general weakness which had persisted ever since. Her appetite had deteriorated during the last three months. In March she had a short course of sulphonamides for a septic finger, and again ten days later for a boil on her back which never healed properly. She did not notice any change in her general condition before and after this treatment. During the last few weeks she rested a good deal, but was not entirely confined to bed.

On examination she appeared a rather pale thin woman with evidence of recent loss of weight. Apart from a radiologically confirmed slight enlargement of her heart and a systolic apical murmur there were no significant changes in her cardiovascular system. Her palate was granular. There were no ulcers in her mouth or pharynx. Her spleen reached 1 in. (2.5 cm.) below the costal margin, and was hard. Her blood count on May 30 was: red cells, 2,550,000; haemoglobin, 48%; colour index, 0.94; white cells, 600 (polymorphs 3%, lymphocytes 78%, monocytes 19%). X-ray films of the skeletal system showed Paget's disease of the right femur.

A diagnosis of agranulocytosis was made, and she was put on treatment which included "cytamen," iron, folic acid, ascorbic acid, the vitamin-B complex reinforced by pyridoxine, as well as blood transfusions (2 pints (1.1 litres) on June 4 and on June 24). She also received large doses of penicillin, and, in the later course of her illness, streptomycin. On June 3 her peripheral count had not materially altered: red cells, 2,580,000; haemoglobin, 49%; colour index, 0.96; white cells, 650 (all lymphocytes). Her bone-marrow count consisted of: blast cells, 0.5%; premyelocytes, 1%; myelocytes, 29%; metamyelocytes, 4%; neutrophil polymorphs, 0.5%; eosinophils, 0.5%; normoblasts, early 3.5%, intermediate 11.5%, late 4.5%; monocytes, 2%; lymphocytes, 43%. The myeloid/erythroid ratio was 1.8:1.

On June 11 her white cells numbered 950 without any lymphocytes being seen. On June 19 her red-cell count was 3,220,000; haemoglobin, 59%; colour index, 0.9. There were 800 white cells, all lymphocytes. On June 23 her temperature rose rather high and remained so for three days in spite of antibiotics. An irritating laryngitis and tracheitis had developed and there was a small clean ulcer on her hard palate. On June 24 her white cells numbered 600. No granulocytes were seen.

A.C.T.H. was started on June 25, and for six days she received 20 mg. six-hourly. On July 1 the dose was cut to 20 mg. twice daily, and the treatment was stopped after a total of 600 mg. had been given in nine days. After 140 mg. of A.C.T.H. had been injected the bone-marrow content was: myelocytes, 16%; metamyelocytes, 13%; neutrophils, 2%; lymphoblasts, 2%; lymphocytes (large and small), 60%; normoblasts, early 1%, intermediate 4%, late 2%. At that time she had 500 white cells per c.mm., with 6% neutrophils and 94% lymphocytes in her peripheral blood. On the sixth day of treatment with A.C.T.H. her temperature again rose and she developed laryngitis and diarrhoea, which did not respond to antibiotics. On the eighth day her peripheral blood count was: red cells, 2,600,000; haemoglobin, 54%; colour index, 0.9; white cells, 450. No granulocytes were seen.

A.C.T.H. was stopped on July 3, as neither the patient's general condition nor her bone-marrow function or peripheral blood showed evidence of recovery. She was again put on the remedies which were given before the trial with A.C.T.H., but her condition steadily deteriorated and the last blood count taken on July 11 (20 hours before her death) revealed only 200 white cells with complete absence of granulocytes. She still maintained her red-cell and haemoglobin level. Her temperature reached 104° F. (40° C.), and the diarrhoea persisted. Pericardial friction rubs were heard and she developed oedema of the legs. On the evening of that day she sank into coma and died in the early morning hours of July 12.

Conclusions

This patient had been ill for many months before she came under observation, and I believe that her blood dis-

order existed before sulphonamides were prescribed. Neither antibiotics nor A.C.T.H. had any appreciable effect on the outcome.

I believe that this case belongs to the group of idiopathic agranulocytosis cases which appear to remain unaffected by A.C.T.H. Caldwell (1950) and McMillin (1951) both deal with drug-induced cases of agranulocytosis successfully treated by A.C.T.H. and cortisone respectively. Dudley Hart *et al.* wrote with reference to A.C.T.H. or cortisone that "they may act only in some cases of acute drug-induced agranulocytosis." My own experience entirely supports their opinion.

Idiopathic agranulocytosis, first described 50 years ago, still remains a problem so far as aetiology is concerned and a challenge in respect to treatment.

Summary

A case of agranulocytosis of unknown origin is described. The patient failed to respond to treatment, which included A.C.T.H. over a period of nine days.

The prognosis for agranulocytosis of unknown aetiology remains grave in spite of the introduction of cortisone and A.C.T.H.

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Medical Memoranda

Fractured Shaft of Femur Complicated by Multiple Systemic Emboli

CASE REPORT

A policeman aged 41 was admitted to hospital on March 4, 1951, having fallen sideways off his bicycle on to his left hip, and sustaining a comminuted fracture of the upper third of the left femur. At the time there was no evidence of a nerve or vascular lesion. X-ray films showed a comminuted pertrochanteric fracture of the femur, with a long posterior fragment. A Steinmann pin was inserted into his tibial tubercle and a balanced skeletal traction set up. It was thought, because of the comminution, that closer apposition of the fragment could be obtained by applying a clamp to the Thomas splint. This did, in fact, improve the alignment.

At 7.40 a.m. on April 4, exactly a month after admission, he had a sudden right hemiplegia. This cleared up rapidly, and when seen again at 11 a.m. he had only a residual right facial weakness. His blood pressure was 100/80. Dr. Kembell Price thought the condition was due to an embolism. At 5 p.m. the patient complained that his right leg was cold and painful for an hour. On examination the right leg felt cold and there was complete paralysis of all his muscles below the knee. His right popliteal fossa and calf were extremely tender. The posterior tibial and dorsalis pedis arteris could not be felt. A diagnosis of popliteal embolus was made.

Operation.—At 8 p.m. skeletal traction was converted into fixed traction and a spinal anaesthetic was given. Exploration of the popliteal vessels was carried out through a long midline incision. It was noted that after the induction of anaesthesia vasodilatation did not occur in the right leg, although it did in the left. The popliteal vessels were exposed. The popliteal artery felt hard and was white. It was opened and a 3-in. (7.6-cm.) clot removed. This, however, was not followed by a sudden spurt of blood from the proximal end, and it was not until the last piece of the clot was removed from the portion of the artery which lay in Hunter's canal that the artery was found to be clear. The

incision in the vessel was sutured with arterial-silk atraumatic needles. All the instruments and the wound were washed with sodium citrate.

Post-operatively he was given 15,000 units of heparin through a polythene tube six-hourly. At 2 a.m., five hours after the operation, I was called to see him because of persistent oozing. This was not severe, and not unexpected in view of the spinal anaesthetic. It was noted at this time, however, that he had made a complete recovery from the paralysis and could actively dorsiflex and plantar-flex his foot. Both his lower-limb pulses had returned. Transfusion was considered because of loss of blood during and after operation and because of the necessity for an adequate blood pressure to maintain a good popliteal circulation, but in view of the recent hemiplegia it was thought inadvisable at that stage.

On April 9 much oedema was present from the popliteal fossa downwards, but there was no evidence of aneurysm. Next day an electrocardiogram showed atrial infarction. This no doubt accounted for the source of his emboli. On the 11th his leg suddenly went blue about half an hour after an injection of heparin. As this was thought to be due to haemorrhage with compression of the vessel, 15 ml. of protamine sulphate was given intravenously. It was decided that in order to try to save his limb a blood drip should be set up.

On April 24 the swelling had gone down, but he had complete sensory-nerve loss from the knee downward. His red cells numbered 3,750,000 and the haemoglobin was 68%. The condition of his leg gradually improved. First protopathic sensation and then epicritic sensation returned.

A final examination on July 4 showed some wasting of the calf muscles and a slight equinus deformity due to fibrosis. He was able to walk fairly well with a raised heel and a toe spring.

I am greatly indebted to Mr. J. M. Turner and Mr. H. J. McCurich for their permission to publish this case.

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Acute Pethidine Poisoning

In a search of the literature only one case has been found where pethidine has been taken with suicidal intent. The satisfactory response to treatment also makes the following case interesting.

CASE REPORT

A married woman aged 43 had suffered from tuberculosis of the bladder for 20 years. She had had a left nephrectomy 20 years ago. Because of the pain and frequency, admission to hospital was arranged for July 22, 1950. She had previously refused to come into hospital, but eventually agreed, stipulating a Saturday. Owing to the shortage of beds it was necessary to cancel this carefully arranged admission at the last minute. The same day she was found unconscious at home. She was brought to hospital accompanied by her mother. The mother's account and the patient's appearance indicated that she was suffering from a narcotic poison. The mother had not brought the remaining tablets, so was sent to fetch them, having identified a tablet of phenobarbitone, 1 gr. (65 mg.), as being similar to those in the box.

The patient was found to be deeply comatose, and there was no response to pressure on the supra-orbital nerves nor to any other stimuli. There was extreme respiratory depression, the rate being 16 per minute and very shallow; pulse rate 90 per minute; temperature 97° F. (36.1° C.); blood pressure 100/65; no sweating. The pupils were equal and contracted, with no response to light, and no tendon jerks were present. There were no plantar reflexes, and no other relevant findings.

TREATMENT

It was clear that whatever tablets had been taken they were not aspirin. Phenobarbitone is the commonest agent

in attempted suicide by drugs, and the pupils were contracted. (Opinions vary on the state of the pupils in barbitone poisoning, but from personal observation the pupils are more often contracted than dilated.) The patient's condition called for immediate treatment, and, as her mother had not returned with the tablets for identification, treatment had to be empirical. She was given picrotoxin, 6 mg. intravenously, with no effect. This was followed two minutes later by amphetamine sulphate, 60 mg. intravenously, with no effect. Three minutes later nikethamide, 6 ml., was given intravenously. In thirty seconds the patient became conscious. Although a little confused she recognized her surroundings, and when questioned immediately replied that she had taken 30 tablets of pethidine (1,500 mg.), as she was "fed up." Her mother then arrived with the box of tablets, which were confirmed as pethidine; 20 of the original 50 remained. The patient was now very emotional and would not co-operate in having her stomach washed out. No further treatment was given, but there was no sign of her relapsing back into coma. At 8.30 p.m. she was sweating and shocked. She had a disturbed night (doubtless due to the amphetamine sulphate), but the next morning she was normal again.

Pethidine is rapidly absorbed, quickly metabolized, and partially excreted unchanged in the urine. Elimination of the ingested pethidine was studied by analyses of urine collections, using the method of Lehman and Aitken (1943), with the following results: 6.7 mg. (49th to 73rd hour after ingestion), 2.8 mg. (81st to 105th hour), 0.6 mg. (105th to 129th hour).

DISCUSSION

The absence of vomiting and sweating in the case reported here is noteworthy. The pupils were small, which is unexpected, as in therapeutic doses pethidine causes mydriasis. Recovery was complete within 24 hours. Way (1946) has pointed out that pethidine may stimulate or depress the central nervous system. With overdoses it is the stimulatory action that is usually seen (for example, tremors, uncoordinated muscular movements, and, experimentally, epileptiform seizures), but in certain individuals (as in this case) the depressant action may predominate.

Cases of acute poisoning by pethidine are few. Experimentally, death results from respiratory failure (Gruber *et al.*, 1941). Polonio (1947) mentions two patients with pethidine addiction who had several crises of respiratory failure which responded well to nikethamide. In two deaths which he observed, necropsies could not be made but "the history and post-mortem appearance of cyanosis and engorged veins alike indicated respiratory failure." The only case found of pethidine being taken with suicidal intent is reported by Cohen (1950).

Nikethamide counteracts the effect of depressants of the central nervous system, but how it does so is obscure. From personal experience it is useful in interrupting pentothal narcosis, the treatment of phenobarbitone poisoning, and acute alcoholism. In this case it was dramatically effective in terminating the coma and respiratory depression, and, although one might have expected a relapse into coma, no further injection was necessary. Perhaps the amphetamine sulphate contributed to the sustained recovery of consciousness. As nikethamide is effective in correcting depression of the central nervous system from such different causes, this suggests that, when confronted with a coma from suspected but unknown poisoning, an empirical trial, as in this case, is well worth while.

I am grateful to Dr. H. L. Milles, under whose care the patient was, and to Mr. H. B. Salt, biochemist, for his help with the urinary estimations.

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