We are grateful to Dr. Leonard Walby, school medical officer to the city of Belfast, for his active help and encouragement, and to his assistants. We thank Dr. W. G. Swann, medical officer of health, Professor A. C. Stevenson and Dr. E. A. Cheeseman for their help and advice. Mr. J. D. Merritt, Mr. S. Crockett, and Miss J. Cooper undertook much of the computing, and Miss P. Stewart and Miss H. Cogger the typing. We are grateful to them and to other colleagues in Queen's University and the London School of Hygiene. We are especially grateful to the Royal Ulster Constabulary and to Divisional-Inspector N. H. Sweny for help in drawing the sample of accident children. We also thank Dr. Harrison, formerly educational psychologist to the Belfast Education Committee, for measuring the intelligence of the sample of children.

REFERENCES

- Bimbach, S. B. (1948). "A Comparative Study of Accident Repeaters and Accident Free Pupils." Thesis No. 1124, New York University.
Brit. med. J., 1957, 1, 753.
 Charles, J. (1954). *Practitioner*, 172, 613.
 Children's Safety Crusade Trust (1953). *The Child on the Road*. Economic Research Council, London.
 Cohen, J., Dearnaley, E. J., and Hansel, C. E. M. (1955). *Operat. Res. Quart.*, 6, 3.
 — (1956). *Ibid.*, 7, 67.
 Gordon, J. E. (1949). *Amer. J. publ. Hlth*, 39, 504.
Lancet, 1957, 2, 990.
 Martin, W. J. (1957). *Brit. J. prev. soc. Med.*, 11, 90.
 Registrar-General (1957). *Statistical Review of England and Wales for the Year 1956*. Part I, Tables, Medical. H.M.S.O., London.
 Webb, W. B. (1955). *Publ. Hlth Rep. (Wash.)*, 70, 951.

EFFECTS OF OXYTOCIN ON THE RESPONSE TO SUXAMETHONIUM*

BY

R. J. HAMER HODGES, F.F.A.R.C.S.

Consultant Anaesthetist, St. Mary's Hospital, Portsmouth

J. R. BENNETT, F.F.A.R.C.S.

Late Senior Anaesthetic Registrar, St. Mary's Hospital, Portsmouth; Consultant Anaesthetist, Chichester

M. E. TUNSTALL, D.A., D.Obst.R.C.O.G.

Late Anaesthetic Registrar, St. Mary's Hospital, Portsmouth; Registrar, Middlesex Hospital, London

AND

R. O. F. SHANKS, D.A.

Late Anaesthetic Registrar, St. Mary's Hospital, Portsmouth

Abnormal responses to the short-acting depolarizing relaxants have often been reported, and the circumstances in which atypical effects are likely to be encountered are becoming more clarified.

It has now been established that following the prolonged administration of depolarizing agents the sensitivity of the patient is changed in such a manner that the threshold of the end-plate to depolarizing influences is raised. This leads to an induced resistance to the depolarizing action of this type of neuromuscular blocking agent and a susceptibility to non-depolarizing agents (Hodges and Foldes, 1956a, 1956b). This tendency to a change in end-plate sensitivity, which predisposes to atypical neuromuscular blocking effects, occurs more rapidly in the end-plates of certain species

where the initial susceptibility to depolarizing agents is low—for example, dog (Foldes *et al.*, 1957). In man, it is also known that the very young are inherently resistant to such agents (Hodges, 1956), and in neonates a change in response is likely to occur more readily (Rees, 1958). In certain pathological states such as myasthenia gravis, and in conditions associated with severe fluid and electrolytic disturbances, similarly predisposing circumstances prevail. It is likely that the pre-existing potassium depletion, combined with the subsequent loss of potassium from the muscles, caused by depolarizing relaxants, may be associated with the resistance and abnormal responses seen in some of these circumstances (Foldes *et al.*, 1957).

Following the continuous infusion of the posterior pituitary extract oxytocin* to obstetric patients, abnormal effects of a similar nature have recently been observed and a preliminary report has been published (Hodges, 1958a). Five cases are here reported, and further experimental clinical evidence is presented to substantiate the hypothesis that the continuous infusion of oxytocin alters the sensitivity of the end-plate in man to the effects of depolarizing relaxants.

All five patients were operated on in the obstetric unit of St. Mary's Hospital, Portsmouth. An anaesthetic technique based on a sleep dose of thiopentone followed by intermittent injections of suxamethonium intravenously and nitrous oxide and oxygen by controlled ventilation through an endotracheal tube, without carbon dioxide absorption, has been used successfully in this unit for a number of years (Hodges *et al.*, 1959). All these patients were anaesthetized in this manner.

Case Reports

Case 1.—A primigravida aged 22 had pre-eclamptic toxæmia. Artificial rupture of the membranes was followed by intermittent infusion of oxytocin over four to five days. Foetal distress ensued in the second stage of labour, and, under the general anaesthetic technique described, episiotomy, rotation of a persistent occipito-posterior lie, and the application of mid-cavity forceps resulted in the delivery of a normal active infant. The procedure lasted 36 minutes, during which time 150 mg. of suxamethonium was administered in intermittent 50-mg. doses. The last dose appeared to produce very little apnoeic effect, but when the procedure was completed the patient was undoubtedly still "curarized," with inability to open her eyes fully, to cough forcibly, or to elevate her limbs. This condition persisted for 30 minutes post-operatively, and was then reversed by the administration of neostigmine 1 mg. administered with atropine 1.2 mg. intravenously. Immediately after the incident the patient's pseudocholinesterase, together with the serum electrolytes and proteins, was estimated and found to be within normal limits, with the exception of a slightly raised serum potassium, which was 5.1 mEq/l.; this later fell to within normal limits (4.5 mEq/l.).

Case 2.—A 1-para aged 24 had artificial rupture of membranes and infusion of oxytocin over three days for toxæmia. Induction of labour failed, and caesarean section resulted in the delivery of a normal active infant. The procedure lasted 40 minutes, during which time 125 mg. of suxamethonium was administered in intermittent doses. When the procedure was completed the patient appeared still "curarized," and remained in this condition for 30 minutes. Subsequently, spontaneous slow recovery of full muscular power took place. Preoperatively, blood estimations showed the haemoglobin to be 57% and the serum potassium to be low (2.6 mEq/l.); this latter was probably associated with some preoperative vomiting.

*"Pitocin" (Parke, Davis) was used in all these investigations.

*Based on a paper presented by one of us (R. J. H. H.) to the Fifth Congress of the Scandinavian Society of Anaesthesiologists, Gausdal, September, 1958.

Case 3.—A multipara aged 29 had pre-eclamptic toxæmia. After artificial rupture of the membranes, oxytocin was infused over a two-day period. Induction of labour failed and infusion was discontinued. Eight hours later foetal distress ensued and caesarean section was performed, resulting in the delivery of an active infant. The initial dose of suxamethonium (50 mg.) intravenously appeared to be ineffective, and two further 50-mg. doses were given in quick succession. After the third dose muscle fasciculations were seen for the first time. Forty minutes after this last dose of suxamethonium the patient appeared to be still "curarized" and only slowly recovered spontaneously. At operation, blood estimation showed the haemoglobin to be 77% and the serum potassium to be raised (5.9 mEq/l.).

Case 4.—A multipara aged 21 was two weeks post-mature. Artificial rupture of the membranes was followed by oxytocin infusion for 24 hours. Induction of labour failed and caesarean section resulted in delivery of an active normal infant. No muscle fasciculations were seen after 40 mg. of suxamethonium intravenously, and this initial dose appeared ineffective. Further intermittent injections of suxamethonium were administered to produce relaxation, and over the ensuing 17½ minutes a total of 180 mg. had been given. Ten minutes after the last dose the patient appeared to be still "curarized" and showed a pronounced muscular weakness and an inability to open her eyes or to cough. Slow spontaneous recovery took place. Blood estimations showed the haemoglobin to be 75%. Other biochemical investigations were not done.

Case 5.—A 4-para had artificial rupture of the membranes for unstable lie, later followed by oxytocin infusion, continued for eight hours. Induction of labour failed and a transverse lie resulted. An active normal child was delivered by caesarean section. Only minimal fasciculations were observed after 50 mg. of suxamethonium intravenously. The procedure lasted 40 minutes, during which time 250 mg. of suxamethonium was given by intermittent injection. After the final dose (25 mg.) of suxamethonium, some respiration returned, but prolonged respiratory depression ensued and full muscle power did not begin to return for 20 minutes.

Clinical Experiments

Certain experiments were undertaken to determine the significance of oxytocin with regard to these findings. The first group of investigations concerned six patients lightly anaesthetized with a sleep dose of thiopentone and maintained with nitrous oxide and oxygen. It was possible to observe and record on a kymograph or a continuously recording spirometer the effects of carefully measured and controlled doses of suxamethonium administered intravenously before and at different intervals after the continued infusion of oxytocin. The patients were at rest and unstimulated during this procedure. After the effects of an initial test dose of suxamethonium had been recorded oxytocin was administered over a period of one to four hours (2 to 5 units in 300 ml. of saline). Immediately after these infusions a second dose of suxamethonium produced, in contrast to the first dose, no muscle fasciculations. Although the durations of apnoea following these second doses were not increased to a clinically significant extent, careful measurements showed that the total duration of respiratory depression (to recovery of full tidal volume) was increased by 50%.

The difference in the effects of the two test doses of suxamethonium was strikingly similar to the difference in effects of two similar test doses of suxamethonium administered before and after the establishment of end-plate resistance, which can be consistently induced by the prolonged administration of depolarizing agents themselves (Fig. 1).

FIG. 1.—The respiratory depressant effects in a healthy adult of two test doses of suxamethonium (20 mg.) administered intravenously before and after recovery from the continuous infusion of suxamethonium (1,000 mg. in 160 minutes).

FIG. 2.—The respiratory depressant effects in a healthy adult of two test doses of suxamethonium (20 mg.) administered intravenously before and after the continuous infusion of oxytocin (5 units in 100 minutes).

FIG. 3.—The respiratory depressant effects in a healthy adult of two test doses of suxamethonium (20 mg.) administered intravenously before and after the continuous infusion of oxytocin (5 units in 137 minutes).

FIG. 4.—Serum potassium levels in four healthy adults at rest during the continuous infusion of oxytocin.

Fig. 1 shows, superimposed on one another, the respiratory depressant effects of two 20-mg. doses of suxamethonium administered to a healthy adult before and after the recovery from the infusion of 1,000 mg. of suxamethonium over a period of 160 minutes.

The first dose produced within 60 seconds a 75% depression of tidal volume, and full recovery took place within two minutes. The second dose did not produce a maximal effect for two minutes, and the total depression even then was only 50% of the normal tidal volume. Full recovery did not take place for five to six minutes.

A similar picture was seen when oxytocin was used (see Figs. 2 and 3). It will be seen that recovery from the initial doses was rapid, but that after the administration of 5 units of oxytocin the recovery from a precisely similar dose was very much less rapid. Furthermore in Fig. 2 it can be clearly demonstrated that the second dose was far less effective.

In the second group of clinical experiments the results concern patients in whom it has been possible to obtain serial serum potassium estimations during the continuous infusion of oxytocin.

Although it has previously been shown that in a normal resting and fasting individual the serum potassium is remarkably stable (S. W. Stanbury, 1958, personal communication), we have found in clinical practice, especially with obstetric patients, that it has been difficult to obtain records in which such extraneous factors that might influence the results could be conclusively excluded. The patients in whom it has been possible to exclude such factors have been few, and at this stage it can only be said that the continuous administration of oxytocin appears to result in an unstable serum potassium. A fall occurs immediately, which in some patients appears to rise after three to four hours and may overshoot the original normal level. On cessation of the infusion the level returns to normal within a few hours and becomes stable again. Fig. 4 shows these results.

Discussion

In considering the significance of these results it is necessary to note that Hawkins and Nixon (1957) have shown that the serum potassium may fall during prolonged labour. It is also known that some conditions associated with pregnancy, dehydration, vomiting, and toxæmia may influence the electrolyte balance and might thereby alter responses to muscle relaxants. It is not thought, however, that these considerations explain satisfactorily the clinical results here reported. It has been our experience that, with the exception of those patients who had had oxytocin previously administered, the reaction of obstetric patients to suxamethonium is essentially normal and we regard the drug as the relaxant of choice in obstetrics.

Oxytocin, representing the oxytocic principle from the posterior lobe of the pituitary gland, may be used in obstetric practice to initiate and augment the uterine contractions of labour. In these circumstances it may sometimes be administered in a continuous infusion for prolonged periods.

The action of the drug is a highly selective stimulation of uterine muscle, excluding the cervix.

It is not thought likely that the minimal changes in blood pressure, cardiac output, and oxygen consumption

which can be shown to follow oxytocin in man (Goodman and Gilman, 1955) would consistently affect the action of suxamethonium to the extent found, although it is known that the duration of effect of relaxants can be associated with the efficiency of the peripheral blood flow.

The action of oxytocin is intracellular, and the mode of action is probably by some induced change in the ionic fluxes (Parke, Davis; personal communication). Recently it has been shown that pitocin increases potassium depression of the myoneural junction, and there is evidence to show that pitocin in a dose of 1.5 m-u./kg. increases the adrenaline relief of curare block (Lockett, 1957a). Lockett (1957b) has shown that 0.005 m-u. pitocin per 50 ml. is sufficient to potentiate potassium depression both of driven papillary muscle and of the rat phrenic nerve-diaphragm preparation.

In experimental circumstances (after a resistance to depolarizing influences has been induced by the prolonged administration of a depolarizing agent) it can be shown, as illustrated in Fig. 1, that the action of suxamethonium is slower in onset, less intense, and longer-lasting than its normal depolarizing action (Hodges, 1957, 1958b; Poulsen and Hougs, 1958). These atypical effects may be in part related to some imbalance of potassium ions following prolonged administration of the relaxants.

It seems a reasonable hypothesis that similar processes are at work here, and that the prolonged administration of oxytocin may affect some redistribution of potassium at the neuromuscular junction and that this may be associated with the altered response seen.

In all five cases recorded here the response to suxamethonium was atypical, and the incidence of these abnormal responses was very much higher than that which might have been expected during a similar series of normal surgical anaesthetics. These five instances occurred in a consecutive series of 350 obstetric surgical procedures, all conducted under the anaesthetic technique described. The most pronounced changes in the neuromuscular blocking action of suxamethonium were observed in those reported cases where the infusion of oxytocin had been prolonged for 24 hours or more.

In the course of clinical practice some anaesthetics were given to patients who had received oxytocin for shorter periods, without any observed abnormal effects. In the more closely observed clinical experiments, however, minor changes in effect of the relaxant were observed, even after very short (two to three hours) administrations of oxytocin, and the whole picture suggests that the infusion of oxytocin was the predisposing factor when atypical effects were observed clinically.

Conclusions

Our conclusions, based on the observations reported, are no more than strong clinical impressions, but they are nevertheless that the intravenous infusion of oxytocin modifies the action of suxamethonium. Fasciculation is minimal or absent, and normal doses of the relaxant are ineffectual in producing apnoea. Neuromuscular block of a non-depolarizing type does occur, however, and is slower in onset than that normally associated with the depolarizing block produced by suxamethonium. The duration of total respiratory depression, in comparison with the typical action expected, is prolonged and recovery may be hastened by the administration of neostigmine.

If the drug (which is now less effective) is administered in doses sufficient to produce degrees of complete relaxation and apnoea normally to be expected with suxamethonium, accumulative effects, overdosage, and slow recovery are to be expected, though likely to be antagonized by the administration of neostigmine. If the hypothesis is correct, that oxytocin modifies the action of suxamethonium by inducing some change in the end-plate reaction, it is likely that the clinical action of D-tubocurarine will be affected also. It would be expected that the increased resistance to depolarization would lead to a susceptibility to the non-depolarizing relaxant. However, we have not been able, as yet, to investigate this possibility in the normal course of our clinical practice.

Abnormal effects following suxamethonium are likely to be avoided by the administration of the relaxant in an infusion, by unhurried induction of the required level of relaxation, and by minimal titrated administration. It has been our practice, however, to advocate an initial dose of 50 mg. of suxamethonium intravenously in obstetric patients as there is a danger of regurgitation in such patients if endotracheal intubation is long delayed. These considerations have been discussed elsewhere (Hodges *et al.*, 1959).

Anaesthetists engaged in obstetric practice should bear in mind the atypical effects which may occur following the use of muscle relaxants, on those occasions when the oxytocic posterior pituitary extracts have been employed previously.

REFERENCES

- Foldes, F. F., Wnuck, A. L., Hodges, R. J. H., Thesleff, S., and deBeer, E. J. (1957). *Anesth. Anal. Curr. Res.*, 36, No. 5, p. 23.
 Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed. Macmillan, New York.
 Hawkins, D. F., and Nixon, W. C. W. (1957). *J. Obstet. Gynaec. Brit. Emp.*, 64, 641.
 Hodges, R. J. H. (1956). *Proceedings of the World Congress of Anesthesiologists, Netherlands, 1955*, p. 247. Burgess Publ. Co., Minneapolis.
 — (1957). *Brit. med. J.*, 1, 648.
 — (1958a). *Ibid.*, 1, 1416.
 — (1958b). *Lancet*, 2, 100.
 — Bennett, J. R., and Tunstall, M. E. (1959). *Brit. J. Anaesth.* In press.
 — and Foldes, F. F. (1956a). *Lancet*, 2, 788.
 — (1956b). *Brit. J. Anaesth.*, 28, 532.
 Lockett, M. F. (1957a). Personal communication cited by Parke, Davis Ltd.
 — (1957b). *J. Physiol. (Lond.)*, 136, 26P.
 Parke, Davis Ltd (1957). Personal communication.
 Poulsen, H., and Houghs, W. (1958). *Acta anaesth. scand.*, 2, 107.
 Rees, G. J. (1958). *Brit. med. Bull.*, 14, 38.

The South-western Regional Cancer Records Bureau has now issued its annual report for 1957. The population of the region is nearly 3 million. According to the report, almost all cancer cases there are now notified to the Bureau. The number of new cases in 1957 was 9,552. Tables show the numbers of cases registered, treated, and alive from 1945 to 1952 classified under different types of malignant growth, while five-year survival rates for treated cases are appended to each table. Much the commonest form of malignant disease registered in 1945–52 was cancer of the breast, with 5,085 cases. Next was cancer of thoracic organs, 2,288 cases, and then cancer of stomach, 2,218. The lowest five-year survival rate was for cancer of oesophagus, 3.1% of cases, followed by cancer of thoracic organs, 5.5%, and of pancreas, 5.6%. Cancer of the eye showed the highest five-year survival rate, with 71.6%. The rate for cancer of the breast was 43.9%.

ACUTE LARYNGO-TRACHEO-BRONCHITIS

AN ACCOUNT OF 122 CASES STUDIED IN THE HOSPITAL FOR SICK CHILDREN, TORONTO*

BY

ANN M. PEACH, M.B., D.C.H.†

AND

ELISABETH ZAIMAN, M.A., B.M.‡

From the Research Institute, the Hospital for Sick Children, Toronto, Canada

During the first world war and the following five years, reports of "non-diphtheritic croup" began to appear. Physicians described cases of illness clinically resembling diphtheria, but without the typical membrane, that did not respond to diphtheria antitoxin. In addition the Klebs-Loeffler bacillus could not be isolated from the throat in such cases. Amongst the names given to this condition were "non-diphtheritic croup," "false croup," "pseudo-croup," and "acute stenotic laryngitis." Baum (1924) proposed the term "acute laryngo-tracheo-bronchitis," and this has been used with minor variations since that time.

The literature was reviewed extensively by Neffson in 1944, and his monograph (Neffson, 1949) summarized the current opinions on incidence, pathology, bacteriology, diagnosis, and management of the condition. Since then the newer antibiotics have been used and evaluated, otherwise the principles of treatment and the criteria for diagnosis have remained unaltered.

The present investigation was undertaken as part of a project to elucidate the aetiological factors in this condition. It has already been reported that some evidence was obtained from studies of tissue culture, using monkey kidney monolayer cultures, that a virus was present in the tracheal secretions of some of the cases (Morgan *et al.*, 1956). Further investigations in 1955–6 yielded more substantial evidence for such a virus aetiology, as a cytopathogenic virus, similar to that isolated by Chanock (1956), was recovered from 10 of the 15 cases studied (Beale *et al.*, 1958).

While the isolation of a virus from cases of acute laryngo-tracheo-bronchitis is of great interest, it has as yet no important practical applications. The present paper records some of the results of an extensive study of laryngo-tracheo-bronchitis in Toronto, where the condition is a common cause for admissions to hospital each winter.

Patients Studied

The majority of cases of acute laryngo-tracheo-bronchitis are admitted to the Hospital for Sick Children, Toronto, during the winter months, although some do occur at other times of the year. This study was carried out during the two winter periods from November to March, 1952–3 and 1953–4. Not all cases admitted to the tracheitis unit of the hospital during those periods were studied, but all severe and moderately severe cases, and approximately one-third of the mild cases, were selected. Severe cases were defined as those children who required tracheotomy to relieve the respiratory

*Aided by a grant from the Canadian Life Insurance Officers Association, Toronto.

†Now at St. George's Hospital, London.

‡Now at the Maudsley Hospital, London.