Pelouze and Bernard (1850) first described the peripheral nature of curare paralysis. Further investigation, begun in 1852 by Claude Bernard, demonstrated the action of curarine to be at the neuromuscular junction (Bernard, 1856). Thus, one hundred years ago, the idea crystallized that the central actions of curare were unimportant or nonexistent, and was given form by such statements as “Mais c’est le contraire qui a lieu, et le curare n’a que l’apparence d’être un agent anesthétique, car l’animal sent, mais il ne peut pas le manifester” (Bernard, 1857); and “La sensibilité est conservé dans l’empoisonnement par le curare; mais cette sensibilité est muette, elle a perdu tous ses moyens d’expression qui sont les nerfs moteur” (Vulpian, 1856). In this way was curare relegated to a class of drugs having only a peripheral action in the animal body, and even today is so classified, despite abundant pharmacological evidence of its central effect in experimental preparations, notably described by Salama and Wright (1950, 1952b), whose work was in a tradition dating back to Tillie (1890), of Edinburgh, the first to suggest a similarity between strychnine and curare.

In doses employed clinically curare generally appears to have purely, or largely, a peripheral action. The purpose of this paper is to describe the circumstances in which such doses may produce an apparent central effect, abnormal and sometimes fatal, presenting as a particular syndrome.

**Clinical Evidence**

Initially, it was through the use of an extremely simple anaesthetic technique (Gray, 1954) that it became apparent that curare might indeed have a central action in some patients. In this technique the patient is allowed to breathe oxygen from a Magill semi-open rebreathing attachment of a Boyle’s machine in order to displace lung nitrogen. Following this, nitrous oxide with about 25 per cent oxygen is given: when consciousness is lost, a full paralysing dose of d-tubocurarine chloride (dTC) of 25–35 mg given intravenously allows easy endotracheal intubation. By this means hypoxia is avoided, a high partial pressure of nitrous oxide in the lung alveoli ensures rapid loss of consciousness, and the least possible disturbance of the myocardium and medullary centres results. Controlled ventilation is always used with these doses of relaxants, which, are supplemented during anaesthesia to maintain the apnoea. At the end of operation the paralysis is
reversed by intravenous atropine followed by adequate doses of neostigmine. The rapid elimination of nitrous oxide (Fink, 1954, 1955; Kety, 1950) means that consciousness is rapidly regained after operation, normally within 5–10 minutes of discontinuing the anaesthetic. Any unduly prolonged period of unconsciousness thus indicates depression produced by another factor—in this technique it can only be the dTC or possibly the neostigmine.

The frequency of the type of reaction to be described must vary, in that it seems to be related to hypokalaemia, thus depending on the pre-operative replacement of body electrolytes and water in depleted patients. Present experience suggests this reaction to be commoner than the myasthenic hypersensitive response, for the detection of which a test dose of antidepolarizing relaxants is recommended (Gray and Halton, 1948).

The following illustrative case reports fall naturally into two groups.

FATAL CASES

CASE 1. A man of 78 years was treated for 8 days in a medical ward for chronic intestinal obstruction caused by a carcinoma of the pelvic junction. This was precipitated into an acute obstruction by the use of barium in X-ray studies. He became grossly distended and vomited considerable amounts of fluid which were inadequately replaced with saline and dextrose.

He was presented for emergency surgery dehydrated, and with electrolyte depletion—serum Na 130.5 mEq/l., K 3.2 mEq/l., Cl 82.4 mEq/l. His blood urea had recently risen to 115 mg per cent.

Premedication was with atropine 0.6 mg and morphine 10 mg.

The patient was given oxygen to breathe for several minutes and then nitrous oxide and oxygen (6 l./min and 2 l./min respectively). Simultaneously an intravenous test dose of 5 mg dTC was given. This did not evoke an abnormal depression of breathing, so that a further 25 mg was given as consciousness was lost, and the patient intubated. He was so restless—moving his arms and legs, shaking his head, opening his eyes, and breathing—that within 10 minutes a further 10 mg of dTC was given. This had little immediate effect, but after about 10 minutes again he suddenly became quiet, remaining thus throughout the operation. Towards the end a further dose of 10 mg dTC was given during closure of the very distended abdomen. This total dose of 50 mg dTC spread over 1½ hours operating time is not considered unusual for the technique employed.

Faint respiratory movements were present at the end of operation, so atropine 1.2 mg was given intravenously, followed by neostigmine 5 mg for reversal of curarization. The effect was barely perceptible. A further dose of 2.5 mg neostigmine was given after ½ hour, and this dose was repeated at hourly intervals. In the meantime, other resuscitative measures were tried, including nalorphine, Megimide (bemegride), nikethamide, alterations in inspired carbon dioxide tension, inflation with pure oxygen, intravenous potassium infusion, and intravenous noradrenaline infusion when it was found that his blood pressure had fallen to about 65 mm Hg systolic. (On admission his blood pressure had been 200/100 mm Hg.) None of these measures produced more than a mild transient response, bemegride being the most effective. After the last dose of neostigmine, when 15 mg had been given altogether over 3 hours, respiration virtually ceased. Despite prolonged ventilation with oxygen, his unconsciousness persisted, together with inadequate respiration and hypotension that responded but poorly to noradrenaline infusion. He died about 14 hours after the operation. Postmortem did not reveal any immediate cause of death: apart from the carcinoma and a polyp of the colon, he had secondary metastatic deposits in the liver, gross coronary atheroma, nodular goitre, and multiple small areas of old cerebral softening. There was no evidence of recent C.N.S. or myocardial damage.

Comment. In the absence of other evidence of poor renal function, the raised blood urea was taken to indicate low excretion through dehydration. This dehydration may also have led to misleadingly high serum electrolyte levels; he had been in negative electrolyte balance for some time. Proportionately there was a far greater fall of serum potassium than of sodium and chloride.

It might be said that hypotension accounted for his death, but it would certainly not account for his clinical state before death. The postmortem findings give no support to this view.

This case indicates that there may be a danger in giving repeated doses of neostigmine, should the initial dose be ineffective.
Case 2. A young man of 23 years, who at the age of 17 years had been found to have tuberculosis of the left kidney and epididymis, with right hydro-nephrosis, suggestive of back pressure. Accordingly a left nephrectomy was done, and the right ureter transplanted into the colon. Recovery from this at first seemed good, although his blood urea was a little raised. Later, over the years, there appeared signs of a metabolic disturbance; he lacked energy, his legs were painful, he became acido tic, and a generalized skeletal osteoporosis appeared. It was deemed desirable to correct this metabolic disturbance, and he was readmitted to hospital in July 1955 for a further operation at which his remaining ureter was reanastomosed to his previously defunctioned bladder through a loop of ileum. Before this operation his pre-existing acidosis had been corrected to 54 vol per cent CO₂, serum Na, K, Ca, and Cl levels were within normal limits, and serum urea was 75 mg per cent. The anaesthetic was induced with thiopentone and DTC, maintained with nitrous oxide, oxygen, and DTC, and reversal of paralysis at the end was satisfactory with atropine and neostigmine. After this his general condition at first improved, but then he began to deteriorate despite a good urine output. He became acido tic, potassium loss was marked and progressive, whilst a much smaller sodium loss occurred, and chloride was well maintained. The blood urea level rose slowly. At first the acidosis was corrigible with oral sodium and potassium bicarbonate, but he continued to decline, latterly noticing weakness of his hands and blurring of vision.

Therefore, a revision operation was undertaken five weeks after the recent anastomosis, at which the relatively simple procedure was undertaken of transplanting the ileal loop with ureter attached from the bladder to an opening on the abdominal wall. Before operation he was weak, acido tic, listless, anaemic (Hb 78 per cent); no recent serum electrolyte levels were known, and he was accepted as a bad anaesthetic risk in a surgical emergency.

Premedication was with 0.6 mg atropine. During pre-oxygenation a test dose of 2.5 mg DTC was given without evidence of sensitivity. When nitrous oxide had produced unconsciousness, 25 mg DTC was given, and intubation was easy. At the end of operation reversal of curarization with 1.2 mg atropine followed by neostigmine 5 mg was barely apparent. Nitrous oxide was later discontinued, but consciousness did not return.

At this time the idea was entertained that this was an abnormal response to the relaxant brought about by potassium loss. No further neostigmine was given, and after a blood sample revealed 29.4 vol per cent CO₂, Na 117.4 mEq/l., K 1.8 mEq/l., Cl 91.5 mEq/l., urea 135 mg per cent, intensive intravenous therapy with potassium and sodium lactate was instituted. Later blood transfusion was given, and it became necessary to maintain his blood pressure with nor-adrenaline.

After nearly 10 grams of intravenous potassium chloride had been given over about 12 hours, sometimes with e.g. signs of toxic hyperkalaemia, the serum level had risen to 2.44 mEq/l. There was now some evidence of lightening coma with improved respiration. Urine output was good (urine K 46 mg per cent, urea 124 mg per cent). Eventually he died about 28 hours after operation. There was no relevant abnormality at autopsy.

Comment. The first revision operation was, in a way, a control for the second. The major recordable differences between the two were the increasing acidosis and the great fall in potassium blood level. These two usually go hand in hand, the former causing the latter (Wright, 1952). This seems to incriminate hypokalaemia in the genesis of the abnormal response.

Anaesthetics have been successfully given in the presence of far higher blood urea levels. Indeed, the chief significance of such raised levels is that they potentiate and prolong the action of barbiturates and thiobarbiturates (Dundee, 1956), neither of which had been used. This metabolic disturbance is not felt to relate to the cause of death.

One possible danger of large intravenous doses of potassium is illustrated, as well as a clinical impression of improvement produced thereby.

Case 3. A man of 64 years with advanced carcinoma of the stomach had been inadequately treated with potassium-free fluids for a week before palliative gastro-enterostomy was to be performed. Two days before operation the serum electrolytes were all within normal limits, but the presence of a blood urea of 115 mg per cent suggested dehydration, confirmed from clinical appearance, and there was anaemia. On these findings, his fluid intake was greatly raised, 5 l. fluid being the positive balance over the next 48 hours. Therefore he probably came to operation with low potassium levels, since this element had not been given, and with an increased anaemia. The day before operation his level of consciousness was described as "poor."

Despite a premedication of atropine 0.6 mg only, he was nearly unconscious on arrival in the anaesthetic room. He was pre-oxygenated, a test dose of 20 mg gallamine was given, this succeeded by a further 100 mg after unconsciousness followed the use of nitrous oxide. Intubation was easy, relaxation good throughout. The usual dose of drugs for reversal of paralysis was ineffective at the end of an operating time of a little less than an hour. Unconsciousness, respiratory depression, and hypotension were marked and persisted after all anaesthetic agent was eliminated. Due to the falsely optimistic result of his previous blood electrolyte estimation, no potassium was given;
a noradrenaline drip was used to maintain blood pressure, and he died 12 hours after operation.

Postmortem he was found to have a carcinoma of the stomach, and some pulmonary oedema, with posterior consolidation of both bases, but no evidence of the immediate cause of death and no visible lesion on sectioning the brain.

Comment. Gallamine was used here because the possibility of an abnormal relaxant reaction was anticipated; the work of Salama and Wright (1952a) suggested that this drug might be expected to have a weaker and more evanescent central action than dTC. However, their experimental observation did not seem to be applicable here, since the abnormal reaction produced appeared similar to those seen after dTC.

CASE 4. A man of 36 years who had had signs of increasing intestinal obstruction for the past eight days, with recent vomiting and gross distension. Peripheral circulatory failure was apparent upon his emergency admission to hospital for laparotomy. He was somewhat restored with intravenous saline, pre-medicated with atropine 0.6 mg and morphine 10 mg, and anaesthesia was induced with thiopentone 200 mg and suxamethonium 100 mg. After intubation, when respiration had begun to return, he was given 35 mg dTC, pethidine 20 mg, and maintained unconscious with nitrous oxide and oxygen. He was found to have a generalized peritonitis caused by perforated diverticulitis of the pelvic colon. During operation the blood pressure fell, being corrected by two intravenous injections of 5 mg methamphetamine.

Reversal was attempted with intravenous atropine 0.8 mg followed by two doses of 2.5 mg neostigmine. Respiration remained shallow, being assisted, using oxygen only. Further doses of neostigmine were given until by an hour after operation he had received 20 mg!

Although no serum electrolyte levels were known, it was thought certain that this man had a degree of potassium depletion. Thus, 3 hours after operation he was started on an intravenous infusion containing 2 grams potassium chloride, and noradrenaline, given over 2 hours. After the blood pressure had responded to the vasopressor, 100 mg hydrocortisone was also added. The hypotension first responded, and later the respiration started to improve; after 1½ hours his tidal volume was judged adequate; a little later he awoke, suddenly.

He was returned to his ward with oxygen mask, and the intravenous infusion still running, containing now noradrenaline and 250 mg aminophyllin. He was confused, restless, and with some moist sounds at the lung bases (over-rapid transfusion?). He relapsed and died a little over an hour later. The manner of his passing was not witnessed by a competent observer.

Comment. The multiplicity of agents used and the lack of biochemical evidence makes this report less instructive. However, it seems reasonable to suggest that hypokalaemia was present in this man. The response of the blood pressure before the use of hydrocortisone might indicate that acute adrenal cortical insufficiency was not involved.

Adrenal cortical hormones are known to lower serum potassium both by increased elimination in the urine and also by a shift of this element from the blood to other body fluid spaces. Such a shift may cause paralysis in susceptible individuals (Pudenz et al., 1938). If potassium depletion is concerned in the genesis of abnormal responses to relaxants, then perhaps the use of cortisone and hydrocortisone may be contra-indicated during anaesthesia with relaxants if there is hypokalaemia. That this danger exists has not yet been proved, but it would seem wise to give intravenous potassium during the 6–8 hours of these hormones' influence in such patients.

CASE 5. A year before the present incident a woman of 52 years had had a left radical mastectomy for a spheroidal cell carcinoma. This was followed by radiotherapy, the radiologist further reporting that five months after her operation there was no evidence of metastases in bone or lung.

Eleven months after operation she had deteriorated, with metastases visible on X-ray in her ribs and lumbar spine. It was proposed to remove both ovaries and the right adrenal gland initially, later her left adrenal gland. Blood chemistry on admission was Na 152 mEq/l., K 4.3 mEq/l., Cl 100 mEq/l., N.P.N. 35 mg per cent.

A routine pre-operative course of cortisone was started: after the initial 100 mg her e.e.g. was recorded and found to be abnormal by virtue of excessive widespread slow activity.

On operation day it was found that no blood had been cross-matched for her use, and the procedure was postponed for four days. The full pre-operative cortisone schedule was then repeated, so that when she finally came to surgery she had had 650 mg in the previous five days. In all this time a constant
watch was kept on her serum potassium; it varied between 4.5 and 5.2 mEq/l.

Premedication was with atropine 0.6 mg and morphine 10 mg.

Induction was with 400 mg thiopentone and 30 mg dTC. After this intubation was difficult due to active closure of the jaw and active movements of the vocal cords. Relaxation was poor—50 mg dTC had been given in the first 1/2 hour and a further 10 mg within the next 1/2 hour. For this reason a little ether was added to the closed circuit, producing better operating conditions.

Near the end of the operation, and a good while after the addition of ether, the blood pressure suddenly fell. It had been well maintained before, nor was any fault of carbon dioxide elimination or hypoxia to be incriminated. The collapse was "peripheral" in the limb vessels rather than "central" in the carotid arteries. Intravenous noradrenaline easily corrected this; there had been minimal blood loss. When respiration had begun to return, reversal of curarization was attempted with atropine 1.2 mg followed by 5 mg neostigmine. This was without effect on respiration, and there was no sign of awakening. Two further doses of 5 mg neostigmine were given within the next half hour without effect. The blood pressure was now becoming increasingly difficult to maintain with noradrenaline.

This unconsciousness persisted, the respiratory depression remained, and the peripheral blood pressure became increasingly refractory to noradrenaline. She died 11 hours after the start of the anaesthetic. Final measures before her death included 20 mg methoxamine, and 100 mg hydrocortisone intravenously. No potassium was given since her postoperative serum level of this was found to be 5.2 mEq/l.

It was specially recorded that although respiration was so shallow and jerky that it required assistance, cyanosis did not readily appear when assistance ceased. (This has been noted in at least two other patients in this series.)

The autopsy revealed widespread metastases of the liver, lungs, and pleura in addition to the bony involvement. A careful search revealed no such deposits in the brain.

Comment. Here the dTC resistance might be ascribed to liver damage from extensive replacement by malignant tissue: unfortunately, no liver function tests were carried out, and the level of serum pseudocholinesterase was unknown. However, other elements in her story suggest that this was not the cause of death.

The dose of cortisone would appear large for a subject such as this patient and liver damage may have potentiated the activity of the hormone. Large doses of ACTH or cortisone may induce a psychotic state with e.g. abnormalities, both of which are readily corrected by giving potassium (Danowski and Tarail, 1953).

Despite the use of ether, a recovery of some respiration at the end of operation suggests that it had been largely eliminated, and was not directly concerned in the fatal outcome.

NON-FATAL CASES

CASE 6. A woman of 41 years had had a long history of Crohn's disease with much surgery, and, for the past three weeks, had experienced increasing intestinal obstruction, culminating in acute pain with vomiting on the day before her admission to hospital. Her blood investigations then showed Na 132.6 mEq/l, K 3.7 mEq/l, Cl 99 mEq/l, P.C.V. 53 per cent, Hb 121 per cent; she was dehydrated.

Replacement fluid was 500 ml saline and 1,500 ml dextrose 5 per cent in water over 12 hours, so that she presented for operation well hydrated, with normal serum Na and Cl levels, but a low serum K of 3.5 mEq/l, and no evidence of acidosis.

Premedication was with atropine 0.6 mg and morphine 10 mg, after which she arrived in the anaesthetic room in a state of extreme and unusual apprehension, despite her many previous surgical experiences. A test dose of 5 mg dTC was given, and this produced a profound and striking change in her mood. She became less talkative, tranquil, drowsy, and perhaps a little confused, in addition to exhibiting the expected partial ptosis. After 5 minutes she complained of some difficulty with breathing. Despite this a further 20 mg dTC was given, followed by 200 mg thiopentone for induction. Intubation was unusually difficult. Jaw relaxation was poor, and there were active movements of the vocal cords, head, arms, opening the eyes, and active breathing. After about 10 minutes of controlled ventilation with nitrous oxide and oxygen these active movements ceased, but 35 minutes after induction a further dose of 10 mg dTC was given since she was breathing deeply. It was noticed that this second dose, which stopped movements of the limbs as well as the breathing, also abolished a previously present corneal reflex, and rendered the pupillary light reflex sluggish. These two signs of central activity returned pari passu with the respiration. During the operation the diseased part of the small intestine was resected, followed by end-to-end anastomosis. Measured blood loss was 10 oz (300 ml), the only replacement being 300 ml of dextrose 5 per cent in water.

Reversal was adequate with neostigmine, although the onset of its action was a little slow. The usual signs of awakening did not appear for at least 45 minutes after discontinuing the anaesthetic—the total anaesthetic time had been 2 hours. Her blood cholinesterase was normal.
Comment. This woman had been extremely active and fit before her admission, presenting at operation as a nearly pure potassium deficiency uncomplicated by any other metabolic disturbance.

The action of the test dose of dTC on respiration would appear to have been a central (subjective) rather than a peripheral affair. The maintenance dose of the drug given during the operation again seemed to have produced a deepening of the central depression already produced by the nitrous oxide.

CASE 7. A woman of 45 years was admitted to hospital as an emergency with acute intestinal obstruction and vomiting of 24 hours' duration. Since it was a Sunday evening no pre-operative biochemical investigations were done. An intravenous saline infusion was started at the same time as the premedication of atropine 0.6 mg and morphine 10 mg. She was alert and cooperative immediately before operation.

A test dose of 10 mg dTC was given. After 2-3 minutes she started to struggle and appeared unconscious, without lash or corneal reflexes. She was intubated without additional drugs, then maintained anaesthetic with nitrous oxide and oxygen. She required very large doses of dTC for continued relaxation—about 5 mg every 10 minutes to a total of 70 mg for an operation lasting an hour.

Reversal of curarization with the usual dose of atropine followed by neostigmine was satisfactory, but there was prolonged postoperative sleep. Questioned the following day, she had no remembrance of her induction or intubation.

Twelve hours after her operation blood taken for biochemical analysis showed CO2 64 vol per cent, Na 134 mEq/l., K 3.33 mEq/l., Cl 100 mEq/l., urea 56 mg per cent.

Comment. This is thought to provide an unequivocal instance of a central action of dTC in clinical dose. The connection with potassium loss is reasonably clear. It is more difficult to explain the extreme and persistent dTC resistance, although the explanation of Dundee and Gray (1953) that this may be due to a low serum pseudocholinesterase might be applicable. Unfortunately, through error, this investigation was omitted in the immediate postoperative period.

CASE 8. A healthy and active man of 60 years was brought to surgery for routine herniorrhaphy. Premedication had been with promethazine 25 mg and atropine 0.6 mg. A test dose of 5 mg dTC produced very pronounced ptosis. Induction was with 25 mg dTC followed by 250 mg thiopentone. Intubation was relatively easy, but despite this he retained full muscle power in his arms, carrying out purposive movements—putting his hand to his face, and grasping a hand placed in his own. This persisted for about 10 minutes after induction, thereby affording several observers the opportunity to test the strength and purposeful nature of his grasp.

As this seemed to be an abnormal response, blood was immediately taken for biochemical tests. These showed that the serum Na, Ca, Cl, alkali reserve, and pseudocholinesterase were all well within normal limits, but that the serum K was inexplicably low at 3.9 mEq/l. In addition, his blood sugar was unchanged before, during, and 1 hour after anaesthesia at 100 mg per cent. The operation lasted 1 hour and a further 20 mg dTC was given. He started to breathe at the end of the operation; the usual dose of neostigmine after atropine resulted in satisfactory reversal, but he slept on for more than 30 minutes after the anaesthetic had ended.

Comment. Questioning later disclosed nothing in the past history of the patient or his family to indicate a disease resembling familial periodic paralysis which may be associated with unexplained falls in serum potassium.

It is of interest to note that although a small lowering of the serum potassium was the only positive finding here, it did not seem to have produced a peripheral sensitivity to dTC, but rather a central effect.

The stable blood sugar is thought to indicate, inter alia, that no great error of anaesthetic technique was made which might have been held responsible for the initial struggling and the prolonged period of postoperative unconsciousness.

This case probably represents the mildest form of this abnormal response with relaxants seen with hypokalaemia. Many observers may have noted that patients who might be expected to be sensitive to anaesthetic agents because of preceding vomiting prove to be unexpectedly "tough," at least during
induction. Present experience suggests that the non-fatal reaction may be seen without hypokalaemia, for instance, in severely jaundiced patients.

**GENERAL CLINICAL PICTURE**

In reviewing these case reports, and other unpublished observations, a general clinical pattern appears, on which the following description is based. The division into two groups falls naturally:

**Group I.**

This includes patients who have had a brief episode of potassium loss—lasting a day or two, often with dehydration. Typical in this class would be the acute high intestinal obstruction, or the patient involved in the metabolic disturbances appearing in the first few days after surgery (Le Quesne, 1954).

In addition, a similar effect has been seen in acutely jaundiced patients. In one at least the blood pseudocholinesterase level was normal.

Into this group would fall those patients with unexplained low serum potassium levels.

The clinical response to relaxants includes:

(a) No peripheral hypersensitivity to a test dose of dTC. Drowsiness distinct from ptosis may be sought after the test dose, but is often an unreliable sign.

(b) A full curarizing dose evokes increased motor activity—generalized struggling, purposive movements of the arms and hands, breathing, and even opening of the eyes. This "excitement phase" is usually transient, lasting about 10 to 15 minutes.

(c) The blood pressure is normal or may be raised.

(d) Normal doses of relaxants are needed during surgery.

(e) Reversal of curarization with neostigmine is satisfactory, although the effect may be a little slow in onset.

(f) Unusually prolonged postoperative drowsiness is a feature.

In all these people the potassium depletion is thought to be largely of the extracellular space only.

**Group II.**

There may not be a clear dividing line between the two groups, postoperative depression becoming more and more prolonged and deep until it is found irreversible.

This second group includes patients who have had prolonged unreplaced loss of potassium, either by vomiting, diarrhoea, or loss into the "third fluid space" within the gut in paralytic ileus. Any form of gross metabolic disturbance may fall within this category (e.g., diabetic ketosis), and it may be possible to induce a suitable state of depletion therapeutically with special diets, kation exchange resins in the sodium phase, or with some steroid hormones. Since the kidney is unable to conserve potassium as it does sodium, prolonged maintenance on potassium free intravenous fluids without other overt loss may lead to severe depletion.

The duration of loss in persons in this group has generally been about one week. The intracellular space thus might be significantly depleted of potassium.

The clinical response to relaxants includes:

(a) Again no peripheral hypersensitivity to the test dose of dTC.
(b) Following the full curarizing dose, there may be a marked "excitement phase" followed by a prolonged, and perhaps permanent, phase of quiescence. There is a real danger here of interpreting the poor relaxation of the "excitement phase" as an indication for increasing the dose of relaxant. However, the apparently most seriously depleted patients did not show any significant "excitement." Whether this indicates a heightened central susceptibility, or whether it reveals that the neuromuscular junction had become more sensitive, is a problem requiring further investigation.

(c) The phase of "depression," which seems to appear in all after a variable period, will include hypotension.

(d) The total need for relaxant during the operation is definitely less—in fact the induction dose may provide several hours' complete relaxation.

(e) Reversal with neostigmine virtually does not occur. Increasing the dose of this antidote had the appearance of increasing the depression.

(f) Postoperative unconsciousness is prolonged in a manner which cannot be accounted for by the anaesthetic agents employed, nor on the degree of surgical trauma. Death commonly follows signs of increasing C.N.S. depression many hours after the elimination of any volatile agents used.

The patients that died presented such a constant group of symptoms that special mention should be made of this.

This "syndrome" comprised the triad of:

1. Persistent unconsciousness after elimination of the anaesthetic agents (as distinct from the relaxants).

2. Persistent hypotension that responded increasingly poorly to intravenous noradrenaline. (Case 1 required 16 mg/l.)

3. Persistent inadequate respiration. In at least some of the patients the respiratory pattern did not resemble that of curarization, in that it was well co-ordinated but entirely insufficient. The term "miniature respiration" is excellently descriptive.

Despite the fact that the foregoing description of an abnormal relaxant response must explain many "anaesthetic deaths," very little seems to have been recorded on this, or any other connection between dTC and hypokalaemia. The present trend to anaesthetic techniques employing minimal doses of depressant drugs with larger doses of relaxants may possibly increase the importance of this hazard and its recognition.

That a small excess of potassium can antagonize the action of dTC at the neuromuscular junction is generally accepted. The observation was first made by Wilson and Wright (1937) and has been well documented since by various methods (Bacq and Goffart, 1939; Hadju et al., 1950; Li et al., 1952; Hazard et al., 1954). Although the subject of controversy, dTC appears to limit the potassium loss during excitation of the neuromuscular junction (Fenn, 1940; Fenn et al., 1951) or when this loss is produced by the depolarizing muscle relaxants (Klupp et al., 1954) which can increase potassium loss over the whole area of end plate and adjacent muscle that they depolarize (Zaimis, 1954).
Again, muscular paralysis and abnormally low levels of extracellular potassium frequently co-exist, although this is not invariable (Danowski et al., 1949). Hypokalaemic paralysis may, however, not be due to an effect on muscle or neuromuscular junction, but to an effect on the C.N.S. (Pudenz et al., 1938). No special investigation could be found of the effect of dTC at the myoneural junction of the potassium depleted skeletal muscle, although it may be relevant to note that lowering the extracellular potassium of cardiac muscle alters the range and nature of its sensitivity to acetylcholine (Graham, 1949).

Thompson and Price (1941) found that improvement by neostigmine of myasthenic symptoms (which in many ways resemble curarization) followed more closely the effect of the drug on the blood potassium than on the blood cholinesterase level. In rats, neostigmine was found to raise muscle potassium.

Thus it seems that hypokalaemic paralysis (associated with curariform paralysis by a tenuous connection) may not result from a peripheral action only. Clinical reports may add further enlightenment, especially those suggesting a central action of relaxants, sometimes in association with hypokalaemia.

One of the earliest of these was by Whitacre and Fisher (1945), who produced loss of consciousness and analgesia with Intocostrin in three patients. Two of these had had severe haemorrhage. From their account it seems unlikely that uncontrolled respiratory depression was a factor in producing the unconsciousness.

Mahfouz (1949) recorded a case where intravenous dTC produced immediate convulsions in a schizophrenic, which he presumed was a central action.

Harris and Dripps (1950) recorded four cases who showed prolonged respiratory depression after decamethonium. This, they considered, suggested a depressant action on the C.N.S., returning respiration being, on occasion, associated with returning consciousness.

Foldes and co-workers (1952) recorded two cases who showed severe residual respiratory depression after using benzoquinonium. Both were dehydrated, with signs of potassium lack, and improved with rapid intravenous infusion of potassium chloride.

Dripps (1953), in discussing abnormal responses to curare, noted that excessive respiratory depression may be seen in patients with potassium lack. This might be a peripheral effect on muscle, but he produced evidence that dTC also produced central effects: movement of all four limbs, or normal neuromuscular transmission (shown by direct nerve stimulation) may be present with prolonged apnoea and unconsciousness. He stated “the conclusion seems inescapable that in some patients respiratory depression need not be associated with block of nerve muscle conduction.”

Little and his associates (1953), in one of the earlier accounts of the use of suxamethonium, reported the observation of central respiratory depression on four occasions. They suggest that these cases were different from the prolonged apnoeas associated with low pseudocholinesterase levels, especially as there were signs of peripheral muscular activity during the respiratory depression. They noted swallowing, winking, and purposive move-
ments of the arms that appear similar to incidents recorded in the present series of cases.

Abbott and co-workers (1954) reported a case of a man with a long-standing pyloric stenosis who failed to respond for five hours after operation with the use of curare. Rapid infusion of potassium chloride intravenously produced a speedy improvement in respiration and a return of consciousness.

Dripps and Severinghaus (1955) have recently reviewed the abnormal effects of dTC on respiration, incriminating both potassium lack and an ability of the drug under certain circumstances to have a central action.

The ideas of a central effect of dTC and of abnormal respiratory depression by relaxants in hypokalaemia are not new; the present series of cases reported seems to establish an association between these two.

HYPOTHESIS

In view of the evidence thus available it is therefore suggested that the observed abnormal responses to relaxants in the presence of hypokalaemia might have a common basis—an abnormal penetration of the C.N.S. by these relaxants.

d-Tubocurarine is a widespread synaptic blocking agent, whether at the neuromuscular junction, in autonomic ganglia, or in the C.N.S. (Nachmansohn, 1948; Chang, 1953; Paton, 1954), and in these three sites potassium will antagonize its action (Salama and Wright, 1952b).

Thus the triad of symptoms described earlier could be accounted for on the basis of interference within the brain of the pathways responsible for consciousness, and of the medullary centres, including the respiratory and vasomotor centres. The interference with vasomotor activity could be accentuated by a blockade of sympathetic ganglia, and of the secretory power of the adrenal medulla, the chromaffin cells of which are functionally comparable to postganglionic neurones (Malméjac, 1955).

DISCUSSION

Although the cases presented suggest an abnormal response dependent on hypokalaemia, with graveness of the response roughly parallel to the degree of depletion, the serum potassium levels have, on occasion, given no indication of this.

Relation to Potassium Metabolism.

It is unfortunate that no simple reliable method exists for estimation of the potassium depletion of a body; the clinical history is often more reliable an indication than biochemical tests.

Body potassium is generally depleted in circumstances which combine decreased intake and increased loss in fluids derived from blood (e.g., urine, gastro-intestinal secretions, plasma exudate). This deficiency of the blood is made good initially from the extracellular spaces, but later the intracellular stores are drawn upon. By far the greater proportion of body potassium is intracellular, so that an insignificant intracellular loss may make good a large blood depletion. When the rate of loss is relatively slow it appears that the deficiency is met initially out of liver and muscle stores, during which time brain potassium is remarkably constant (Fenn, 1940; Ferrebee et al., 1941; Darrow and Miller, 1942; Davenport, 1949; Wood-
bury and Davenport, 1949). But rapid loss of this element may draw upon normally stable brain stores which are then unusually slowly replaced (Swinyard, 1949). In all this metabolic activity the blood level of potassium is merely a reflection of the traffic between the intracellular spaces and sites of absorption and loss. No reliable information of cell levels of potassium is obtained therefrom without a background of clinical history. On the clinical history available, therefore, it is suggested that the fatal cases seen, because they occurred after a period of prolonged loss, might have resulted from depletion of the intracellular phase of neurones in the C.N.S. of their potassium.

**Blood Brain Barrier.**

The generally assumed absence of central effects with relaxants is thought to depend on their selective exclusion by the blood brain barrier mechanism. This is despite evidence that dTC may pass the blood C.S.F. barrier to attain concentrations in the theca as high as in the blood (Mahfouz, 1949). Positively charged ions in general are able to penetrate the blood brain barrier (Friedemann and Elkeles, 1934), and dTC may, in fact, be regarded as a positively charged ion at the pH of body fluids (Kalow, 1954). However, one notable difference between brain and C.S.F. which affects the entry of substances into them from blood is the abundant lipoid of brain. Thus the inability of relaxant drugs to enter brain substance may depend on their lack of lipoid solubility, a property apparently linked with the methylated quaternary ammonium groups upon which their particular pharmacological activity depends (Nachmansohn, 1948; Wright, 1952).

Despite this apparent importance of a purely physical property in the barrier, the blood brain barrier should be regarded as a function of living cells, including the capillary endothelium within the C.N.S. only (Friedemann and Elkeles, 1934; Friedemann, 1942; Broman and Lindberg-Broman, 1945), the extracellular ground substance of the brain, manufactured by astrocytes (Hess, 1955a, 1955b; Annotation, 1955), the neuroglia itself (Clemente and Holst, 1954; Rodriguez, 1955), and the cell membrane of the neuron (Aird and Strait, 1944). It would be wrong to assume that this important function depends on the purely physical properties of membranes (Cohen, 1927; Wright, 1952), especially when such physical properties (depending on lipoid solubility, molecular size, or molecular ionization) may be overridden so that certain desirable substances are taken up by the brain (Friedemann, 1942; Albert, 1952). For these reasons, factors which depress cell vitality may be expected to alter the selectiveness of the barrier. In fact, using appropriate methods, increased permeability may be shown to follow physical and chemical injury, such as after hypoxia, dehydration, histotoxic drugs, etc. (Hurst and Davies, 1950).

On this basis it did not seem unreasonable to suggest that loss of potassium, which is such an important intracellular element, might affect the blood brain barrier. Preliminary experiments on rats carried out in this department so far indicate that even minor degrees of depletion cause a marked interference in barrier permeability. Again, this seems to conform with the concept that the barrier may
depend on a stable electrical charge within a molecular frame of such a nature that loss of base from the brain tissue (acidosis) impairs the barrier (Report, International Congress of Neuropathology, 1955).

Lastly, it should be recorded that Broman and Lingberg-Broman (1945) have found experimentally that bile salts will assist the entry of non-lipoid soluble substances into the brain. For this reason, it is felt, apparent central effects of dTC, according to the nonfatal pattern here described, have been noted in severely jaundiced patients.

Whatever the mechanism of exclusion of relaxants from the brain, experimental evidence exists that by raising the intravenous dose to about 3 to 10 times the paralysing dose, consistently demonstrable interference with C.N.S. function will result (Bernhard and Taverner, 1951; Bernhard et al., 1951; Ostow and Garcia, 1949; Pick and Unna, 1945). If this indicates a "threshold," then like other body thresholds it may be altered by appropriate means.

**Effect of dTC within the Brain.**

The convulsive properties of intrathecal dTC have long been known experimentally, and on occasion observed clinically in man (Dundee, 1955). The investigation of Salama and Wright (1950, 1952a, 1952b) is representative of this knowledge and has shown a general sequence of motor effects with increasing dose. At first there is stimulation (increased reflex excitability) followed by disorganization (convulsions) ending in suppression of activity (paralysis). Their observation of spontaneous-like movements of forelimbs, wide opening of eyes, and respiratory stimulation are perhaps relevant to the discussion.

D-Tubocurarine is widely held to be a general synaptic blocking agent (Paton, 1954), at least in those junctional areas where acetylcholine is the chemical transmitter. It would appear that cholinergic transmission is of importance in the integrated function of the C.N.S. (Feldberg, 1945, 1950; Feldberg et al., 1953; Goodman and Gilman, 1955). There is experimental evidence that dTC may depress the function of the brain stem reticular formation (Ostow and Garcia, 1949) and of intercortical association tracts (Hart and Marrazzi, 1953). In this wise might dTC produce unconsciousness in a way not unlike anaesthetics, which appear to depress rapid synaptic transmission in the brain before affecting axon conduction or metabolism (Brookes and Eccles, 1943; Butler, 1950; Larrabee and Posternak, 1952; French et al., 1953a, 1953b; Rossi and Zirondoli, 1955).

There is the further relevant experimental observation that large doses of dTC, given intravenously or subcutaneously, may abolish all recordable electrical activity in the brain (Ostow and Garcia, 1949; Pick and Unna, 1945). That this is due to total synaptic block seems improbable when there is evidence that acetylcholine is not the only synaptic transmitter in the C.N.S. (cf. Feldberg, 1950). Perhaps a clue to the cause of this total interference is offered by the work of Chang (1953), who showed there to be both a (extracellular) synaptic blocking effect of dTC, and also an (intracellular) effect producing a modification of transmission in the axon. If the belief in the
essential role of acetylcholine in nerve transmission is accepted (Bullock et al., 1947; Nachmansohn, 1948), then the potent inhibitory properties of dTC on brain cholinesterase (Todrick, 1954) are of significance. It has been shown that the anticholinesterase DFP can destroy body cholinesterases, and abolish all nerve transmission, thereby causing death (Nachmansohn, 1948). It has also been shown that dTC, normally unable to penetrate nerve, will block nerve transmission after micro-injection into the axon (Grundfest et al., 1952). This requires confirmation (Hodgkin and Keynes, 1956).

The immediately preceding discussion is highly speculative, but it may suggest an explanation for the double nature of the response described, and it may point to a further danger. The properties of neostigmine, including anticholinesterase activities and lack of lipid solubility, are similar to dTC. If it is postulated that dTC penetrates the brain in certain circumstances the possibility must exist that neostigmine will do likewise in similar circumstances. Thus unwanted side effects might occur in just those patients who show this abnormal susceptibility to dTC. As has been shown experimentally, the central synaptic block of dTC may be reversed by neostigmine, but not the interference with axon conduction (Chang, 1953). Indeed, the two anticholinesterases, acting together, might intensify the latter effect.

PROBLEMS OF TREATMENT

It is as yet too early to define lines of treatment with any certainty: but it is a strong clinical impression that large repeated doses of neostigmine may be detrimental (when the antidote does not act it is natural to increase the dose), just as rapid intravenous infusion of potassium may be beneficial. To some extent this has been borne out in practice (Riding, 1956).

The physiological treatment would appear to be the replacement of lost potassium, other electrolytes, and water. Short of intrathecal potassium replacement, which may produce tetany convulsions (Mullin et al., 1938), as well as the more desirable respiratory and vasomotor stimulation (Bekaert, 1950), rapid intravenous infusion may be the preferred route in view of the urgency of the situation.

The total body potassium may be in the region of 4,000 mEq (Fenn, 1940), of which 1,000 or more may be lost (cf. Evans and Milne, 1954). Since the total extracellular potassium is only 140–180 mEq, the danger is apparent of extracellular overloading by the rapid replacement of the required amount.

However, there are ways of decreasing the toxicity of intravenous potassium. Intravenous calcium will antagonize the dangerous effects of a raised blood potassium (Fenn, 1940) and the administration of glucose and insulin hasten the shift of potassium into the intracellular space (Nabarro et al., 1952) where it is required. Electrocardiographic monitoring during the infusion may forewarn of toxic effects.

As always, it is better to prevent the sometimes serious effects that relaxants may produce in hypokalaemia by an intelligent anticipation of the possibility, which should also suggest the choice of alternative anaesthetic methods, combined with proper pre-operative preparation.
Loss of tissue potassium follows operations, during dehydration, starvation, diarrhoea, vomiting, and metabolic disturbances, notably acidosis. Diabetic coma, Cushing's syndrome, and the use of adrenal corticoid therapy will also produce such a loss (Danowski and Elkington, 1951). The forewarning offered by any such incident in the patient's recent past is often more important in assessing the anaesthetic risk than much biochemical data.

SUMMARY AND CONCLUSIONS

Eight cases are described of abnormal responses to the antidepolarizing relaxants, D-tubocurarine chloride and gallamine. A disturbance of potassium metabolism was common to every case, sometimes associated with dehydration and other electrolyte depletion. The nature of these abnormal responses indicates a central action of these drugs, sometimes with fatal results.

For more than ten years competent observers have reported abnormal, apparently central, actions of all the relaxants in common clinical use. In many of these potassium depletion was a complicating factor.

Two general features are frequently recorded: an apparent resistance to the relaxant—either depolarizing or antidepolarizing—seemingly produced by central motor stimulation. The other feature is respiratory depression linked with unconsciousness.

For such central actions to occur, the relaxant must pass the blood brain barrier; this may be achieved with high blood levels of the drug, but it would appear that the threshold for penetration may be lowered in certain disturbances of water and electrolyte metabolism, of which potassium depletion may be the essential common feature.

Reasons for this disturbance of the blood brain barrier are discussed together with aspects of the central action of D-tubocurarine chloride that might account for the observed clinical effects.

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