Case 3

A man aged 43 was well until December, 1949, when he first noticed swelling of both ankles. This subsided spontaneously during the next few weeks. In October, 1950, he first complained of diarrhoea, characterized by four or five frothy, yellowish, watery stools a day. This continued intermittently for eleven months and he was admitted to the Royal Infirmary, Edinburgh, on September 14, 1951, for investigation. During the preceding months he had lost 42 lb. (19 kg.) in weight in spite of a reasonably good appetite. There was no history of abdominal pain. The family, social, occupational, and past histories revealed no information of diagnostic value.

On examination he was seen to be a thin, pale, middle-aged man. The tongue was atrophic. The respiratory, nervous, and cardiovascular systems were normal except for the presence of hypotension; his blood pressure was 90/60. The liver and spleen were not palpable and no abdominal masses were felt. He had gross clubbing of the fingers. There was minimal sacral oedema, but a moderate degree of bilateral ankle swelling. *X*-ray examination of the chest, urine analysis, and the stool benzidine test were negative. The initial blood count was haemoglobin, 69%; red cells, 4,600,000; colour index, 0.75; mean corpuscular volume, 86.9 μ^3. The serum calcium was 7.7 mg. per 100 ml., and Trousseau's sign was positive. The serum sodium equalled 136 mEq./l. (312 mg. per 100 ml.); serum potassium, 4.1 mEq./l. (16 mg. per 100 ml.); plasma albumin, 2.37 g.%; and plasma globulin 2.21 g.%. Liver-function tests were negative. The Robinson–Kepler–Power water test gave a positive result. The glucose-tolerance curve was flat. 17-ketosteroid excretion was 8.4 mg. per 24 hours. A three-day fat-balance study showed that there was only 66% fat absorption and a barium meal gave evidence of a "deficiency" pattern.

About a month after admission the patient developed frank tetany with carpal spasm. This was relieved with antitetanic therapy, including calcium gluconate, "parathormone," and vitamin D. The Sulkowitch test consistently revealed the absence of calcium from the urine. A diagnosis of idiopathic steatorrhoea was made and he was given folic acid, 20 mg. daily, ferrous sulphate, 4 gr. (0.26 g.) thrice daily, multivitamin therapy, added salt (10 g. daily), and added protein ("casinal"), 100 g. daily. A total of 100 mg. of intravenous iron was given during his last week in hospital. At the time of his discharge (December 11) he was subjectively much improved. Moreover he had gained 28 lb. (12.7 kg.) in weight, the blood pressure had risen to 100/74 and the serum calcium to 11.3 mg. per 100 ml. The haemoglobin level was 77%. He was having only one or two stools a day and was completely free of oedema.

He returned to work during January and February, 1952, but had to stop because of weakness. In May he developed colicky abdominal pain which gradually increased in severity. Laparotomy was carried out in another centre, and a tumour of the ileum was found completely obstructing the intestinal lumen. Microscopically this was a reticulosarcoma which had invaded the adjacent mesenteric glands. The tumour was resected. Although relieved of his obstructive symptoms the patient continued to feel tired and was readmitted to the Royal Infirmary, Edinburgh, in September. The liver was now palpable three fingerbreadths below the right mid-costal margin and a chest *x*-ray film showed consolidation in the left lower lobe with a large hilar shadow on the left side, suggesting metastatic tumour formation. The patient has continued to become progressively weaker.

Summary and Conclusions

Two cases of tumour of the small intestine are presented in order to emphasize that an obscure anaemia may exist for months or years before obstructive symptoms occur, an abdominal mass is felt, or positive radiological evidence is obtained. The difficulty in arriving at an early correct diagnosis is evident. It is suggested that the presence of a hypochromic anaemia, with a persistently positive stool benzidine test, the origin of which cannot be explained by clinical, instrumental, or radiological investigations, is an indication for laparotomy. If such an anaemia is refractory to oral iron therapy, this is an additional reason for operation, as it suggests that the loss of blood is of a degree that cannot be counteracted by iron therapy or that malabsorption of iron from the small intestine is occurring.

The third case is described because of the rarity with which the clinical and biochemical features of idiopathic steatorrhoea are associated with a neoplasm of the small intestine (Fairley and Mackie, 1937).

We wish to thank Professor L. S. P. Davidson for his help in the preparation of this paper; Dr. Bruce Cruickshank, who examined and described the pathological specimens; and Mr. F. Gabel, of the Derbyshire Royal Infirmary, who kindly supplied the operative notes of Case 3.

REFERENCES

Ewing, J. (1940). *Neoplastic Diseases: A Treatise on Tumours*, 4th ed., p. 721. Saunders, Philadelphia.
Fairley, N. H., and Mackie, F. P. (1937). *British Medical Journal*, 1, 375.

THE SYNDROME OF HIGH-TITRE COLD HAEMAGGLUTINATION

BY

M. G. NELSON, M.D., M.R.C.P., D.T.M.&H.

AND

R. J. MARSHALL, M.D., M.R.C.P.I.

From the Royal Victoria Hospital, Belfast

Occasional normal sera contain an antibody which agglutinates red cells in the cold, but it is usually present only in low titre. The physiological significance of this agglutinin is unknown and its presence is of practical importance only in blood transfusion work. A considerably raised titre of such a cold agglutinin is commonly found in cases of virus pneumonia, and rarely in a variety of unrelated conditions, including haemolytic anaemia, hepatic cirrhosis, and trypanosomiasis. In cases in which the titre is exceptionally high, exposure to cold may result in marked agglutination of red cells in the vessels of the extremities, with symptoms of vascular insufficiency. This is usually a transient phenomenon occurring at the height of the illness or during convalescence.

Cold agglutinins are, however, sometimes found in the blood of persons who have not suffered from any recent illness. They appear suddenly in very high titre and are persistent rather than transient. They give rise to a prolonged illness characterized by Raynaud's phenomenon, peripheral gangrene, intravascular haemolysis, haemoglobinuria, and anaemia.

We have recently had the opportunity of studying two further cases of this syndrome.

Case 1

A 47-year-old cycle-repairer noticed in the winter of 1950 that at times his hands became numb and blue up to the wrists and the fingers dead-white. After each attack he experienced abdominal discomfort and passed black urine. At no time was there numbness or cyanosis of the feet, but the tip of the nose often became blue, and this he recognized as a sign of an impending attack. He was careful to avoid exposure to cold, as he soon realized that

this was the cause of his trouble. However, during the autumn of 1951 further severe attacks occurred when out of doors in cold weather. Mild attacks of digital ischaemia without haemoglobinuria resulted from slight exposure to cold induced in his ordinary occupation by handling cold metal tools or bicycle components. There was no history of pneumonia or of any other serious illness, and until the onset of the present condition he had been able to work for long hours in cold surroundings without ill effects.

On admission to hospital there was no pallor of mucous membranes or any icterus. The skin of the distal segments of the digits was atrophic, but the colour was normal and all peripheral arteries pulsated strongly. The temperature was 98° F. (36.7° C.), pulse 90, blood pressure 138/86. He had bilateral direct inguinal hernias. Otherwise physical examination was negative. The urine contained no protein, red cells, or reducing substances, and there was no excess of urobilinogen. Renal-function tests showed normal excretion and radiological examination of the kidneys showed no opaque calculi.

Clinical Investigations

Exposure to Cold.—The patient was taken for a walk in the hospital grounds on a cold afternoon—temperature 42° F. (5.5° C.)—with the hands exposed. After 25 minutes both hands became numb and blue. Samples of blood were collected at hourly intervals after exposure; there was well-marked haemoglobinaemia in the first specimen, but not subsequently. This haemoglobinaemia was followed by haemoglobinuria, which was maximal two hours after the exposure to cold.

Rosenbach Test.—The right arm was immersed for 15 minutes in water at 54–57° F. (12–14° C.). Blood samples were taken immediately afterwards from both arms. The chilled hand showed ischaemic changes, but there was no oedema or allergic reaction to cold such as is seen in patients with syphilitic paroxysmal cold haemoglobinuria. Blood serum from the chilled limb was cherry-red, while that from the non-immersed limb was pink. Haemoglobinuria did not occur. The haemoglobin levels in the samples of serum are recorded in the Table, which also shows the results of similar experiments in Case 2 and in a case of syphilitic paroxysmal cold haemoglobinuria. Spectroscopic examination of serum from the chilled limb revealed no pigment other than oxyhaemoglobin, even in a thickness of 4.5 cm.

Results of Rosenbach Test

Case	Free Haemoglobin (mg./100 ml. Serum)		
	A	B	C
1	18	190	110
2	45	220	28
J.	19	250	47

Cases 1 and 2 suffer from high-titre cold haemagglutination, and J. from syphilitic paroxysmal cold haemoglobinuria. Column A = levels of free Hb in blood from right arm before its immersion in water at 54° F. (12° C.) for 15 minutes. Column B = levels of free Hb in blood from right arm following immersion. Column C = levels of free Hb in blood from left (non-immersed) arm.

Observations on the Vessels of the Chilled Conjunctiva.—The anaesthetized conjunctiva was examined in a warm room with a slit-lamp corneal microscope, and its circulation was noted to be normal. Following the direct application of ice to the conjunctiva the blood stream slowed and became fragmented, small clumps of cells alternating with stretches of clear plasma. On subsequent warming the circulation quickly became normal.

Examination of Nail-bed Capillaries after Chilling.—This was unsatisfactory, as the heat of the microscope lamp rapidly warmed the chilled finger-tip.

Laboratory Investigations

On admission the haemoglobin was 88% Haldane (13 g.%); erythrocytes, 4,120,000 per c.mm.; leucocytes, 9,950 per c.mm., with normal distribution; reticulocytes, 0.5–1%; platelets, 224,000 per c.mm.; E.S.R., 33 mm. in 1 hour at 72° F (22° C.) and 31 mm. in 1 hour at 50° F. (10° C.) (Wintrobe method); osmotic fragility of erythrocytes normal. The blood group was O($\alpha\beta$) rhesus-positive (anti-D) and the Coombs test was strongly positive. Serum bilirubin was 0.8 mg. per 100 ml.; serum proteins, 6.7 g. per 100 ml. (albumin 4.55 g., globulin 2.15 g.). A differential count on marrow aspirated from the iliac crest showed a normal distribution with 24.5% normoblasts of all stages of development.

The Wassermann and Kahn reactions were negative. The serum contained a cold agglutinin active against his own and homologous erythrocytes to a titre which has remained persistently high during the period that he has been under investigation. When this test is carried out with normal saline as diluent the titre at 32° F. (0° C.) has been 1:20,480, but using bovine albumin as diluent the titre is enhanced many-fold, and has been as high as 1:327,680. The activity of this agglutinin falls sharply between 50 and 68° F. (10 and 20° C.) and is completely inhibited at body temperature.

Temperature	Titre	Temperature	Titre
32° F. (0° C.)	1:20,480	68° F. (20° C.)	1:1,280
50° F. (10° C.)	1:20,480	98·6° F. (37° C.)	0

No cold haemolysin could be detected in the serum using the technique described by Dacie and de Gruchy (1951).

The cold agglutinin was found to be absorbed on to the surface of erythrocytes collected from the patient's blood, which was allowed to clot at room or refrigerator temperature but not at 98.6° F. (37° C.). If these erythrocytes were repeatedly washed with warm saline the cold agglutinin was eluted from the cells. A Coombs test then carried out on such washed cells was found to give a positive result, which indicated the presence of an adsorbed cold immune body. The presence of this incomplete immune body can also be demonstrated by adding homologous cells to the serum, chilling the mixture, eluting the cold agglutinin with warm saline, and testing the washed cells with anti-human globulin serum, when a positive result is also obtained. This immune body is regarded by Ferriman *et al.* (1951) as an incomplete cold antibody, and is probably an enhanced titre of the incomplete cold antibody described by Dacie (1950a) in normal sera.

The Donath–Landsteiner test has been repeatedly carried out both without acidification and after adjusting the *p*H to 6.6. It has always been negative. A control Donath–Landsteiner test carried out on the serum of a patient with syphilitic cold haemoglobinuria has been persistently positive, and this reaction has been enhanced by acidification.

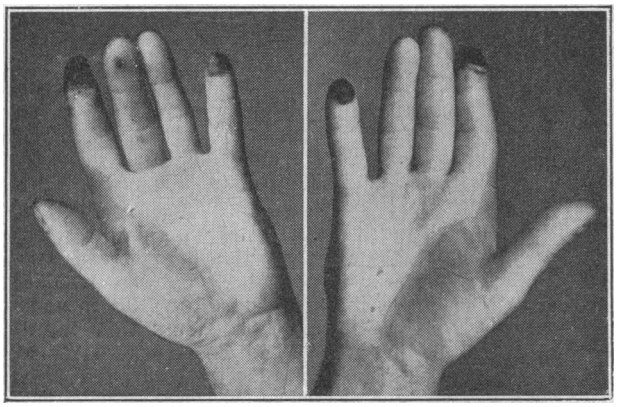
Treatment

The patient was advised to avoid unnecessary exposure to cold by wearing woollen mittens and remaining indoors as much as possible. In order to obtain peripheral vasodilatation tolazoline hydrochloride and nicotinic acid were given by mouth, but there was no evidence that they brought any lasting benefit.

Case 2

A 40-year-old fitter noticed during the winters of 1949 and 1950 that both hands became numb and painful during frosty weather. The hands were deeply cyanosed and the digits showed blue-and-white mottling; there was also cyanosis of the nose and ears, but the feet remained normal. During a cold spell in December, 1951, the tips of both the index and little fingers gradually became dry, black, and extremely painful. The only previous illness was pneumococcal lobar pneumonia in 1947, which had responded satisfactorily to chemotherapy.

On admission to hospital there was a moderate pallor of exposed mucous surfaces but no icterus. The hands showed mottled bluish discoloration, and the fingers were waxy-white, with shiny atrophic skin. Light touch and pin-prick were not appreciated. There was dry gangrene involving the distal segments of the index and little fingers of both hands (see illustration). Arterial pulsation was good in the radial and ulnar arteries, and there were no changes in the



Photograph of the hands of Case 2, showing symmetrical digital gangrene.

vessels or skin of the feet. The temperature was 97° F. (36.1° C.), pulse 84, blood pressure 180/90. No other abnormality was detected on clinical examination. The urine contained no protein, red cells, or excess urobilinogen; there was no haemosiderin in the urinary deposit. *X*-ray examination showed moderate enlargement of the left ventricle; there were no bony cervical ribs.

After nine days' treatment with local heat to the hands and vasodilator drugs there was no improvement in the gangrene, and the tips of both forefingers were amputated.

Clinical Investigation

Exposure to Cold.—Five days after amputation of the gangrenous finger-tips the patient was up and about in the ward, when he developed a severe attack of digital ischaemia. The amputation stumps were particularly painful, and the tip of the nose and right ear became blue. It was noted that pressure on an area of cyanosis failed to produce blanching (negative Parisius phenomenon). The pain and vascular changes were relieved after a few moments' immersion of the hands in water at 104° F. (40° C.).

Rosenbach Test.—As in Case 1, serum from the chilled limb contained a large amount of free haemoglobin (see Table). Spectroscopic examination showed, in addition to oxyhaemoglobin, a weak band at 630 mμ. It was mostly but not completely removed by bringing up to *p*H 9, and formed a small amount of haemochromogen (band 560 mμ) in Schumm's test. This could have been methaemoglobin mixed with a little methaemalbumin, but the amount present was minute.

Observations on the Chilled Conjunctiva.—The changes following the application of ice to the conjunctiva were similar to those noted in Case 1.

Laboratory Investigations

Initially the haemoglobin was 57% Haldane (8.4 g.%); erythrocytes, 2,650,000 per c.mm.; leucocytes, 7,350 per c.mm., with normal differential count; reticulocytes, 2.5%; osmotic fragility of erythrocytes normal. Sedimentation rates per hour determined by the Wintrobe method were: 50° F. (10° C.), 22 mm.; 72° F. (22° C.), 45 mm.; 98.6° F. (37° C.), 21 mm. The blood was group A(β) rhesus-positive (anti-D), and the Coombs test was positive. Serum bilirubin was 1.8 mg. per 100 ml.; serum proteins, 6.6 g. per 100 ml. (albumin 3.8 g., globulin 2.8 g.); thymol turbidity, 2.5 units; alkaline phosphatase, 9 (King–Armstrong) units; bromsulphthalein retention, 5% in 30 minutes. Sternal marrow showed normoblastic hyperplasia with a preponderance of intermediate forms.

The Wassermann and Kahn reactions were negative. An agglutinin active in high titre in the cold against the patient's own and homologous erythrocytes was present in the serum. It has been tested for on six occasions, and with a saline diluent the titre has been relatively fixed at 1:20,480. A higher titre was obtained using bovine albumin as diluent (1:81,920). The agglutinin is most active between 32 and 50° F. (0 and 10° C.), and its activity diminishes rapidly above 68° F. (20° C.)

Temperature	Titre	Temperature	Titre
32° F. (0° C.) ..	1:20,480	68° F. (20° C.) ..	1:1,280
50° F. (10° C.) ..	1:20,480	98·6° F. (37° C.) ..	0

On frequent testing no cold haemolysin could be demonstrated either with or without acidification of the serum, using the technique described by Dacie and de Gruchy (1951).

An incomplete cold antibody was also present in this serum as demonstrated by a positive Coombs test after elution of the complete cold antibody as in the previous case.

The Donath–Landsteiner reaction gave equivocal results. On two occasions it was negative even with acidification, but on two other occasions haemolysis occurred with acidified serum although all controls were negative.

Treatment

A course of 100 mg. of A.C.T.H. daily for six days produced no clinical or haematological remission. Urethane was then tried, and a total of 63 g. was taken over a period of three weeks. After ten days the titre had fallen to 1:2,048, but despite continuance of treatment the titre rose to its original level and there was no clinical improvement. Peripheral vasodilator drugs were given as in Case 1, and again had no effect. The only effective measure consisted in the avoidance of undue exposure to cold surroundings.

Discussion

The onset of the disease in both cases was characterized by the sudden spontaneous appearance of numbness and cyanosis of the hands during exposure to cold. These changes are produced by massive agglutination of erythrocytes in the blood vessels. This phenomenon can be demonstrated by examining the conjunctival vessels under the slit-lamp microscope after instilling iced water into the conjunctival sac (Iwai and Mei-Sai, 1925, 1926), when slowing and fragmentation of the blood column can be directly observed. That a similar process occurs in the extremities is inferred from the absence of blanching following pressure on the cyanosed fingers (negative Parisius phenomenon). Attempts to examine the nail-bed capillaries of the chilled finger directly with the capillary microscope were not successful, as the heat of the microscope lamp warmed the part and reversed the process of agglutination. Further observations carried out on our two cases have shown that the attacks of numbness and cyanosis of the hands can be adequately explained by intravascular haemagglutination (Marshall, Shepherd, and Thompson, 1953).

When exposure to cold is excessively prolonged thrombosis may occur in the vessels distal to the blocked area. This is irreversible and when extensive enough leads to gangrene, which has been described as an unusual complication of high-titre cold agglutination by McCombs and McElroy (1937), Benians and Feasby (1941), Stats and Bullowa (1943), Carey, Wilson, and Tamerin (1948), and Ferriman *et al.* (1951). In our second patient, whose occupation entailed the handling of sheet-metal plates out of doors, prolonged exposure resulted in the development of symmetrical digital gangrene. Microscopical examination of the amputated finger-tips revealed thrombi, and such histological evidence as was available was consistent with these having been initiated by stasis.

It is surprising that the clinical symptoms are not always related to the titre of cold agglutinins. In the case recorded by Erf (1945) there were no symptoms directly referable to haemagglutination, although the titre was reported as 1:4,194,304. It may be that activity of this agglutinin in the body does not parallel that *in vitro*, or that, as Hennemann (1951) has suggested, the thermal amplitude of the antibody is the important factor in determining the occurrence of symptoms.

Exposure to cold causes not only intravascular haemagglutination but also haemolysis. This seems to be a purely local phenomenon, and can be demonstrated by

chilling a single limb from which blood samples are collected before and after cooling (Rosenbach test). Stats and Bullowa found only oxyhaemoglobin in serum from the chilled limb, and concluded that simple haemolysis occurs without alteration of the blood pigment. Serum from one of our cases also showed oxyhaemoglobin alone, but in the other there was in addition a small amount of a pigment which may have been a mixture of methaemoglobin and methaemalbumin. Although haemoglobinaemia in the single chilled limb is a constant feature in these patients, insufficient pigment enters the general circulation to produce haemoglobinuria during the performance of the Rosenbach test.

There is a wide divergence of views regarding the mechanism of haemolysis. It seems that intravascular stasis in small vessels contributes to haemolysis by allowing more time for the erythrocytes to agglutinate under the influence of cold, and that "cohesion of erythrocytes may lead to their prompt mechanical destruction while in motion in the circulation," as suggested by Shen, Castle, and Fleming (1944). This mechanistic concept is supported by the experiments of Stats (1945), who showed that when mixtures of sera containing cold agglutinins and homologous cells were shaken during refrigeration at 32° F. (0° C.) haemolysis resulted. In contrast with this theory of mechanical fragility, Dacie (1950b) claims to have detected the presence of a haemolysin in the serum. It is demonstrable only by altering the *p*H of the mixture to the physiological range or a little below it, and the titre is low. We have made repeated attempts, using an identical technique, to detect such a haemolysin in our two cases, but without success.

The anaemia found in patients with this condition is of the haemolytic type. It should be proportional to the extent of intravascular haemolysis as judged by the degree of haemoglobinaemia and haemoglobinuria. However, no distinct relationship between these manifestations and anaemia may be evident. In one of our cases there was well-marked anaemia in the absence of haemoglobinuria.

It is claimed by Benians and Feasby (1941), Helwig and Freis (1943), and Forbes (1947) that the E.S.R. increases when the test is performed at low temperatures owing to the enhanced activity of the agglutinins. However, Stats and Wasserman (1943) maintain that the increased viscosity of blood at low temperatures may retard the E.S.R., and this occurred in the patient reported by Mellinkoff and Pisciotta (1949). In Case 1 a reduction in temperature from 72 to 50° F. (22 to 10° C.) had no significant effect upon the E.S.R., but in Case 2 there was marked retardation.

The treatment of this condition is very unsatisfactory. Some authors have claimed that the use of vasodilator drugs has procured improvement in the Raynaud phenomenon, but in our cases they had no effect. Since there is no evidence that an excessive vasomotor tone contributes to the digital ischaemia, it is not surprising that sympathectomy failed to produce relief in the case recorded by Hanns (1943). The most effective measure consists in avoiding exposure to a cold environment by keeping the extremities well wrapped up and remaining indoors as much as possible during the winter. Attempts have been made to prevent the formation of cold agglutinins or to inactivate them, but without success. Bateman (1949) administered heavy doses of salicylates, which have been shown in animal experiments to be capable of blocking the antigen–antibody reaction, but there was no significant improvement either in the titre of cold agglutinins or in the symptoms. A short course of A.C.T.H. produced no change in one of our patients, and Ferriman *et al.* also noted no benefit from it. More prolonged treatment of the same case with urethane, undertaken in the hope of inhibiting the activity of the reticulo-endothelial system as a producer of immune bodies, was similarly without lasting effect.

Summary

Two cases are reported which readily developed the Raynaud phenomenon and intravascular haemolysis on exposure to cold. One showed, in addition, bilateral symmetrical gangrene of the finger-tips and severe haemolytic anaemia, while the other was subject to attacks of haemoglobinuria. Examination of the serum of both cases revealed cold agglutinins in high titre. Treatment is unsatisfactory, and the only effective measure is the avoidance of cold surroundings.

We wish to thank Dr. S. B. Boyd Campbell and Dr. J. T. Lewis for permission to publish these cases, Professor D. C. Harrison for performing the spectroscopic analyses, and Mr. D. McA. Mehaffey for the photography.

REFERENCES

Bateman, J. C. (1949). *Arch. intern. Med.*, **84**, 523.
Benians, T. H. C., and Feasby, W. R. (1941). *Lancet*, **2**, 479.
Carey, R. M., Wilson, J. L., and Tamerin, J. A. (1948). *Harlem Hosp. Bull.*, **1**, 25.
Dacie, J. V. (1950a). *Nature, Lond.*, **166**, 36.
—— (1950b). *J. Path. Bact.*, **62**, 241.
—— and de Gruchy, G. C. (1951). *J. clin. Path.*, **4**, 253.
Erf, L. A. (1945). *Amer. J. clin. Path.*, **15**, 210.
Ferriman, D. G., Dacie, J. V., Keele, K. D., and Fullerton, J. M. (1951). *Quart. J. Med*, n.s. **20**, 275.
Forbes, G. B. (1947). *British Medical Journal*, **1**, 598.
Hanns, A. (1943). *Sang*, **15**, 506.
Helwig, F. C., and Freis, E. D. (1943). *J. Amer. med. Ass.*, **123**, 626.
Hennemann, H. H. (1951). *Ärztl. Wschr.*, **6**, 413.
Iwai, S., and Méi-Sai, N. (1925). *Jap. med. Wld*, **5**, 119.
—— —— (1926). Ibid., **6**, 345.
McCombs, R. P., and McElroy, J. S. (1937). *Arch. intern. Med.*, **59**, 107.
Marshall, R. J., Shepherd, J. T., and Thompson, I. D. (1953). *Clin. Sci.* In press.
Mellinkoff, S. M., and Pisciotta, A. V. (1949). *Ann. intern. Med.*, **30**, 655.
Shen, S. C., Castle, W. B., and Fleming, E. M. (1944). *Science*, **100**, 387.
Stats, D. (1945). *J. clin. Invest.*, **24**, 33.
—— and Bullowa, J. G. M. (1943). *Arch. intern. Med.*, **72**, 506.
—— and Wasserman, L. R. (1943). *Medicine, Baltimore*, **22**, 363.

CONTINUOUS SUCCINYLCHOLINE CHLORIDE WITH PETHIDINE IN ABDOMINAL SURGERY

BY

G. HERINGTON, M.B., B.S., D.A.

Consultant Anaesthetist, Wanstead Hospital

AND

E. JAMES, M.D., D.P.H., D.A.

Medical Superintendent, Rush Green Hospital, Romford

The sequence of thiopentone, nitrous oxide and oxygen, and a relaxant and controlled respiration, aptly described by Gray and Rees (1952) as a pyramid having as its base apnoea with sides consisting of narcosis, relaxation, and analgesia, has for some time held an important place in anaesthesia for abdominal surgery. This technique produces excellent operating conditions, but the use of longer-acting relaxants such as D-tubocurarine chloride and gallamine triethiodide creates special problems, in particular the difficulty in controlling the duration of relaxation without the use of antidotes. The anaesthetist, faced with the problem of obtaining relaxation for peritoneal closure, is loath to give a further injection of a long-acting relaxant, and may use some less satisfactory alternative.

Even when relaxants are withheld during the latter stages of a major abdominal operation the patient is often left in a state of partial curarization, and the anaesthetist must either accept this or administer neostigmine. Here one encounters varying opinions, some advocating neostigmine in every case, some never. However, the decision to give or withhold neostigmine is a delicate one, and each case must be judged on its merits.

The side-effects of neostigmine, such as bradycardia, salivation, and vomiting, and the occasional occurrence