increase the voltage from the battery, or, thirdly, change the low-voltageappings on the transformer if a choice is provided. Start with the 5-volt tapping, but if the buzzing or the shock is too weak change to the 3-volt position. At its minimum the shock should be almost imperceptible and at its maximum it should be unbearable.

TABLE II.—Components Required and Their Approximate Cost

1 push-button switch	1s. 6d.
1 4-8-volt buzzer (miniature type)	5s. 0d.
1 small transformer, about 50 : 1 ratio	7s. 6d.
(The above three items are such as are used for a house door-bell)	
1 grid-bias battery, 9 volts	1s. 9d.
1 potentiometer, 2 megohms, log. track	2s. 6d.
1 knob for above	9d.
1 box (cigar-box ideal)	—
1 armband with electrodes	—
	19s. 0d.

The drain on the battery is about 300 mA as measured on a D.C. meter. This should allow several hours' operation, and as the buzzer is actually in operation for only about 30 seconds per session, battery wastage is no great problem.

Summary

A simple apparatus which can deliver a painful electric shock to the subject for aversion therapy is described. It has advantages over nausea-producing drugs, particularly in allowing

the patient to treat himself even at home. The use of the apparatus is illustrated by cases of fetishism, obsessional ruminations, smoking, writer's cramp, and alcoholism. Technical details are given of the components and their assembly which requires only the most rudimentary knowledge of electricity.

We thank Profesor T. Ferguson Rodger, in whose department the work was carried out, for his encouragement, and Drs. J. M. Carlisle and B. G. Young for allowing us to include their results in our figures.

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Familial Sensitivity to Suxamethonium Due to Atypical Pseudocholinesterase*

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Soon after the introduction of suxamethonium ("anectine," "brevidil M," "scoline," etc.) into clinical anaesthesia in 1951, the occasional occurrence of prolonged paralysis, even in the absence of excessive dosage, was reported (Love, 1952; Gould, 1952; Harper, 1952). In some of the early cases the aetiology was obscured by factors such as the concomitant use of curare or what would now be considered heavy doses of central depressants. Hyperventilation may also have delayed the return of spontaneous respiration. The introduction of the dibucaine¹ test (Kalow and Genest, 1957; Kalow and Staron, 1957) has facilitated accurate diagnosis in the cases where the apnoea is due to the presence of an atypical form of pseudocholinesterase.

Types of Neuromuscular Block

Prolonged apnoea after suxamethonium may be due to central respiratory depression, to peripheral neuromuscular block, or to a combination of both. The peripheral neuromuscular block may be attributed to one or more of the following four mechanisms:

1. *Succinylmonocholine and Choline Block*.—Suxamethonium is normally broken down to succinylmonocholine and choline. The succinylmonocholine in turn is broken down to succinic acid and choline. The monocholine and to a less extent choline

have each a weak depolarizing action. However, effective concentrations of these substances are unlikely to accumulate unless massive doses of suxamethonium have been given—for example, 1.5 to 2 g. (Wylie and Churchill-Davidson, 1960).

2. *Dual Block*.—After an intravenous injection of suxamethonium, certain individuals develop a non-depolarizing block at the motor end-plate following the original depolarizing block. This is usually seen after multiple doses of suxamethonium, but occasionally it appears even after a single dose. Patients with myasthenia gravis are particularly prone to develop this type of response (Churchill-Davidson, 1955). This type of block is temporarily improved by edrophonium and is reversed by neostigmine.

3. *Deficiency of Normal Type of Pseudocholinesterase*.—As pseudocholinesterase is normally responsible for the rapid destruction of suxamethonium, any reduction in its activity will prolong the effect of the drug. The production of this enzyme is depressed by certain pathological conditions. These include liver disease, severe malnutrition, and hypoproteinaemia other than that due to renal disease. Its action is inhibited by organophosphorus compounds such as are used in nerve gases and

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¹ Cinchocaine (B.P.C.) ("nupercaine").

insecticides. Complete absence of pseudocholinesterase has been reported (Hart and Mitchell, 1962).

4. *Presence of an Atypical Form of Pseudocholinesterase.*—Some people possess an atypical form of the enzyme which has little effect on the breakdown of suxamethonium. Since this is their only recognizable abnormality, such patients usually present as cases of unexpected prolonged apnoea following a single dose of the drug. This is an inherited defect which the anaesthetist may encounter approximately once in every thousand cases. The genetics of the condition have been reviewed by Lehmann and Liddell (1962). The typical and atypical forms of pseudocholinesterase differ in their activity in the presence of dibucaine. The normal enzyme is inhibited to a much greater extent than the atypical form, which is virtually unaffected. This fact has been used by Kalow and Genest (1957) and Kalow and Staron (1957) to estimate the proportion of normal enzyme which is present in the serum. With the "dibucaine No.," which is defined as "the percentage inhibition of cholinesterase activity with dibucaine," it is possible to identify three groups of people who from genetic studies can be classified as abnormal homozygotes (dibucaine No. 30% or less), heterozygotes (dibucaine No. 40 to 75%), and normal homozygotes (dibucaine No. over 75%). During the past nine months we have encountered seven persons in whom an atypical form of pseudocholinesterase was present. As this is a relatively rare characteristic we feel it would be of value to report these cases. In each instance blood from the patient and, where possible, from close relatives was obtained for estimation of the dibucaine No.

Case 1

A 51-year-old married woman was anaesthetized for treatment of bilateral varicose veins. Premedication was with pethidine 100 mg. and atropine 0.6 mg. one hour before operation. Induction of anaesthesia was with thiopentone 250 mg. followed by suxamethonium 50 mg. to facilitate endotracheal intubation. It was intended to allow spontaneous respiration with nitrous oxide, oxygen, and 1% halothane, and the patient was ventilated with this mixture. However, when no muscle tone or respiratory effort was present after 10 minutes the halothane was switched off and ventilation continued with nitrous oxide 3.5 l./min. and oxygen 1.5 l./min., using the Coxeter-Mushin absorber with fresh soda-lime.

An attempt was made to restart spontaneous respiration by adding 5% carbon dioxide to the mixture for 30 seconds with the absorber out of circuit. This had no effect, nor did the intravenous injection of 2 ml. of nikethamide. Controlled ventilation was therefore continued as before until spontaneous respiration returned one hour later. The patient made an uneventful recovery.

Her dibucaine No. was later found to be 49%.

The patient, her mother, daughter, and four of her siblings are heterozygous. There are no abnormal homozygotes (Fig. 1).

FIG. 1.—Family tree of Case 1. The figures on the charts refer to the dibucaine Nos.

Case 2

A 24-year-old primigravida was anaesthetized for caesarean section. Premedication was atropine 0.6 mg. Anaesthesia was induced with thiopentone 250 mg. followed by suxamethonium 100 mg., and the trachea was intubated with a No. 9 cuffed oral

tube. Intermittent positive-pressure ventilation was then started, using nitrous oxide 3.5 l./min. and oxygen 1.5 l./min. through fresh soda-lime in a Coxeter-Mushin absorber.

Ventilation was continued as described until the end of the operation one hour later, the patient being apnoeic throughout although no further suxamethonium had been required. At this time 5% carbon dioxide was given for 30 seconds with the absorber out of circuit, but the patient remained apnoeic. Ventilation was continued for a further one and three-quarters hours before respiration recommenced spontaneously two and three-quarters hours after the induction dose of suxamethonium.

The patient's dibucaine No. was 24%, and the baby, which cried immediately at birth, had a dibucaine No. of 71% at the age of 5 months.

The patient and her younger sister are both homozygous for the atypical enzyme. Both her parents, another sister, and her baby daughter are heterozygous (Fig. 2).

FIG. 2.—Family tree of Case 2.

Case 3

A boy aged 8 was having an operation for the correction of strabismus. Premedication was with quinalbarbitone 60 mg. orally one and a half hours before operation and atropine 0.6 mg. subcutaneously 30 minutes before operation. Anaesthesia was induced with thiopentone 200 mg. and suxamethonium 40 mg. He was intubated and ventilated with nitrous oxide 6 l./min. and oxygen 2 l./min. through a Magill attachment. Halothane 1% was added initially, but was turned off after four or five minutes when no signs of returning muscle tone were seen.

Forty-five minutes after induction the first respiratory efforts, with marked tracheal tug, appeared and ventilation was considered to be adequate after a further 20 minutes. He recovered consciousness a few minutes after the nitrous oxide was discontinued.

His dibucaine No. was found to be 21%.

In this union of two heterozygotes (Fig. 3) all the children are homozygous—two normal and two abnormal.

FIG. 3.—Family tree of Case 3.

FIG. 4.—Family tree of Case 4.

Case 4

A boy aged 10 was admitted to hospital for tonsillectomy. His parents informed the house-surgeon that their son's younger sister "had not breathed for three hours after the anaesthetic" when a cyst was removed from her eye in another hospital some months previously. They brought a letter from their general practitioner which also contained this information.

In view of this the boy's dibucaine No. was estimated and was found to be 26%. He was therefore anaesthetized for the tonsillectomy with nitrous oxide, oxygen, and halothane. Anaesthesia and operation were uneventful.

Both parents and one of their daughters are heterozygous. The son, in whom we avoided a prolonged apnoea, is homozygous for the abnormal gene; so is the other daughter, whose apnoea in another hospital led to investigation of this family (Fig. 4).

Case 5

A married woman aged 36 had an elective caesarean section for contracted pelvis. Her case-sheet for a previous confinement, which included a caesarean section, in another hospital had been consulted, but the details of the anaesthetic had not been transcribed into her present case-sheet.

Premedication was with atropine 0.6 mg. subcutaneously 30 minutes before operation. After thiopentone 200 mg. and suxamethonium 50 mg. she was intubated and ventilated with nitrous oxide 3 l./min. and oxygen 2 l./min. through a Coxeter-Mushin absorber with fresh soda-lime. The baby cried immediately on delivery. Forty-five minutes later, at the end of the operation, there was still no sign of spontaneous respiration nor of any reflex movement.

One hour and 45 minutes after induction the patient was ventilated for 15 seconds with 5% carbon dioxide with the absorber out of circuit. This resulted in respiratory movements, with marked tracheal tug, but the minute-volume was only 2 litres. Respiration was therefore assisted, and edrophonium 10 mg. was injected intravenously. The minute-volume increased to 6 l./min. and atropine 0.6 mg. followed by neostigmine 2.5 mg. was therefore given. The improvement in ventilation was maintained, and as her colour did not deteriorate on breathing air she was extubated and recovered consciousness very quickly.

Her dibucaine No. was 11%.

On being questioned later, the patient said that during the previous operation, six years before, the anaesthetist "had trouble with her breathing." The notes of this operation were obtained, and revealed that adequate respiration did not return until four hours after induction. The picture was complicated on that occasion by the fact that 50 mg. of suxamethonium had been followed by 12 mg. of D-tubocurarine. However, in the light of this second episode and the low dibucaine No. it is reasonable to postulate that the first apnoea was also due primarily to suxamethonium.

As the family of this patient are in Eire we have been unable to contact them. Her husband is normal, and as she is homozygous for the abnormal gene it is presumed that all her own children are heterozygous.

Case 6

A married woman aged 72 underwent dilatation and curettage for investigation of post-menopausal bleeding. She also suffered from chronic bronchitis.

Premedication was with heptabarbital ("medomin") 400 mg. given orally five hours before operation and atropine 0.6 mg. given intravenously immediately before induction. (The anaesthetist was Dr. G. B. Hendry.) Anaesthesia was induced with thiopentone 250 mg. and was maintained with nitrous oxide, oxygen, and halothane 1%. Because she was too "tight" for adequate pelvic examination, suxamethonium 30 mg. was injected intravenously. Fifteen minutes later, as she was still apnoeic, carbon dioxide 10% was added to the nitrous-oxide/oxygen mixture for 12 "breaths." This had no effect, and after a suitable interval nikethamide 6 ml. was injected intravenously. Apnoea persisted and endotracheal intubation was carried out without any reflex response. Ventilation with a mixture of nitrous oxide and oxygen (75%–25%) was maintained by a cyclator, the minute-volume being controlled at 8 l./min.

One hour after the administration of the suxamethonium her trachea was aspirated. This produced a minimal movement of her diaphragm. After a further 50 minutes feeble respiratory efforts were seen, but no reading could be obtained on a Wright's respirometer. At this stage an electromyogram was obtained and the tracing showed the typical fade and post-tetanic facilitation of a curariform block—that is, a "dual block" had developed (electromyography by Dr. W. L. M. Baird).

Edrophonium 10 mg. was then given, with improvement in the tidal volume to 400 ml., and the respiratory rate was 18–22/min. The reversal of the block was demonstrated on the electromyograph. Tracheobronchial toilet was again carried out and she was given atropine 0.6 mg. followed by neostigmine 1 mg.

Respirations remained adequate and she was returned to the ward three and a quarter hours after the administration of suxamethonium.

Her dibucaine No. was found to be 24%.

The husband is normal, and as the patient is homozygous for the abnormal enzyme the children should all be heterozygous. In fact, one of them is normal (Fig. 5).

FIG. 5.—Family tree of Case 6.

Case 7

A spinster aged 58 was anaesthetized for a spline osteotomy to the left hip-joint. She had suffered from rheumatoid arthritis for many years and had been receiving prednisolone 10 mg. daily for approximately five years. Premedication was by intramuscular cortisone 100 mg., pethidine 75 mg., and atropine 0.6 mg. one hour before operation.

Anaesthesia was induced with thiopentone 175 mg., and suxamethonium 75 mg. was given to facilitate endotracheal intubation. The patient was then ventilated with nitrous oxide 3.5 l./min., oxygen 1.5 l./min., and halothane, using the Coxeter-Mushin absorber with fresh soda-lime. The halothane was administered from a Goldman vaporizer in the expiratory side of the circuit; the control lever was at the second mark from the "off" position. After 10 minutes no return of muscle tone or respiratory effort was seen, so the halothane was switched off and ventilation continued as above, using nitrous oxide and oxygen only.

No attempt was made to restart spontaneous respiration or to hyperventilate the patient. After 55 minutes inadequate respiratory efforts began; these were not judged to be adequate for a further 30 minutes, during which time respiration was assisted. Her subsequent progress was uneventful.

The patient's dibucaine No. was found to be 60%. Only one other member of her family is alive, and he was not available for investigation.

Discussion

Lehmann and Ryan (1956) wrote: "It is important for people to know that they have a low pseudocholinesterase level. They should be given a letter to be handed to the anaesthetist should they ever require an operation. . . . It now seems to us that not only should every patient who has a prolonged apnoea after suxamethonium be examined for a lowered pseudocholinesterase level, but that his relations should be investigated as well."

This lowered pseudocholinesterase activity may be demonstrated by the use of test papers such as the "acholest,"² but it should be emphasized that estimation of pseudocholinesterase activity alone will not detect the presence of the atypical form of the enzyme. A sensitive person, particularly one heterozygous for the abnormal enzyme, may have a normal or only slightly decreased esterase activity, and only the dibucaine No. will show the qualitative difference. The abnormal homozygote generally has a decreased esterase activity in addition to a low dibucaine No.

In determining the incidence of this condition Kalow and Gunn (1958) found 191 heterozygotes and five homozygotes with the abnormal esterase in 4,570 subjects examined. Lehmann and Liddell (1962) think that anaesthetists using suxamethonium must therefore expect to encounter prolonged apnoea due to this hereditary abnormality in about one case in every thousand. In Glasgow Royal Infirmary and associated hospitals, where suxamethonium is widely used, six such cases have occurred in the last nine months. It has previously been stated (Lehmann and Liddell, 1962) that the occasional occurrence of a prolonged

² Makers of Acholest: Oesterreichische Stickstoffwerke Aktiengesellschaft.

apnoea does not justify anaesthetists in abandoning the use of suxamethonium; similarly, the occurrence is so uncommon as to make it impracticable to test every patient prior to operation. We feel, however, that once an untoward reaction has been noted in one patient it should be possible to avoid a similar episode in the same patient or his relatives at a later date.

In our own series of seven patients, one (Case 5) did not appreciate the necessity of informing the anaesthetist of her previous difficulty, and since the original case sheet was not available at the time of her recent operation no trouble was anticipated. This incident could have been avoided. One patient (Case 2) has a sister who had an apnoea following suxamethonium seven years previously. If she and her family could have been investigated then, the patient's apnoea would have been avoided. Case 3 has been fully investigated since his apnoea. He is on a waiting-list for tonsillectomy, and we hope that this complication will be avoided then. In Case 4 the fact that the parents and general practitioner were informed of the prolonged apnoea of the patient's sister alerted us to the possibility of this problem also arising with her brother. He was investigated, found to have a dibucaine No. of 26%, and anaesthetized with a technique avoiding suxamethonium.

All persons who are homozygous for the atypical enzyme—that is, who have dibucaine Nos. of 30% or less—are sensitive to suxamethonium. Cases 1 and 7 in our series come into the intermediate category—that is, dibucaine No. between 40 and 75%—and both had periods of prolonged apnoea. It has been suggested that apnoea occurring in such patients is due to heterozygosity of the atypical pseudocholinesterase with a third variant of the enzyme, which also fails to break down suxamethonium (Lehmann *et al.*, 1963). This third variant was described by Harris and Whittaker (1961), who used inhibition with fluoride for its detection, and derived the fluoride No. in a similar manner to the dibucaine No.

Since it seemed possible that Cases 1 and 7 might be examples of this doubly abnormal heterozygosity, the fluoride Nos. were estimated. One patient (Case 1) whose dibucaine No. was 49% had a fluoride No. of 55%, and the other (Case 7) whose dibucaine No. was 60% had a fluoride No. of 52%. Thus it would seem that these two patients are heterozygous for the atypical (dibucaine-resistant) and the normal enzymes. So far as we are aware, apnoea in patients of this type has not previously been reported. It would therefore seem that patients with dibucaine Nos. in the intermediate range should be treated as potentially sensitive to suxamethonium, irrespective of their fluoride Nos.

It is our practice to provide every sensitive individual with a typewritten card (Fig. 6) and to encourage them to memorize the phrase, "sensitive to scoline" (the proprietary name is used because it is easier to remember). The importance is impressed upon them of producing the card or of passing on the information on any admission to hospital. It is obviously important also that the case sheets of such patients should be clearly marked.

In the family tree of Case 6 one of her daughters was found to have a dibucaine No. of 83% (Kalow—homozygous normal) despite the fact that her mother had a dibucaine No. of 24% (Kalow—homozygous abnormal). These results have been checked by repeating the tests, and they are difficult to explain. Kalow and Staron (1957) and Harris *et al.* (1960) each report one family who did not follow this strict genetic pattern. They suggest the possibility of "modifying" genes at other loci or, alternatively, a different phenotype.

Another point of interest was the occurrence of dual block. This was proved in one patient (Case 5) by the therapeutic trial of edrophonium and in a second patient (Case 6) by electromyography. While dual block is said to be uncommon after a single dose of suxamethonium, its occurrence in cases with atypical pseudocholinesterase is not surprising, since the persistence of the drug in the blood-stream after a single dose is equivalent to multiple doses in a normal individual.

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BRING THIS CARD WITH YOU ON ADMISSION TO
HOSPITAL.

Name

This patient has an atypical pseudocholinesterase and is
VERY SENSITIVE TO SCOLINE.

FIG. 6.—Card to be presented by patient.

Conclusions and Summary

A series of seven cases possessing an atypical form of pseudocholinesterase is reported. Six of these cases presented as a prolonged response to suxamethonium. The familial incidence is demonstrated.

Of the 33 persons tested, eight, including five of the seven original patients, were homozygous for the abnormal gene and 19 were heterozygous, of whom two were sensitive. The population at risk is therefore greater than the actual incidence of apnoea.

The procedure recommended by Lehmann and Ryan (1956) following the discovery of a sensitive individual is quoted.

The importance of warning all patients, their relatives, and their general practitioners of their abnormality is re-emphasized, and the necessity for clearly marking hospital case-sheets is stressed.

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