Mention must also be made of the effect of the climate on the anæsthetist and his assistants. After prolonged exposure to high temperatures and high humidity, even the best men showed a loss of interest and keenness in their work and a tendency to general lethargy.

Major R. P. Harbord asked what was the evidence for the statement that atropine disturbs the heat regulating mechanism more than hyoscine?

Cases coming to operation in the forward areas with malaria were uncommon during the campaigns about the Mediterranean.

Pentothal had been a useful anæsthetic for maxillo-facial surgery in some cases for it shortened the period before intubation and minimized aspiration.

Dr. V. Goldman, in reply to Major Harbord, said that although atropine and hyoscine are close chemical relatives, they produce some different effects when administered. The effects of atropine tend to be excitant, those of hyoscine depressant. Apart therefore from their similar drying effect on mucous membranes, atropine is an opponent of anæsthesia, whereas hyoscine is an adjuvant. Adriani states that the temperature regulating centre is stimulated by large doses of atropine[1]; and it is well known that atropine increases the basal metabolic rate.

Dr. G. S. W. Organe asked Dr. Pleasance whether in view of the extremely low incidence of thrombosis he had found after pentothal all patients had been examined with this possibility in view or whether these were merely the cases in which symptoms had presented.

Dr. R. E. Pleasance replied that, as far as was possible, all patients had been examined with this possibility in view.

[1]Adriani, John (1942) Pharmacology of Anæsthetic Drugs, Second Edition, p. 54. Springfield.

[*March* 1, 1946]

A Milestone in Anæsthesia?

(d-Tubocurarine Chloride)

By T. Cecil Gray, M.B., Ch.B., D.A., and John Halton, M.B., Ch.B.

History.—Curare, the South American arrow poison, has been known since Hakluyt published his account of Sir Walter Raleigh's voyage up the Amazon in 1595.

The exact origin of this "flying death" is still veiled in mystery. Its actual preparation is surrounded by all the esoteric magic and superstition of these strange people descended from the Aztecs, and very little more is known about it now than was discovered by Charles Waterton, a traveller of Lancashire origin, in his journey to the wilds of Demerara in 1812—a journey undertaken with the special object of investigating the origin and preparation of the Wourali poison.

This explorer wrote a book "Wanderings in South America" in 1812, and the description therein of the distillation of the arrow poison from the vine Wourali, the addition of sundry noxious substances, including Indian pepper and the pounded fangs of the Labarri snake, is well worth reading. He tells most vividly of the effects of the poison on various animals. In 1840, Claude Bernard confirmed the observations of Waterton, and attributed the effects of the poison to paralysis due to interruption of the neuromuscular conducting mechanism.

In 1935, Harold King gave the name d-tubocurarine to an alkaloid isolated from tube curare, but little was known until in 1938 Richard Gill (1940), who lived for many years among the Amazons and in the jungles of Ecuador, brought to the United States samples of raw material and of the various plants used in its preparation, and Professor McIntyre (1943) of the University of Nebraska, together with the firm of manufacturing chemists "Squibbs," prepared an extract of standard potency which they labelled "Intocostrin".

In this country, curare was first used by Cole in 1934, Mitchell in 1935, and Ranyard West in 1936, all of whom used it in the treatment of tetanus.

In 1940, Bennett, of Nebraska, described the prevention of trauma during convulsive therapy by the intravenous injection of intocostrin.

In January 1942 Griffith (1944) first used the drug as an aid to anæsthesia in the Homœopathic Hospital of Montreal. It is interesting to note that up to April 1945 Griffith (1945) had only used intocostrin in 300 cases. Since then there has been a flux of articles from

American anæsthesiologists, but one has gained the impression that they have not fully appreciated its full field of usage nor its importance to the patient.

J. Halton first used d-tubocurarine chloride in November 1944 in an attempt to overcome the disadvantages of the barbiturates consequent on their use as the sole agent to produce anæsthesia in thoracic operations, but it was not until April of last year with the advent of regular supplies that we began to realize its great possibilities. Intocostrin was tried, but it seemed to be unreliable in potency, perhaps due to the instability of the solution, and no definite results could be forecast with the samples that we employed. As a result, we returned to the crystalline extract, d-tubocurarine chloride, prepared by Burroughs Wellcome & Co. This has proved of constant potency and very satisfactory.

Pharmacology.—Pharmocologically, the exact nature of the drug is wrapped in much the same mystery as the preparation of the crude poison. The crude extracts are obtained from various vines and plants, and the very nomenclature used to describe these extracts is an indication of our ignorance. Thus that variety delivered to the importers in gourds has been known as "Calabash" or "Gourd" curare, that delivered in earthenware pots as "Pot" curare, and that in bamboo tubes "Tube" curare. This latter is a brown or black shiny resinoid mass, and it is from this variety that the crystalline extract "d-Tubocurarine Chloride" is obtained. Table I shows the alkaloids that have been isolated from the crude extracts.

TABLE I

Tube curare	→ Tubocurarine →	Tubocurarine chloride ($C_{36}H_{41}O_6N_2Cl_2 \cdot 2H_2O$)	
	→	Curine ($C_{36}H_{38}O_6N_2$)	Weaker in action. Toxic to heart.
Calabash curare	→	Curarine ($C_{19}H_{26}ON_2$)	Extremely potent. Similar effects to tubocurarine. Related to strych.
Pot curare	→	Protocurine ($C_{20}H_{23}O_3N$)	
	→	Protocuridine ($C_{36}H_{38}O_6N_2$)	
	→	Protocurarine ($C_{19}H_{23}O_2N$)	Only one giving curare action.

Physiology.—Curare has no action when taken by mouth, hence the perfect safety of the native when he ate his victim after a day's hunting. This immunity is due to detoxication by the liver and not to destruction by the digestive juices. It must be injected either subcutaneously or intravenously. Subcutaneously administered, its action appears in about twenty minutes, but intravenously the action commences within ten seconds, and takes three to four minutes to reach a maximum.

Having entered the circulation it is in part changed by the liver and in part excreted via the kidneys unchanged (Boehm, 1920). It may be noted, in passing, that in the presence of renal damage of any consequence an otherwise safe dose may well cause considerable embarrassment.

It is necessary for a moment to consider the action of curare on (*a*) the neuromuscular mechanism, and (*b*) the nervous system.

(*a*) Claude Bernard (1840), in his classical experiments on frogs, showed that curare produced paralysis of voluntary muscle by an interference with the nerve impulse at the neuromuscular junction. In the curarinized animal both the nerve and muscle are still capable of responding to stimuli, but the break occurs at the junction of the two.

The work of Dale, Feldburg and Vogt (1936), and Brown (1937) and others, leads us to believe that on stimulation of a nerve to voluntary muscle, acetylcholine is produced at the neuromuscular junction, and that curare produces its paralysing effect by preventing the action of this on the receptor substance of the muscle.

While on this subject it is useful to consider the action of physostigmine which is said to be the natural and physiological antidote to curare.

Normally, acetylcholine is neutralized by an enzyme, cholinesterase, present in the tissues. Physostigmine prevents this neutralization, and so allows an abnormal and excessive barrage of acetylcholine to play on the receptor substance; this may succeed in overcoming its inhibition by curare.

In this series physostigmine has been used on two occasions, and we were not impressed by its action. However, many workers have reported dramatic results, and this is a substance that should always be at hand when and wherever curare is being used.

That, briefly, is how curare produces its relaxation, which makes it of such great value to the anæsthetist.

(*b*) *The effect of curare on the nervous system.*—Acetylcholine appears to perform some function in the transmission of nerve impulses through the ganglia of the autonomic system, and possibly also through all the synapses of the central nervous system. In the same way that curare prevents the acetylcholine-receptor substance union at the neuromuscular junction, so too does it in the autonomic nervous system.

Although this is said to be only a secondary effect of curare, exerted perhaps only in the presence of large doses, yet it may well be of importance clinically.

In the first place, curare appears to depress markedly the laryngeal and bronchial reflexes, preventing that troublesome complication and bane of the anæsthetist, spasm. Secondly, the effect on the gut has been of some interest. Solis-Cohen (1928) states categorically that curare causes contraction of the gut, and Griffith (1945), the pioneer, has stated that in cyclopropane-curare anæsthesia the gut is indeed contracted, but Cullen (Gross and Cullen, 1945) has produced experimental evidence in animals that it is flaccid and inactive. We have noted marked contraction and activity in most cases, but in others, including most of those anæsthetized with barbiturate-curare only, this irritability has been absent. It is difficult to come to any conclusion in this matter, as the gut reaction will vary with the premedication and the anæsthetic agents. All the anæsthetic and narcotic drugs, not to mention atropine, act on the autonomic ganglia, and it may well be that we are observing a summation of these effects in conjunction with curare.

A clinical difficulty arises in cases of ulcer perforation when we believe that this very real activity of the gut may be responsible for flooding the peritoneal cavity with stomach contents. Furthermore, in a case undergoing transplantation of the right ureter under cyclopropane curare anæsthesia, the ureter had to be inserted into the ascending colon, as the descending part was so contracted that it was impossible to mobilize it. This excessive contraction is never seen when the barbiturates are used to produce anæsthesia.

Present pharmacological opinion is that the liver and kidneys are completely unaffected by curare, but its action on the heart and cardiovascular system is a matter of some importance. The information available up to now has been of doubtful value, for one has never been quite certain which particular extract or preparation was being used. Certain extracts of curare, curine in particular, are known to be potent cardiac poisons. As it seemed that tubocurarine was a definite and specific substance it was clearly of value to investigate its cardiac effects further. Moreover, our clinical results led us to believe that the drug might have some effect on the myocardium.

This work is still in progress, but one of us (T. C. G.) has observed the effect of tubocurarine on the electrocardiogram in a number of cases in the human subject, and with the assistance of Dr. Gregory, of the Department of Physiology in the University of Liverpool, has estimated the result when this material is injected into the Starling heart-lung preparation in dogs. The investigation has progressed sufficiently for us to say that d-tubocurarine produces no effect on the electrocardiogram in the doses in which it is used clinically (fig. 1), and on injection into the heart-lung preparation in dogs, using a dosage vastly greater than anything ever likely to be used in humans, no effect whatever has been observed on the cardiac rate output, or on the venous pressure. As the output is maintained and the venous pressure unaltered, it can justifiably be assumed that there is no alteration in the coronary flow.

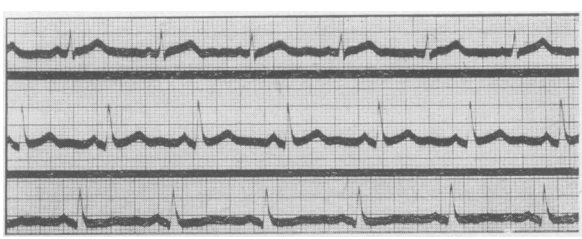

FIG. 1.—Electrocardiogram taken seven minutes after the administration of 0·5 gramme pentothal and 20 mg. curare.

It must be emphasized that, in spite of this, curare must be used only with the greatest possible care to maintain full and very complete oxygenation, otherwise the patient's condition will rapidly deteriorate. Especially is this so in those cases having a poor myocardium, for they cannot cope with any sub-oxygenation after curare.

In clinical dosage, little or no effect can be observed on the blood-pressure. Depression may be observed when a large dose of curare is injected quickly, especially if in association with a barbiturate (fig. 2).

Conversely, a slight rise has been occasionally noted (fig. 3), a fact that may be accounted for by the quixotic action of curare on the autonomic nervous system, or in some cases by inadequate ventilation of the lungs with consequent accumulation of carbon dioxide.

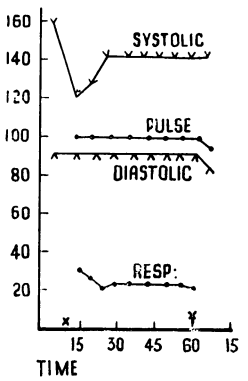

FIG. 2.—Blood-pressure, pulse and respiration in a male patient aged 49, undergoing cholecystectomy, with continuous pentothal and curare anæsthesia. (Note initial depression of systolic pressure.)

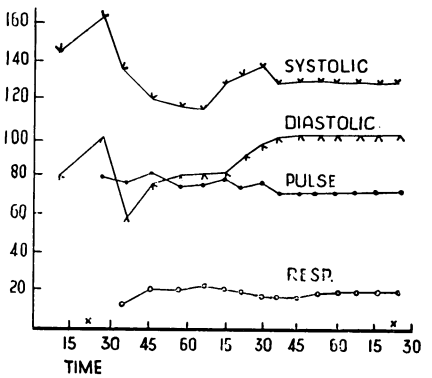

FIG. 3.—Blood-pressure, pulse and respiration in a male patient aged 48, undergoing a partial gastrectomy under pentothal and curare anæsthesia. (Note (i) initial rise in blood-pressure, and (ii) perfect stabilization during the last hour.)

The amazing effect of the arrow poison when injected into an animal has been most beautifully described by Waterton and is worthy of quotation:

"Having procured a healthy full-grown fowl, a short piece of poisoned blow-pipe arrow was broken off and run up into its thigh, as near as possible betwixt the skin and the flesh, in order that it might not be incommoded by the wound. For the first minute it walked about, but walked very slowly, and did not appear the least agitated. During the second minute it stood still, and began to peck the ground; and ere half another had elapsed it frequently opened and shut its mouth. The tail had now dropped and the wings almost touched the ground. By the termination of the third minute it had sat down, scarce able to support its head, which nodded, and then recovered itself, and then nodded again, lower and lower every time, like that of a weary traveller slumbering in an erect position, the eyes alternately open and shut. The fourth minute brought on convulsions, and life and the fifth terminated together."

In the conscious human subject the muscles of the eyes, mouth and fingers are affected first, then those of the trunk and limbs, and finally the diaphragm. Consciousness is retained, and recovery occurs in the reverse order, being complete in about thirty minutes from a single injection. American workers (Whitacre and Fisher, 1945) have actually pushed the drug beyond the stage of diaphragmatic paralysis, and obtained unconsciousness. This seems to us a completely unjustifiable procedure, and the narcosis may well have been due to anoxia, although curare may have some action on the synapses of the central nervous system, in view of the fact that there is some evidence that here too acetylcholine plays some part in impulse transmission.

Technique.—The tubocurarine when first received must be sterilized. It has been our custom to autoclave the dry powder at 10 lb. pressure for thirty minutes, and cultures taken from the solution have proved sterile. Moisture must not be allowed to enter the phial during autoclaving as the powder becomes discoloured and presumably unfit for use.

After the usual premedication, in our cases morphia 1/6 grain and atropine 1/150 grain to 1/100 grain, anæsthesia is induced with whatever may be the agent of choice.

The curare, not itself an anæsthetic, is used as an adjuvant in order to obtain good relaxation at any time and in a very light plane. It is injected as and when required, allowing the requisite three to four minutes for it to take effect.

Three main techniques have been employed:

(1) The single dose method, for the induction of anæsthesia, short operations and endoscopies, oral and anal.

Employed in this way a mixture of 15 mg. of tubocurarine with 0·5 gramme of pentothal is injected fairly rapidly. After two or three minutes respiration becomes very shallow or ceases altogether, the jaw is completely relaxed and there is no spasm or cough when an airway is inserted or an endotracheal tube is passed. Furthermore, the

patient is able to tolerate straight away, without distress, an anæsthetic vapour strong enough to maintain the anæsthesia should this be desired. Induction time is thus tremendously shortened.

With this dose bronchoscopy is easily performed, and because of the relaxation of the pharyngeal and anal sphincters, œsophagoscopy or sigmoidoscopy can be carried out with ease.

Patients recover quickly after this form of administration.

(2) For longer procedures in conjunction with the intermittent injection of an intravenous barbiturate. A remote control tap has been devised which facilitates this technique. Its use overcomes two difficulties of administration, namely, the arm can be placed in any position during the operation without fear of the intravenous needle becoming displaced, and precipitation of the barbiturate by the curare is prevented. This is of little importance where pentothal is concerned, since the precipitation is reversible, but it is of major importance if kemithal or other barbiturate is used. The essential details of this apparatus were shown later to the Meeting in a film.

After an induction as described above, small increments of barbiturate and curare are made. 0·1 gramme of pentothal and 2 to 4 mg. of curare are given from time to time as the reaction of the patient to stimuli and the demands of the surgeon dictate. If the length of the operation is such that a dose of more than 1·5 grammes of pentothal or 3 to 4 grammes of kemithal has to be exceeded, which occurs very rarely, we prefer to continue the anæsthesia with minimal amounts of cyclopropane or ether.

(3) As an adjuvant to inhalational anæsthesia. The intermittent fractional injection of a total dose of 15 to 30 mg. of curare is utilized to produce relaxation while still keeping the patient in a light plane of anæsthesia.

Whichever of these three methods is used, oxygen must be supplied in abundance, and preferably by means of a closed circuit, for by this means adequate and complete ventilation of the lungs can be ensured. The importance of this artificial ventilation of the lungs in cases of overdosage must have been known to the Indians of old, for our respected friend Waterton (1812) mentions that: "It is supposed by some that wind introduced into the lungs by a small pair of bellows would revive the poisoned patient, provided that the operation be continued for a sufficient length of time." In order to confirm this, this enterprising traveller performed the following experiment:

"A she-ass received the Wourali poison in the shoulder, and died apparently in ten minutes. An incision was then made in its windpipe, and through it the lungs were regularly inflated for two hours with a pair of bellows. Suspended animation returned. The ass held up her head and looked around, but the inflating being discontinued she sank once more in apparent death. The artificial breathing was immediately recommenced, and continued for two hours more. This saved the ass from final dissolution; she rose up and walked about; she seemed neither in agitation nor in pain."

Was this, written about the year 1812, the first description of controlled respiration, a technique the knowledge and practice of which is common and essential in modern anæsthesia?

Dosage.—The margin between effective and over-dosage is small. In our opinion no exact dosage for weight scale can be worked out, but the very obese require a little more than average and the extremes of age considerably less. Further, it must be remembered that in computing dosage 1 mg. of d-tubocurarine chloride is approximately equivalent to 6·6 units or milligrams of intocostrin. 20 mg. is sufficient to relax the average healthy adult's abdomen; and 25 mg. to paralyse the diaphragm. The effect of this initial dose will last for a varying time up to forty minutes. There is some temporary cumulative effect, so that subsequent doses must be considerably less, and it has been found satisfactory to use 2 to 4 mg. increments for maintenance. We have never had to use a total dosage of more than 45 mg. of tubocurarine, even when prolonged diaphragmatic paralysis was desirable.

Both extremes of age are very susceptible to curare, and small doses only must be used. In the aged—and the drug has been used in patients over 80—an initial dose of 10 mg. is suitable. Children up to 12 years should not be given more than 6 mg. for induction.

It has been stated that when ether is being used the dose of curare should be reduced by one-third, ether itself being said to have a curariform action. This, in our opinion, is a wrong approach to a correct clinical observation.

We had employed curare in only a few cases when it became obvious that some form of synergism existed between the drug and the barbiturates, and a further synergism between this combination and any inhalational agent which might be used, such as ether or cyclopropane.

Four facts led us to this conclusion:

(1) From experience we know the dose of barbiturate required to prevent "movement response" to painful stimuli (incision of the skin) in the average patient. For convenience let us call this the minimal anæsthetic dose (M.A.D.).

(2) Curare is not an anæsthetic, and in small doses does not prevent movement. 17·5 mg. were given to a conscious patient. He was still able to react by movement to a noxious stimulus.

(3) The administration of the combination of 15 mg. of curare and a dose of barbiturate less than the M.A.D. produces a completely anæsthetic and motionless patient.

(4) If any inhalational anæsthetic is used to supplement this barbiturate-curare combination, only a minimal amount is required to produce deep anæsthesia.

Signs of anæsthesia and curarinization.—One of our first observations was that here one is deprived of all the ordinary classical signs for estimating the depth of anæsthesia. The eye reflexes, corneal and conjunctival, owing to paralysis, are absent or sluggish, and the ordinary respiratory signs are modified, for at any rate in upper abdominal operations sufficient curare must be given to paralyse the intercostals. The three criteria which do remain are the pulse, respiratory rate, and the anæsthetist's experience.

Frequent observation of the pulse is essential; the first sign of inadequate anæsthesia is a rising pulse-rate and failure to notice this may result in the onset of severe shock due to inadequate narcosis. An increase in respiratory rate will also give warning, provided the patient is not apnœic.

The anæsthetist's experience is often the best guide as to the amount of any particular anæsthetic required to keep a patient in a light plane, and the necessity for the would-be user of curare to have this experience cannot be over-emphasized. At the same time, the danger of a paralysed patient waking up and becoming all too conscious of what Sassoon describes as "the dull opiate throb which was his wound" is non-existent, for in the dosage in which it is used, as already stated, curare does not prevent the small movements of a limb which indicate returning consciousness. An observation was made by Ranyard West (1936) that some specimens of curare had a "lissive" action, producing relaxation without actual paralysis. With tubocurarine a perfectly relaxed abdominal musculature may be present in a patient who is still able to respond to painful stimuli by movements of a limb.

There are two signs of curarinization which must be mentioned. The first is the typical respiration characterized by a pushing-out of the lower part of the chest and of the abdomen with each diaphragmatic contraction, and accompanied by a jaw and tracheal tug. This is not the same as the gasping respiration seen in deep ether anæsthesia, when a partially paralysed respiratory centre is endeavouring to cope with the situation. It is at this point that all effort should be concentrated on ensuring full ventilation of the lungs. Should this not be maintained, the condition will deteriorate, and the surgeon will be embarrassed by the exaggerated diaphragmatic excursion. In this event control of the respiration with the rebreathing bag is easily attained.

The second sign, and a most valuable one, is the ease with which the lungs may be inflated by pressure on the rebreathing bag (Morton, 1945). The absolute intercostal and abdominal relaxation, with the complete absence of laryngeal spasm, makes this manœuvre easy and satisfying.

Recovery.—Any therapeutic innovation must be judged first on the dangers involved in its exhibition to the patient, and secondly on the results obtained.

In respect of the dangers involved in the use of this drug they are real, but so are they throughout the whole realm of anæsthesia. It can be stated that in the hands of the competent anæsthetist, fully conversant with the treatment of the apnœic patient, and with the dosage and technique already described, far from being a danger it will prove an incomparable boon.

Regarding the second criterion, the results of the administration of tubocurarine may be regarded from the point of view first of the surgeon and secondly of the patient.

To the surgeon the results must be satisfactory, for he is presented with "blotting-paper" relaxation at any time and quickly, together with a quiet operating field.

In respect of the patient, many factors must be considered. Dr. Ralph Waters (1944) made a most important observation when he said that the relief of pain has always exacted a price, due in some part to the toxicity of the drugs used, but more often through ineptitude in the care of the patient when under their influence. This price is paid in the operating theatre, and afterwards in the ward. For one pneumonia caused by ether vapour, many more are caused by mechanical obstruction of the airway during the operation or in bed when the patient is lying motionless on his back recovering from the anæsthetic, possibly inhaling vomitus or septic oral secretions.

Again, vomiting with varying degrees of liver and kidney damage may be caused in some part by the anæsthetic agent exhibited, but more often by long periods of anoxia attendant on its use.

How does the method we have described compare with these dicta? First consider the drugs. Curare is completely and very rapidly eliminated. There is no evidence that it has any latent toxicity. The same holds good for the barbiturates in the doses in which they are used. If inhalational anæsthesia is employed to supplement, the amount is so small that the risk of toxic after-effects is non-existent or greatly reduced. During the anæsthesia the patient is ventilated by an atmosphere rich in oxygen and since spasm of the cords is completely eliminated the chance of anoxæmia arising is extremely remote. Vomiting in thoracic cases is now a thing of the past. In abdominal cases, while the incidence appears unchanged, the degree of severity is very much less.

It is on return to the wards that the biggest price is so often exacted. But in these patients the essential reflexes are fully recovered prior to leaving the theatre, and within half an hour they are co-operative, able to do breathing exercises, to cough and expand their chests, and can be left with safety to look after themselves. This has meant a tremendous reduction in post-operative pulmonary morbidity.

Between us we have given curare to 1,049 cases, and Table II shows the extent of the ground we have covered.

TABLE II.

Thoracic operations.		
Pneumonectomies	15	
Lobectomies	38	
Thoracotomies	73	
For stricture of the œsophagus	2	
Cervical sympathectomy	1	
Thoracoplasties	211	
Subphrenic abscess	1	
Minors	183	
		524
Abdominal operations.		
Gastrectomies	38	
Other gastrics	22	
Cholecystectomies	43	
Upper laparotomies	15	
Lower laparotomies	25	
Splenectomies	2	
Œsophageal myotomies	2	
Hydatid cyst of liver	1	
Excision of rectum	12	
Entero-anastomoses	6	
Hemicolectomies	15	
Appendicectomies	12	
Lumbar sympathectomies	2	
Pre-sacral neurectomies	1	
Gynæcological	14	
Genito-urinary	25	
Epigastric herniæ	2	
Incisional herniæ	2	
Inguinal herniorrhaphies	8	
Minors	22	
		269
Head and neck operations.		
Thyroidectomies	5	
Other major	3	
Laryngeal intubations only	35	
		43
Orthopædic operations.		
Major	47	
Minor	166	
		213
	Total	1,049

Two deaths which might be attributed to the anæsthetic have occurred. They happened early in the series. The post-mortem findings in each case showed gross myocardial damage, and that, coupled with a degree of anoxia which should never have been per-

mitted, but ordinarily would have been tolerated, probably terminated life. It is our opinion that anoxia and not curare was responsible for these fatalities.

The assessment of results following thoracic operations is difficult. Comparative figures are hard to obtain, anæsthetic methods have been constantly changing, and with the advent of curare more extensive surgery has been successfully practised on cases of the poorer risk type, a fact which speaks for itself!

Table III shows the incidence of post-operative pulmonary morbidity in patients undergoing operations in the upper abdomen. These are compared in column 3 against the figures given by three observers, King (1933) and Campbell and Gordon (1942) using various types of anæsthesia for similar operations. It is necessary to point out that it has been considered a post-operative complication if a patient develops a cough with any physical signs, or suffers aggravation of an existing chest disease.

TABLE III.

Operation	No. of cases	Pre-op. chest condition: Minor	Pre-op. chest condition: Major	Post-op. chest condition	Comparative figures
Partial gastrectomy	38	26·3%	—	18·4% }	38·3%
Gastro-enterostomy	22	27·3%	—	12·7% }	(King, 1933)
Cholecystectomy	43	16·0%	2·3%	7·0%	24·1% (King, 1933)
Upper laparotomy	15	20·0%	13·3%	6·7%	
Other upper abdom. operations...	7	—	14·3%	14·3%	
Total percentages		22·5%	3·2%	12·5%	56·5% (Campbell and Gordon, 1942)
Total number of cases	125	27	4	15	

We have for long subscribed to the view that heavy premedication with opiates is a thing to be deprecated. The result of this, even before the introduction of curare, was the occasional occurrence of restlessness post-operatively, especially when the main anæsthetic agent was one of the barbiturates. The restlessness which has occurred in a small proportion of these cases has, we are sure, been due to following this principle. Coupled with this, the patients are so well that they are able to exhibit a well-marked second stage "coming up," as it were. They are very conscious of any noxious stimuli, such as wound pain, splintage, or inflated catheters.

This unease has only been transient, and does not occur since we adopted the rule of giving as a routine 1/6 grain morphine and 50 mg. pethedine prior to leaving the theatre.

Indications for use.—Every thoracic and abdominal case undergoing a major operation is benefited by the exhibition of curare. The thoracic case benefits from curare in several ways. It is our considered opinion that for this type of surgery the barbiturates are probably the best agents, always provided that the dosage can be kept at a minimum. By their use the inhalation of irritating vapour is avoided, respiration is quiet and, since they are rapidly eliminated, post-operative toxic sequelæ do not appear, and recovery is rapid and uneventful. The addition of curare to this form of anæsthetic technique considerably reduces the amount of the barbiturate required. Cough and spasm are eliminated and control of diaphragmatic movement can be achieved rapidly and at will, yet the full cough reflex is present before the patient leaves the table.

Curare is of very special benefit to the poor-risk patient. The bad chronic chest case who must undergo a major operation even in the upper abdomen is a subject who will owe a lot to the arrow poison.

In peripheral circulatory failure we see a state of affairs that really does call for its use.

In deep anæsthesia the vasomotor central control is disturbed. This has been demonstrated by Zweifach and co-workers (1945) in a series of experiments on animals, in which they observed the power of adjustment of the capillaries of the mesentery to graduated bleedings under various anæsthetics. Under all deep anæsthesia with the possible exception of cyclopropane, the vasomotor compensatory reaction was lost so that the animal did not respond to transfusion as it should. This may not occur under light anæsthesia, and a glance at the pressure curves of patients undergoing abdomino-perineal operations, a procedure likely to cause a degree of shock and involving a change of position, shows striking clinical confirmation of this.

It will be seen that in fig. 4, where the anæsthetic was cyclopropane and ether carried to a deep plane, the blood-pressure falls progressively when the patient is put into the lithotomy position. This phenomenon has been observed constantly and the chart

shown is typical of twenty such. Fig. 5 is illustrative of six similar cases anæsthetized in a light plane with the help of curare. No fall in blood-pressure occurs on the change of position. We attribute this to an intact vasomotor central mechanism, which enables the patient to adapt his circulation to the altered circumstances.

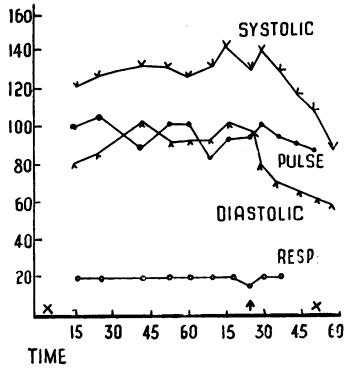

FIG. 4.—Blood-pressure, pulse and respiration in a male patient aged 41, undergoing abdomino-perineal excision of the rectum. Anæsthesia: Hexobarbitone induction, cyclopropane and ether maintenance. (Note the blood-pressure falls when the patient assumes the lithotomy position as indicated by the arrow.)

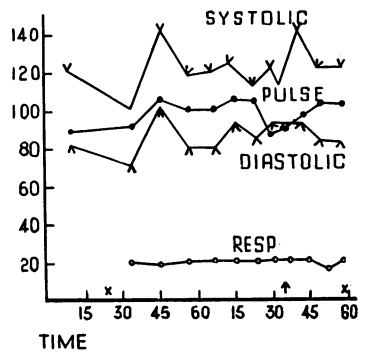

FIG. 5.—Blood-pressure, pulse and respiration in a female patient aged 41, undergoing abdomino-perineal excision of the rectum. Anæsthesia: pentothal and tubocurarine, with minimal cyclopropane. (Note the blood-pressure remains steady when the patient assumes the lithotomy position as indicated by the arrow.)

Contra-indications.—Curare should never be used by anyone who is not fully conversant with the care of the apnœic patient. Anoxia appears easily and is more serious, especially when there is cardiac inefficiency. Despite laboratory evidence that the drug has no cardiac action, clinically there is no doubt that with this form of anæsthesia patients do not tolerate even a slight degree of anoxæmia.

In abdominal operations when used with cyclopropane it may cause excessive contraction of the gut, and so render surgery more difficult.

Curare should not be used in cases of intestinal obstruction with distension, unless particular care is taken to avoid the uncontrolled regurgitation of the intestinal contents in these patients whose every natural protection has been removed. This also applies to cases with a lung abscess.

The dosage may have to be modified in the presence of renal damage of any consequence.

West has described the occurrence of excessive bronchial secretion and spasm in some of the cases he treated for tetanus. In our series of cases, including many oral endoscopies, this has never been observed.

Finally, this drug should not be used in cases suffering from myasthenia gravis.

Conclusion

The road lies open before us, and with a grave and insistent warning to the inexperienced that we are dealing with one of the most potent poisons known, we venture to say that we have passed yet another milestone, and the distance to our goal is considerably shortened.

We express our deep gratitude to Professor Charles Wells, Mr. H. Morriston-Davies, Dr. Minnitt, Mr. J. A. Martinez, and our friends and colleagues, the surgeons, who have made this work possible.

Bibliography

BENNETT, A. E. (1940) *J. Amer. med. Ass.*, **114**, 322.
BERNARD, C. (1840) Note sur la Curarine et ses Effets physiologiques, Paris.
BOEHM (1920) Handbuch der experimentellen Pharmakologie, **2** (Pt. 1), 179. Springer, Berlin.
BROWN, G. L. (1937) *J. Physiol.*, **89**, 220.
CAMPBELL, G. M., and GORDON, R. A. (1942) *Canad. med. Ass. J.*, **46**, 347.
COLE, L. (1934) *Lancet* (ii), 475.
DALE, H. H., FELDBERG, W., and VOGT, M. (1936) *J. Physiol.*, **86**, 353.
GILL, R. C. (1940) White Water and Black Magic. New York.
GRIFFITH, H. R., and JOHNSON, G. E. (1944) *Canad. med. Ass. J.*, **50**, 144.
—— (1945) *Canad. med. Ass. J.*, **52**, 391.
GROSS, E. G., and CULLEN, S. C. (1945) *Anesthesiology*, **6**, 231.
KING, D. S. (1933) *Surg. Gynec. Obstet.*, **56**, 43.
KING, H. (1935) *Nature*, **135**, 469.
McINTYRE, A. R., and KING, R. E. (1943) *Science*, **97**, 69, 516.
MITCHELL, J. S. (1935) *Lancet* (i), 262.
MORTON, H. J. V. (1945) *Proc. R. Soc. Med.*, **38**, 441.
SOLIS-COHEN, S. (1928) Pharmaco-therapeutics. New York, 1728.
WATERS, R. (1944) *Minnesota Med.*, **207**, 909.
WATERTON, C. Wanderings in South America. (*See* Everyman's Series) Dent, London. First published in 1812.
WEST, RANYARD (1936) *Lancet* (i), 12.
WHITACRE, R. J., and FISHER, A. J. (1945) *Anesthesiology*, **6**, 124.
ZWEIFACH, B. W., HERSHAY, S. G., and ROVENSTINE, E. A. (1945) *Surgery*, **18**, 48.

Professor Charles A. Wells mentioned that much of the work had been done in, and with the co-operation of, the Department of Surgery for which he was newly responsible in Liverpool.

Every advance demanded its own sacrifice, but in this instance there had been no human sacrifice. To the contrary, he was satisfied that many patients were alive and well to-day who would not have survived other anæsthetics and, further, that satisfactory operative relief had been made available, through curare, to many patients to whom it would otherwise have been denied.

The surgeon was given a quiet field with full relaxation without apparent prejudice to the general condition of the patient. If the anæsthesia was becoming light, warning was often given by phonation or the movement of a limb. Abdominal straining was a late feature of the waking process and a deeper plane could be recovered in a few seconds, before any embarrassment was experienced.

On returning to the wards, the patients not only wakened quickly but were unusually co-operative and were able to begin, almost at once, the limb movements and breathing exercises which were so vital to quick recovery and low morbidity.

Dr. F. Prescott described some experiments that he had made in collaboration with Dr. Organe. In the unanæsthetized subject it was found that 10 mg. of d-tubocurarine chloride intravenously had very little effect in relaxing voluntary muscle. Only the muscles of the face and eyes were affected to any extent. A dose of 20 mg., however, produced paresis of the muscles of the face, neck, arms, legs and abdomen in that order. Speech was lost but not the cough reflex. Respiration was not consciously affected, but spirometer readings showed that the tidal air was diminished by about one-third. A dose of 30 mg. intravenously produced complete paresis of all voluntary muscle and almost complete cessation of respiration, necessitating artificial respiration to prevent asphyxia. No analgesic action was observed. A test was made to see if fractional administration gave relaxation without respiratory suppression. A dose of 30 mg. given intravenously at the rate of 1 mg. per minute did not produce adequate relaxation. The subject was not curarized and was able to sit up ten minutes after the injection. A curarizing dose in the conscious patient lasts for twenty to thirty minutes. A more prolonged effect without depression of respiration was produced by giving 15 mg. intravenously and 15 mg. simultaneously by the intramuscular route.

Dr. F. Barnett Mallinson said he was surprised at the condemnation of intocostrin. He had been using this preparation of curare since the end of 1944 and he had been very satisfied with the results. Using intocostrin only he found himself very much in agreement with the speakers' experience of curare, and would add that he had never had to use prostigmin.

He had never used the Burroughs Wellcome preparation, first, because intocostrin has worked so well; second, because shortly after he published his preliminary report on curare in anæsthesia (*Lancet*, July 21, 1945) he had had two reprints and a personal communication from Dr. Ranyard West (*Journ. Physiol.*, 1938, p. 437; *Lancet*, February 19, 1938, p. 432) whose work had already been quoted by Dr. Gray, warning him of the dangers of bronchospasm. This he had never encountered with intocostrin. He would like to ask the speakers whether they had encountered this complication. Also did they consider that the Burroughs Wellcome preparation would become available in solution, like intocostrin?

Liberal oxygen should always be a feature of the accompanying anæsthesia, and he suggested that cyclopropane was thus the best. On the other hand, 2·29 grammes pentothal (a pretty big dose) with N_2O-O_2 for a normal length gastrectomy seemed likely to have been sufficient in itself and hardly to have needed the addition of curare.

A true evaluation of the real safety of curare must await cases in their tens of thousands. Chloroform was widely considered to be the most dangerous of all anæsthetics; but taking into account its accepted mortality rate, it might require some 4,000 administrations before the anæsthetist had a death. He doubted if the total published administrations of curare yet reached 4,000.

Dr. T. A. B. Harris noted, in the series of cases described, that d-tubocurarine had been used in 126 genito-urinary cases. Since, as far as is known, curarine is excreted from the body solely by the kidneys, would Drs. Gray and Halton consider renal inefficiency to be a contra-indication to the use of curarine?

Dr. C. Langton Hewer queried the method of sterilizing curarine chloride. He doubted whether autoclaving the ampoule did in fact sterilize the contained powder.

Dr. Hewer also described several cases of ocular paresis which had occurred after curare had been used. In a series of 37 administrations (mostly for gastrectomy) 19% of patients complained afterwards of difficulty in fully opening their eyes or of blurred vision. In every case symptoms had disappeared by the fourth day. Dr. Hewer pointed out that in myasthenia gravis, a condition very similar to curarization, the patients often complained first of the same symptoms.

Dr. G. S. W. Organe stressed the importance of adequate ventilation as well as adequate oxygenation. In one experiment on a conscious subject the tidal volume was reduced to less than 100 c.c. Although, breathing pure oxygen, there was no cyanosis, there was considerable distress and a feeling of suffocation due, probably, to accumulation of carbon dioxide. The dose was extremely critical. After 10 mg. tubocurarine intravenously on the same subject, the minute volume was 12 litres; after 20 mg. it fell to 7½ litres and after 30 mg.

to only 2 litres. In curare we had not found the answer to all post-operative complications—in one man with perforated gastric ulcer there developed a post-operative lobar collapse. The general condition of patients after major upper abdominal operations was as good as when muscular relaxation had been obtained with intercostal nerve block and the procedure involved was much simpler and quicker. Tracheal intubation was not called for in such cases as it was particularly easy to maintain a clear airway. He had not seen bronchospasm and had used curarine chloride to relieve laryngospasm.

Dr. A. H. Galley, in answer to a query raised by Dr. Geoffrey Organe over an experiment he had performed on a conscious colleague by injecting tubocurarine chloride, said that the respiratory distress suffered by the subject of Dr. Organe's experiment was due to an accumulation of carbon dioxide in the blood-stream in excess of the normal. If one was subjected to simple and uncomplicated oxygen lack, unconsciousness would ensue without any feeling of distress; but, if one held one's breath, or the air passages were blocked, or ventilation became so shallow as to interfere with respiratory exchange, then carbon dioxide—having little or no means of escape—would accumulate with subsequent distress. Although this feeling would not be experienced by the unconscious patient, Dr. Organe's experiment did remind them that such shallow breathing would inevitably lead to carbon dioxide accumulation with the well-recognized cycle of events which led to circulatory collapse. It might be better, therefore, always to employ closed circuit machines when administering oxygen to curarinized patients.

Dr. H. W. Loftus Dale had also observed that operations such as cholecystectomy, gastrectomy, and abdomino-perineal excision of rectum could be performed under light cyclopropane anæsthesia and curare with no, or insignificant, alterations in pulse and blood-pressure.

Since curare produces no sensory loss, and only light planes of general anæsthesia were employed, there seemed nothing to prevent "nocioceptive" afferent stimuli from reaching the vasomotor centre. Unless this could be explained by synergism between curare and the general anæsthetic agent, as suggested by the openers, doubts must be cast on the theories of Crile and others concerning "reflex shock". A practical point: In one case in which an endotracheal tube packed off with gauze was used to protect the tracheo-bronchial tree against aspiration, a seal tested and found gas-tight became totally inadequate after the injection of curare owing to relaxation of the pharyngeal muscles, and a considerable amount of extra packing was required to ensure against leakage.

Dr. J. W. Trevan said that there was little doubt that the active principle of intocostrin was d-tubocurarine. This was claimed by the makers, and the speaker had examined the alkaloid separated by Dr. Copp from a sample of intocostrin, which accounted for the activity of the extract and which as far as tests could be carried out on the small sample proved to be d-tubocurarine. He found that 1 unit of a sample of intocostrin he had examined was equal in activity to 0·17 mg. of d-tubocurarine. He said that confusion had arisen by labelling doses in terms of milligrammes of a preparation of curare. d-Tubocurarine apparently differed from crystalline curarine from strychnos species in having a strong curarizing activity without other marked toxic properties. d-Tubocurarine was derived from chondrodendron tomentosum. Prostigmine and physostigmine were true antagonists to d-tubocurarine, in a dose about 1/20 to 1/10 of the dose of d-tubocurarine. Very large overdoses (3 to 4 times paralysing dose) were not, however, antagonized by prostigmine or physostigmine. He saw the experiment on Dr. Prescott and could not agree that the prostigmine injected did not accelerate his recovery. The antagonism of tubocurarine by prostigmine on isolated voluntary muscle was quite certain.

The Openers, in reply, expressed their interest in Dr. Prescott's observations; clinically they were of great value. Answering Dr. Mallinson they reiterated their remarks on the inconsistent action of intocostrin. d-Tubocurarine chloride, on the other hand, was a specific alkaloid and produced a constant and predictable action in the human subject and on experimental animals. The gastrectomy which required 2·29 grammes of pentothal lasted two hours yet the patient was able to answer questions before leaving the theatre; his recovery was uneventful. Was Dr. Mallinson able to produce that result with pentothal alone?

Comparison between chloroform and tubocurarine was not logical, for while the former was a proved somatic poison, all clinical and laboratory evidence showed that this was not so with the latter drug. In reply to Dr. Harris, gross renal damage, proved or suspected, was a contra-indication to full doses of tubocurarine.

In reply to Dr. Langton Hewer, no case of ocular paresis had been seen in the series under discussion. With regard to sterilization, it was admitted that the method at present in use was open to criticism and it was under review. Nevertheless, samples of the solutions taken at random had always proved sterile.

All the points made by Dr. Organe were of great importance. They could not be stressed enough especially to those anæsthetists who were about to use tubocurarine for the first time.

Dr. Trevan's observations were noted with interest and further clinical investigations would obviously have to be made.