barium has flowed into multilocular pericolic abscess cavity.

suppuration and necrosis in the pericolic and retroperitoneal tissues (Fig. 4). Extension of the process was by numerous sinuous tracks, so that on tissue section there were numerous apparently isolated foci of suppuration in the fibro-fatty tissue surrounding the diseased colon. These findings explain the rapid clinical deterioration and the difficulty of obtaining surgical drainage without further spread of infection. Surgical exploration should be undertaken early in these patients, before the likely onset of such complications as pylephlebitis, and if the findings are such that simple drainage will not be effective, the diseased colon and the surrounding infected tissues should be removed. No attempt should, however, be made to re-establish bowel continuity by simultaneous anastomosis.

In the case of pericolicitis with fistula, the inflammatory changes are less diffuse and the systemic disturbance is less severe. This complication may be insidious and give rise to so little disturbance that in elderly patients only palliative treatment is necessary. In many instances carcinoma can be excluded only after operation and pathological study. Immediate dissection and removal of the diseased colon is desirable and appears possible in almost all cases, but the question whether or not simultaneous bowel anastomosis should be performed will depend on the extent of the disease and the operator's assessment of the risks involved.

Discussion

Acute intestinal obstruction secondary to diverticulitis has been observed only in cases where the small bowel has become involved in the colonic disease by formation of bands or adhesions. In those patients with clinical

evidence of obstruction of the left half of the colon, x-ray and pathological study has confirmed that the bowel lumen is diminished. On section of the gut the mucosa is seen to be thrown into deep folds and there is muscle hypertrophy. These two changes appear to be mainly responsible for the narrowing of the lumen of bowel, and it does not seem as if the fibrosis which is also present is ever sufficient to cause stenosis. These findings are similar to those observed by Phillips (1953) in cases of jejuno-ileal diverticulosis and suggest that the obstructive features are due to bowel dyskinesia.

Follow-up of patients who have had proximal colostomy performed for relief of chronic intestinal obstruction has shown that the disease may progress in spite of this, and that deterioration is more likely if precautions have not been taken to avoid overspill of faeces into the distal loop of the colostomy and the diseased bowel segment. The aim of treatment, therefore, in patients with obstructive features should be removal of the diseased colon. Operation should be advised early so that resection and re-establishment of bowel continuity by anastomosis may be safely performed.

Massive bleeding from diverticula has been observed in seven instances—two duodenal, two jejunal, and three in colonic cases. No common precipitating factor such as trauma or infection likely to determine the time of onset of bleeding has been noted. In the case of bleeding from duodenal or jejunal diverticula the patient may present with haematemesis or melaena or both these features. With bleeding from a colonic diverticulum there is melaena, and at operation for bleeding diverticulum of ascending colon it was observed that none of the altered blood in the bowel had passed proximal to the ileo-caecal valve. During emergency operations for gastro-intestinal haemorrhage, diverticulosis must therefore be excluded as the cause. If diverticula are present it is still difficult to decide which, if any of them, is the source of the bleeding. It may be more common from diverticula which are the site of chronic inflammation, and inspection may reveal thickening of the wall, increase in subserous fat, or narrowing of the diverticular neck.

The presence of an enterolith in or adjacent to a diverticulum may also render it suspect. On the other hand, there was no evidence of pre-existing inflammatory change in the single case of bleeding colonic diverticulum examined. Moreover, the diverticulosis may be much more diffuse than pre-operative investigations suggest. Pre-operative barium-enema examination in this patient with bleeding colonic diverticulum had shown diverticula in the sigmoid colon only, but at operation there were diverticula scattered along the whole colon. At operation the bowel may be opened to permit inspection of the suspect diverticulum from its mucosal aspect. Alternatively, the suspected segment of bowel may be removed and immediately examined. The localization and control of such bleeding may necessitate extensive bowel resection and operation should be undertaken in severe or recurrent cases.

Summary

Ten patients with uncomplicated duodenal diverticula and two who presented with haematemesis and melaena have been studied.

A case of fatal bleeding from a jejunal diverticulum, and a second which withstood bowel resection for acute diverticulitis of jejunum and later presented with haematemesis, are described.

The clinical features and findings at follow-up examinations in 90 cases of colonic diverticula are summarized, and one case of acute diverticulitis of caecum is recorded.

The relative incidence of the various complications of colonic diverticula given, and the findings at operation and on later pathological study of material from these cases are described. The principles which should govern management of these complications are discussed.

Diverticulosis has been found to be an important cause of chronic or recurrent dyspepsia. It should be regarded as a disease of the whole length of the intestine although the occurrence of a complication may direct attention mainly to one segment of the bowel.

I am indebted to my colleagues on the staff of the Departments of Pathology and X-ray Diagnosis for their kind co-operation in the investigation of the patients on whom this article is based. Mr. C. R. Strother-Stewart, Mr. J. R. S. Paterson, and Mr. A. R. Kirby were surgical registrars at this hospital during the period covered in this review, and it is a pleasure to record my gratitude for their enthusiasm.

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HEPARIN-LIKE ANTICOAGULANT OCCURRING IN ASSOCIATION WITH CHRONIC NEPHRITIS

BY

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In the case here reported a heparin-like circulating anticoagulant developed during the course of chronic nephritis and caused a haemorrhagic diathesis.

Circulating anticoagulants occur either spontaneously or as a result of transfusions. The presence of antihæmophilic globulin (A.H.G.) was noted in approximately 40 cases of hæmophilia A reported in the literature. A case has been described in Turkey (Frank and Peçikyan, 1954), and at our clinic we have a case of hæmophilia A in which A.H.G. occurred as a result of transfusion (Ulutin, Karaca, and Gürson in press).

Six cases of Christmas disease showing anti-plasma-thromboplastin component (anti-P.T.C.) have been described. Hörde (1955) drew attention to the existence of an inhibitor belonging to factor V. A case of anti-ac-globulin was reported by Ferguson *et al.*

(1957). Alexander (1955), Wagner, Brannan, and Brinkhous (1955), and Jügens (1955) described cases in which anti proconvertinaemia could be demonstrated. Brünimann (1954) described the formation of an antibody against fibrinogen caused by repeated transfusions in a case of congenital afibrinogenaemia.

Search of the literature has brought to light descriptions of five cases of circulating anticoagulant, with haemorrhagic diathesis, in normal subjects without any apparent cause. Anticoagulants have been reported during pregnancy or parturition in 13 cases. Other diseases during the course of which anticoagulants have been reported to occur are syphilis, tuberculosis, rheumatism, myocardial infarction, pemphigus (while being treated with arsenic), and lupus erythematosus. Conley *et al.* (1948) described the occurrence of a circulating anticoagulant, with haemorrhagic diathesis, in the course of chronic nephritis. A similar case is reported below.

Case Report

The patient, a 32-year-old man, had acute nephritis eight years before admission to hospital. For the last two years he complained of headache and pallor of the skin. A week before admission his nose and gums began to bleed. On the day before admission he had a severe headache and his temperature rose to 37.6° C. He was admitted to hospital with the diagnosis of meningitis.

On examination his skin was pale, his gums were bleeding, and there were hæmatomata in the subcutaneous tissues. His blood pressure was 190/120. A systolic murmur was heard in all cardiac areas, and the second aortic sound was accentuated. Nothing abnormal was found in the respiratory, gastro-intestinal, and urogenital systems. Neck stiffness was present, Kernig's sign was positive, and there was some impairment of consciousness. The spinal fluid was blood-stained, confirming the diagnosis of subarachnoid hæmorrhage. The erythrocyte count was 2,800,000, Hb 40%, leucocytes 6,800. The peripheral blood picture was normal. Urine analysis showed albuminuria; the sediment contained abundant erythrocytes and granular casts. Urine specific gravity was 1011. Blood urea was 90 mg./100 ml; urea clearance 40% of normal; glomerular filtrate 35 ml. It appeared that in the course of chronic nephritis a subarachnoid hæmorrhage had occurred.

The bleeding gums and skin hæmatomata drew our attention to the possibility of the existence of a haemorrhagic diathesis. Coagulation studies performed on November 1, 1955, gave the following results: bleeding time, 2½ minutes; coagulation time, 18 minutes (Lee and White method); retraction normal; platelet count, 220,000 (Fonio method); Rosenthal's heparin clotting-time, 120 minutes (normal 30 minutes); prothrombin time (Quick) 18 seconds (normal 12 seconds); antithrombin time (Winterstein) 25 seconds (normal 14 seconds). We found an abnormal result with the thromboplastin generation test of Biggs and Macfarlane and of Douglas (Fig. 1). During the performance of this test, the addition of normal A1 (OH)₃-treated plasma and normal serum or normal platelet suspension to the patient's blood did not produce any increase in the information of thromboplastin. When the patient's A1 (OH)₃-treated plasma or his serum was added to normal blood, the formation of thromboplastin was highly inhibited.

In *in vitro* experiments the addition of protamine sulphate and toluidine blue corrected the prolonged coagulation time and antithrombin time (1% toluidine blue solution or 1% protamine sulphate was added to the patient's blood or plasma in the ratio of 1 to 10). With the protamine titration method of Allen *et al.* (1949) clotting