Venographic appearances in all these types of cases could be of great help to the planning of the operation—as regards both its indication and its nature. In tropical splenomegaly the absence of collaterals and the normal appearance of the intrahepatic radicles would signify absence of portal hypertension and liver changes and therefore splenectomy alone would be justified. On the other hand, the presence of such changes would often indicate a shunt procedure in addition. In infrahepatic obstruction the venogram would help the surgeon to anticipate the exact site and often the nature of the obstruction. For splenic vein obstruction, splenectomy would suffice in many cases, whereas in cases of portal vein obstruction a shunt operation would again be indicated.

In portal hypertension due to cirrhosis of the liver, visualization of a patent portal vein would enable the surgeon to plan a portacaval shunt if necessary, whereas its non-visualization—as in one of our cases—would indicate portal vein thrombosis and would preclude such a procedure. Further, the presence of secondary portal hypertension in cases of suprahepatic obstruction, as judged by the presence of collaterals, would lead to consideration of portacaval anastomosis.

Summary and Conclusion

Splenoportal venography has been performed successfully in 46 cases, 32 of which were operated on. The operative findings are correlated with the venographic appearances.

The clinical material consisted of 12 cases of tropical splenomegaly of uncertain origin, 13 cases of splenomegalic cirrhosis, 8 cases of portal cirrhosis, 1 case of biliary cirrhosis, 1 case of subacute hepatic necrosis with nodular hyperplasia, 6 cases of infrahepatic obstruction, and 5 cases of suprahepatic obstruction.

Four types of characteristic venographic patterns are described and discussed. These are for: (a) tropical splenomegaly of uncertain origin uncomplicated by cirrhosis of the liver; (b) infrahepatic obstruction of the portal venous system; (c) intrahepatic obstruction due to cirrhosis of the liver and splenomegalic cirrhosis; and (d) suprahepatic obstruction of the hepatic venous outflow.

The value of portal venography in assessing the presence of portal hypertension and cirrhosis of the liver is discussed. Visualization of the collaterals is one of the earliest indications of portal hypertension.

In infrahepatic obstruction, portal venography gives an accurate indication of the site and some indications of the type of obstruction.

The venographic findings could be of great help in the planning of a suitable operative procedure in abnormalities of portal circulation.

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NEOSTIGMINE-RESISTANT CURARIZATION

BY

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One of the greatest attractions of the competitive myoneural blockers is their reversibility by antidote drugs. Indeed, it has become almost an article of faith with those who use agents of this type that it is safe to maintain curarization right up to the time at which the abdomen is closed, in the sanguine expectation that the paralysis will then be undone by neostigmine. It was therefore somewhat disquieting to be called by a registrar some two years ago to see a patient in whom the administration of this drug had failed to produce the expected recovery. Since that date four other cases of this type have been reported to me by registrars. Details of a sixth case were received from another source.

The Syndrome

In every instance the patient was elderly and dilapidated, and yet, though ill, was fit by ordinary standards for general anaesthesia. After premedication with morphine and atropine or papaveretum and scopolamine in safe amounts, anaesthesia was induced with a suitably small dose of thiopentone; the patients were intubated with the aid of suxamethonium, and breathing began again after a perfectly normal interval of a minute or two. Subsequently, anaesthesia was maintained with nitrous oxide and oxygen, together with small doses of pethidine and thiopentone. Relaxation was obtained in four of the cases by giving gallamine triethiodide and in two from D-tubocurarine. In none of the cases was the dose excessive for the duration and magnitude of the operation performed. At the end of the operation neostigmine was given in two lots of 2.5 mg., each with 1/100 gr. (0.65 mg.) of atropine. Spontaneous respiration returned, but in every case its amplitude was insufficient to maintain life. The patients continued with depressed respiration until, in spite of adequate assistance of the breathing, death from circulatory failure ensued some 6 to 8 hours after the end of the operation.

Apart from maintenance of adequate ventilation the following resuscitative measures were employed.

Vasopressor drugs were given in all instances to maintain the blood pressure when it declined. "Tensilon" was given to three of the six patients in repeated doses of 10 mg. with sufficient atropine (usually 1/200 gr.—0.32 mg.) to prevent muscarinic effects. It produced only an evanescent improvement in the breathing, which after some five minutes returned to its previously depressed inadequate level. Additional increments of 1.25 mg. of neostigmine also improved the situation a little in these cases, but there was again a tendency to relapse after some 10 to 20 minutes. In no case was it possible to obtain complete recovery by giving this drug, but its administration never aggravated the situation. All the patients received a large dose of nikethamide, which produced in its turn an even more poorly sustained period of recovery. The intravenous administration of potassium in the form of Nabarro's solution was tried in two of the cases. In one of these there was a definite improvement, although completely normal respiration did not recover before ultimate circulatory failure occurred. In the other instance where this solution was used no response whatever was obtained.

The surgical conditions from which these patients were suffering were all of the nature of an ileus with or without peritonitis. Two of them had acute cholecystitis. In another case the source of the infection was not apparent even at necropsy, and in yet another a 36-hour perforation of a

gastric ulcer was the underlying lesion. The fifth case had had a resection of the colon some three weeks previously. A week before he had had a leak from his suture line with the development of peritonitis and subphrenic abscess. The last case was of acute colonic obstruction in an elderly man.

Discussion

Cases of extreme sensitivity to myoneural blocking agents of the anti-depolarizing or competitive type have already been recorded by Gray and Halton (1948) and Condon (1951). In these cases, however, the main feature of the condition was an abnormal sensitivity to normal doses of the drugs. In the cases which I have described, however, ordinary doses of the relaxant drugs were required to produce abdominal relaxation. In some of them, indeed, spontaneous respiration became depressed after the administration of the relaxant, but was not in fact abolished until just before closure of the abdomen; in other words, the essential problem in the patients under review was not that they were abnormally sensitive to the relaxant drug, but that its curarizing effect persisted long beyond its normal span, and, further, that it could not be undone by neostigmine.

Most of the patients were already extremely ill when they came to operation, and it might seem possible that death was coincidental to the administration of the relaxant. In fact, however, though circulatory depression was present at the end of the anaesthesia in these cases, there was certainly enough circulatory activity to convey all the vasopressor and analeptic drugs from the place of their injection to the site where they acted. Further, in three of the cases there was a definite though fleeting response to the administration of tensilon. It would therefore seem as if there was some major abnormality of the physiology of the myoneural junction which made these patients fail either to recover spontaneously or to respond to neostigmine. The only other point of interest is that in all the instances described death was not due to respiratory insufficiency but to circulatory degeneration and peripheral vascular failure, which developed at varying times after the operation in spite of adequate artificial respiration.

One rather attractive explanation of the syndrome will unfortunately not bear detailed inspection. It might seem possible that in these cases the neostigmine had itself become a myoneural blocking agent or that it had produced an excess of acetylcholine which had interrupted conduction at the end-plate. If either of these events had occurred the injection of more neostigmine would have intensified the paralysis rather than relieved it. Similarly, it is unlikely that tension would have improved such a situation.

Block of the respiratory centre itself by curarizing drugs has been described (Ellis *et al.*, 1952). This condition is said to be reversible by nikethamide. There was, however, no sustained response to respiratory stimulants in these cases. Further, the type of breathing which was present was that characteristic of a fully active respiratory centre struggling hard to overcome a barrier of peripheral curarization rather than that of a central depression of breathing.

Lastly, it is possible that a hypercarbia due to insufficient ventilation may have been responsible. It is certainly true that a state of respiratory depression and persistent myoneural block can arise after the administration of suxamethonium in experimental animals exposed to high concentrations of carbon dioxide (Davis *et al.*, 1955). Scurr (1954), too, has reported a case where seeming curarization due to decamethonium was relieved by hyperventilation. A similar case has been reported by Gray and Fenton (1954) in a patient to whom D-tubocurarine had been given. Manual hyperventilation of my patients, however, produced no improvement. Indeed, its result was always temporarily to aggravate the respiratory depression. Further, in one case a slow recovery of myoneural block during the post-operative period was directly demonstrated by faradic stimulation of the flexor muscles of the forearm at a motor point.

It is interesting that while this material was being collected four other cases were submitted to me where neostigmine-resistant curarization seemed to have occurred, but where, in fact, the history made it clear that carbon dioxide narcosis was the essential lesion.

If it is accepted that the condition was in fact due to neostigmine-resistant myoneural block, it is pertinent to ask what was responsible for its persistence. It seems possible that some disturbance of the plasma electrolytes may be the explanation, for it is well known that in experimental animals abnormalities of the sodium-potassium balance at the end-plate can seriously interfere with its function. In patients of the type described such an upset was quite likely to be present. For they were extremely ill, and, further, had a gross disturbance of gastro-intestinal function. Vomiting had occurred in some, and in all some degree of ileus was present. Several of them had had considerable amounts of isotonic sodium chloride, with or without dextrose, infused intravenously in the hours or days preceding operation. Further, it is by no means impossible that elderly patients, especially women living by themselves, would have been for some time on a diet deficient in potassium. Deficiency of this ion in the body must therefore be considered as a cause of the disturbance.

It is admitted that the serum potassium level, determined in only one case, and that on a specimen which had stood overnight, proved to be normal, but an intracellular potassium deficiency may, especially in acidotic states, occur even if the concentration of the circulating ion remains unchanged. Further, in one case electrocardiographic evidence was obtained of the characteristic changes produced by potassium deficiency. Also, it was possible to obtain a temporary improvement in this patient's condition by injecting fluid containing this substance; in another case the transfusion of stored blood which has a high potassium content also produced a marked improvement. The evidence for potassium deficiency is, however, really slender, and it is advanced only as a tentative hypothesis upon which further work may be based. The main purpose of this article is, indeed, to draw attention to this condition, which does not seem to have been described so far, in the hope that further work on its aetiology will be stimulated thereby.

It is interesting that Dripps (1953) reported a group of cases in which much less lethal prolongation of the action of both decamethonium and D-tubocurarine occurred. After reviewing the various possible aetiological factors he reached virtually the same conclusions as those set out in this paper. Foldes *et al.* (1952) have also reported recovery from respiratory depression due to "mytolon" after the administration of potassium. I would, however, caution against the indiscriminate administration of potassium in cases of this kind. For an additional case of the type described in this paper seen lately had a serum potassium of 38 mg. per 100 ml.

From the practical point of view it is important to recognize the type of patient in whom competitive myoneural blocking agents are likely to be neostigmine resistant—that is, the elderly patient with ileus—and to use in them either some form of regional analgesia or a suxamethonium drip which allows the myoneural block to be more readily modified to meet the immediate needs of the individual patient. If competition blockers must be used they should be given only in amounts which will not seriously interfere with breathing.

Summary

In six elderly patients curarization produced by anti-depolarizing myoneural blocking agents persisted after the administration of seemingly adequate doses of neostigmine. It seems possible that this disturbance was due to an upset of the electrolyte balance in these patients; but the evidence is slight, and further investigation is required to elucidate the problem.

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TREATMENT OF ADDISON'S DISEASE

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Differences of opinion still exist concerning the best method of treating patients with Addison's disease. The first real advance came with the discovery of deoxycortone acetate (D.C.A.), and early work with this substance was reported by Simpson (1938). It was soon clear, however, that D.C.A. provided only partial control. Patients remained liable to hypoglycaemic attacks, while any severe stress would still precipitate a dangerous and often fatal crisis. When cortisone became available it was evident that this substance exerted a profound effect: hypoglycaemia was abolished and the patient's improved energy, well-being, and weight gain, with improved ability to withstand stressful situations, clearly demonstrated its usefulness.

At first cortisone and D.C.A. were used together (Thorn *et al.*, 1951; MacNeal, 1951; Laurie, 1951; Fourman and Horler, 1954). Sorkin and Soffer (1953) state that D.C.A. is the most important hormonal preparation necessary in the maintenance of a patient with Addison's disease. They believe it should be employed in all cases because of its striking ability to correct disturbances in sodium and potassium metabolism. Thorn (1955) states that the amount of cortisone or hydrocortisone required to restore to normal the metabolism of sugar, etc., is too small to assure a normal electrolyte and water balance, and so he advises the addition of 10–15 g. of sodium chloride daily, or, in the majority of cases, D.C.A. with a normal sodium and potassium intake.

On the other hand, Simpson (1953) believed that when cortisone became freely available it would provide the basic treatment, supplemented, if necessary, with additional salt or D.C.A. Hart (1954) treats his adrenalectomized patients and patients with Addison's disease with cortisone alone and finds they can be maintained quite satisfactorily without D.C.A. Bishop (1955) states that cortisone has to a large extent supplanted D.C.A.

It was because of this conflict in opinion that we decided to test the effectiveness of various forms of treatment on patients with Addison's disease under their normal modes of life. In particular we were anxious to see if they could be kept in good health on cortisone alone.

Method

To determine the most suitable method of treatment, four patients with Addison's disease were studied over a prolonged period. Three of these were considered to have severe Addison's disease, while the fourth was a moderately severe case. The patients were treated for periods ranging from 9 to 21 months with D.C.A., sodium chloride, and cortisone (combined therapy), and for a period ranging from 6 to 10 months with cortisone alone. Each patient was assessed in detail before beginning treatment, when D.C.A. and salt were withdrawn, and at the end of the period with cortisone alone. As a safeguard every patient was interviewed monthly, and their blood pressure and weight were recorded.

During each of the major examinations careful attention was directed to the following factors: (1) energy and capacity for work and recreation; (2) sense of well-being, emotional tone, and mental state; (3) libido; (4) incidence and severity of infections and crises; (5) weight; (6) blood pressure; (7) pigmentation; and (8) electrolytes and blood count. Clinical details of the four patients, together with treatment adopted, are given in Table I.

Results of Treatment

Energy and Capacity for Work.—The degree of weakness and prostration suffered as a result of the illness was generally severe. In Case 1 the diagnosis had been made in 1950 and treatment with D.C.A. given. While this had restored his energy to some extent, it was apparent that he was unable to undertake all the heavy work of the farm, and required additional help from his neighbours. Owing to increasing weakness he had received a further implant of 250 mg. of D.C.A. two months before we saw him in a typical Addisonian crisis. In Cases 2 and 3 progressive weakness occurred until work became impossible. A more fluctuating weakness characterized Case 4, and for weeks at a stretch this patient was unable to do much housework; at other times she had more energy, but most household duties were a burden to her. However, before treatment with combined therapy began, she had been confined to bed for some weeks because of weakness and nausea, and was admitted to hospital for detailed investigation of her adrenal function and reserve. In these cases, with treatment the improvement in symptoms was striking, and energy returned to normal in three and nearly to normal in the other. There was no noticeable change in energy when D.C.A. and salt were stopped. The farmer (Case 1) and storeman (Case 3) both do heavy work and say they feel normal in every way on cortisone alone. One housewife (Case 2), who has a family of five to look after, is as fit and well on cortisone as on the combined treatment. The other housewife (Case 4), the only patient whose return of energy has not quite matched her original strength, felt no alteration in strength when D.C.A. and salt were withdrawn.

Sense of Well-being, Emotional Tone, and Mental State.—Three patients were mentally dull and two were depressed when untreated. All returned to normal on combined treatment, and there was no alteration in this when D.C.A. and salt were withheld.

Libido.—This was stated to be normal in one before treatment began and remained unchanged. In two, libido was depressed before treatment and improved with combined therapy. The improvement was maintained on cortisone alone. One patient had complete absence of libido following hysterectomy previously, and treatment did not alter this. Improvement in libido is likely to be related to the change in the patient's general condition rather than to any specific effect of the cortisone.

Incidence of Infections and Severity of Crises.—One patient, despite an implant of D.C.A. and additional salt therapy, was admitted to hospital in a severe crisis. One patient developed a crisis in hospital following anaesthesia for gastroscopy. A third patient had experienced recurrent