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PANEL DISCUSSION

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Prof. J. Stovner, Oslo
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Dr. H. C. Churchill-Davidson, London

1. Foldes: **Introduction**

Ladies and gentlemen,

To start the ball rolling we have arranged for a brief presentation on some aspect of the clinical use of relaxants by each member of the panel. Subsequently, I shall ask the audience for questions and comments and will also encourage the members of the panel to discuss any controversial point that may come up.

Today you have already heard something on the influence of hyper- and hypoventilation on the effect of neuromuscular blocking agents. Prof. Vourc'h and Prof. Crul have some interesting new data on the effects of hypercarbia, and hypocarbia respectively. First, I would like to ask Prof. Vourc'h to discuss his observations on the influence of hypoventilation on the action of neuromuscular blocking agents.

2. Vourc'h[1]: **Metabolic acidosis and acute post-operative respiratory insufficiency**

That metabolic disturbances could alter the response of striated muscles to muscle relaxants has been suspected for some years. The term "neostigmine-resistant curarization" has been used to describe a condition in which respiratory activity cannot be resumed at the end of an operation, in spite of adequate doses of neostigmine.

Bush and Baraka (1964); Baraka (1964), Cohen et al. (1965), Feldman (1963), Katz and Wolf (1964) have shown that a raise of pCO_2 inhances the action of d-tubocurarine, both in intensity and duration, while a lowering of pCO_2 reduces it.

However, pCO_2 is only one of the factors involved in the maintenance of

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homeostasis; it represents the volatile component of the Henderson-Hasselbach equation, and in a normal invividual the lungs adjust its level to keep a steady pH of 7.45.

The metabolic component of the equation must also be considered and is of paramount importance. Even though pCO_2 is kept within normal range (40 mm Hg) any modification of plasma bicarbonate will shift the blood pH either towards the acid, or the alkaline side, and this, in turn, may interfere with the respiration and muscle tone.

Regulatory mechanisms (respiration, kidney function) are set to keep the pH constant. Any deviation is compensated in a normal individual. The lungs are very effective in clearing any CO_2 in excess. They cannot be expected to hypoventilate to raise the pCO_2 which would mean inducing hypoxia. The kidneys have a considerable capacity for dealing with long-term alkalaemia or acidaemia within limits, but it takes some time before their action becomes effective.

In clinical practice, patients are not always in a normal, steady state; they may suffer from lung disease (which means hypoxia and respiratory acidosis); they may have metabolic alkalosis or acidosis, hyper- or hypokalaemia, hyper- or hypocalcaemia, natraemia. These disorders are likely to affect the myoneural junction and the respiratory center.

Most cases involved in so-called "neostigmine resistant curarization" are patients with mixed respiratory and metabolic acidosis. Their condition may be unknown or badly assessed when they are operated in an emergency. The anaesthesist will tend to ventilate them as he would a normal case, according to the various nomograms (Ratford's, Nunn's), to keep the pCO_2 at a normal level. This corresponds in fact to a hypoventilation in such circumstances and can only lower the blood pH to a dangerous level.

A typical example is that of diabetic coma: the plasma bicarbonates are low; the patient hyperventilates to adjust the blood pH, and his pCO_2 is low. Should he be anaesthetized, curarized, and his pCO_2 brought back to normal, it would upset the narrow equilibrium achieved and induce a decompensated metabolic acidosis incompatible with life.

Most physiology text books consider that blood pH lower than 6.8 or higher than 7.6 are incompatible with life. Such deviations can be achieved very easily in case of hypo- or hyperventilation, especially if there are underlying metabolic disturbances.

Furthermore, the patient's lungs may be incapable of responding to the demand (in case of emphysema, pleural effusion, pneumothorax, lung resection, etc.) or his respiratory center may be depressed by drugs (morphine, barbiturate, etc.).

The situation may, therefore, arise of a patient who, at the end of an operation, does not resume breathing or muscular activity. He may have received a muscle relaxant of some kind, though this complication may also occur in the absence of muscle relaxants. This raises two different problems: diagnostic and therapeutic.

Table I

Case No.	Operation	Anaesthesia			During respiratory arrest				After recovery				Onset of accident after operation	Arrest of	
		thio-pentone g	d-tubo-cura-rine mg	time (hours)	HbO_2 %	pH	pCO_2 mm Hg	CO_2 total mEq/l	HbO_2 %	pH	pCO_2 mm Hg	CO_2 total mEq/l		resp.	circ.
1	Uretheral catheterization	0.30	0	1	88	7.22	53	20.5	98	7.35	26	19	10 min	+	
2a	Colocystoplasty	1.30	38	8	87	7.13	59	21	97	7.4	26	17	15 min	+	+
2b	Colostomy	0.55	19	2	73	7.2	43	20	96	7.36	25	24	5 min	+	+
3	Small bowel obstruction and diabetes	0.33	24	2½	88	7.2	51	21	98	7.4	29	20	45 min	+	
4	Prostatectomy	0.40	10	1	96	7.15	51	20	98	7.5	19	16	90 min	+	+
5	Aorto-femoral graft	0.40	56	8	87	7.2	58	21		7.44	28	19	30 min	+	

Clinical implications.—Only very few articles have dealt with this problem except on theoretical lines. BROOK and FELDMAN (1962) and FELDMAN (1965) have clearly seen the issues and recommend to treat those cases with hyperventilation and alkalinisation to restaure a normal pH. JENKINS (1961) had already published three cases which can be compared with ours, although they lack laboratory evidence.

We present six cases of patients, apparently partly or completely curarized at the end of an operation, who did not respond to neostigmine; one of them had received a single dose of suxamethonium, though his condition appeared to be identical with that of the others. Biological studies show conclusively that in all cases not curare but the underlying metabolic disorder was the major factor. The corresponding data are shown in Table 1. One must consider that the first sample of arterial blood was taken when resuscitation had been already started and that undoubtedly the figures were much worse during the acute episode of respiratory depression.

The six cases follow a similar pattern. It will be seen that in one case the patient received no d-tubocurarine at all; however, at the end of the procedure, he appeared deeply curarized like all the other ones. Curare, therefore, is not the common factor (though it may have played some part in the etiology of the accident). Some patients received neostigmine in adequate doses without any improvement. Case 2 had two similar episodes (a and b).

Metabolic acidosis is certain in four cases (case 1: recurrent carcinoma of the rectum, involving both ureters with anuria; case 2: carcinoma of the bladder with ascending pyelonephritis; case 4: small bowel obstruction on a diabetic patient operated after 10 days; case 5: prostatotomy). It is most likely in case 6: aortic graft on a patient with arteriosclerosis and disturbed kidney function. The degree of the acidosis, however, was not impressive, and before the operation it was fairly well compensated. pCO_2 was only mildly raised, and much higher figures are often met without such serious consequences.

In all cases the common factor is a decompensated metabolic acidosis of rapid onset, due to hypoventilation with a sharp fall of blood pH. Beyond certain critical values, acidosis (and inhalation of CO_2) has a depressant action on the respiratory center and the circulation.

Obs. 1. Mr. L., 55 year old patient, operated in 1964 for rectal carcinoma (amputation) under general anaesthesia and muscle relaxants without complications.

In 1965, anuria through local recurrence involving the bladder and both ureters. Blood urea was 290 mg; total CO_2, 10 mEq. The patient is put under peritoneal dialysis, and ureteral catheterization performed under general anaesthesia. Premedication: atropine 0.5 mg. Anaesthesia: thiopentone 300 mg, succinylcholine 80 mg; intubation; nitrous oxide and oxygen. Total operating time: 60 min spontaneous respiration throughout.

At the end of the procedure, respiration seemed adequate, the patient responded to stimuli, and the endo-tracheal tube was removed.

Ten minutes later, he was found to be unconscious, with marked hypoventilation. He was intubated, ventilated with a Bird respirator.

The post-operative course was uneventful.

Obs. 2. Mr. B., 66 year old patient, was admitted for carcinoma of the bladder.

In a first stage, a colocystoplasty was performed under general anaesthesia.

Premedication: pethidine 100 mg, atropine 0.5 mg. Anaesthesia: thiopentone 1.3 g. d-tubocurarine 38 mg. Respiration was controlled thoughout with nitrous oxyde and oxygen, and blood losses compensated. At the end of the procedure, the patient's condition was satisfactory, and he was extubated.

Two hours later, after a period of progressive dyspnea, respiratory arrest and loss of consciousness with pupillary dilatation. The patient was ventilated with air (without intubation) and given 500 ml of 1.4% bicarbonate solution. This restored normal respiratory function (case 2a).

One month later, he had a colostomy; the premedication was the same; he received 550 mg of thiopentone and 19 mg of d-tubocurarine for a total operating time of two hours. Respiration was controlled with nitrous oxide and oxygen. The patient was awake at the end of the procedure.

On account of the previous incident the patient was kept under close supervision. Five minutes later he was complaining of dyspnea, with cyanosis, loss of muscle strength; he was given 1 mg of neostygmine. In spite of this, he had another episode of respiratory and cardiac arrest 15 min later, with pupillary dilatation and absence of corneal reflexes. He was intubated, massaged, and in a few minutes he was in normal condition (case 2b).

Obs. 3. Mrs. B., 70 year old patient, was admitted for strangulated hernia with small gut obstruction. She had diabetes (blood sugar level 330 mg%); ECG was normal.

Operation was performed under general anaesthesia (premedication: pethidine 50 mg, atropine 0.5 mg. thiopentone 330 mg, d-tubocurarine 24 mg). Respiration was controlled with nitrous oxide and oxygen.

The patient was kept intubated since she responded poorly to peripheral stimuli, although respiration was adequate. 30 min later, after an episode of dyspnea, respiratory arrest. ECG showed auricular fibrillation. The patient was ventilated with a mixture of air and oxygen for 45 min; she could then be extubated.

The following day she was in good condition; ECG was compatible with hyperkalaemia (6.2 mEq/l).

Obs. 4. Mr. A., 79 year old patient, had been suffering from urinary retention and infection due to a prostatic carcinoma. An acute episode of bacteraemia, with high temperature and cardio-vascular collapse, had led to his hospitalization; this was treated successfully by antibiotics and corticoids. A few days later a prostatectomy was performed.

Premedication: pethidine 100 mg, scopolamine 0.5 mg. Anaesthesia was carried out with thiopentone (400 mg), nitrous oxide and oxygen. The patient was intubated under suxamethonium and then received 10 mg of d-tubocurarine. Ventilation was controlled throughout the procedure, which took one hour.

The patient seemed to respond to call at the end of the operation; he was extubated and taken to the recovery room; five minutes later he was found to be unconscious, with absent corneal reflexes and a poor ventilation. He was insufflated with air and oxygen through a mask, then intubated. An ECG showed a quadrigeminate rhythm; blood pressure was high (200/12 Hg) but rapidly fell to very low figures (40 mm Hg systolic), while respiration stopped and pupils dilated.

He was put on a respirator and given 500 ml of 1.4% bicarbonate.

30 minutes later, the ECG was normal, the blood pressure had returned to preoperative level; respiration was normal, the patient conscious; he could be extubated two hours later.

Obs. 5. Mr. K., a 58 year old patient, admitted for advanced arteritis for aortic femoral bypass.

The operation was performed under general anaesthesia (premedication: pethidine 100 mg, atropine 0.5 mg. thiopentone 400 mg, d-tubocurarine 56 mg). Total operation time: eight hours.

The patient was awake at the end of the procedure and extubated. 30 min later a respiratory arrest occurred, with hypertension (200/70) and coma. He was intubated and ventilated for three hours. Twelve hours later, he was extubated and in normal clinical condition. The metabolic acidosis in this case may have been due to the circulatory arrest induced by aortic occlusion (1 hour) on a patient already in poor condition.

This is often met in patients with respiratory insufficiency, and their clinical condition resembles that of residual curarization: shallow breathing, with tugging; depressed muscular activity and muscle tone; reflexes depressed or absent. This condition does not respond to either respiratory or circulatory stimulants, but to ventilation and correction of the acid-base disorder.

Discussion. – *1. Etiology.* Although the ultimate cause of this complication is undoubtedly a decompensated mixed acidosis, one must consider the possible role of *anaesthetic agents:*

- Morphine and morphine-like drugs are well known to induce coma in respiratory cripples. In out cases, patients had normal respiratory function, and although they received opiates in their premedication, they were in good condition before being anaesthetized.
- Barbiturates have a similar, though less pronounced action. In our cases the total amount used was usually small; patients were awake as soon as the acidosis had been corrected.
- Electrolyte imbalance may be involved (particularly hyper- or hypokalaemia); this was not to be seen in our series.
- *Surgical trauma* is a factor of acidosis and pain from the wound (laparotomy, thoracotomy) is likely to depress the respiration. In our first case this was not a factor; in the other ones respiration was normal after the acidosis had been corrected.
- *Curare.* While it is certainly true that acidosis enhances the action of d-tubocurarine and gallamine, we do not feel that it may account for the facts observed. One patient (case 1) received only a single dose of suxamethonium, and his condition was undistinguishable from that of the others; neostigmine had no action; the doses of curare were rather small considering the type and length of the procedures and the last injections given at least 30 min before the end of the procedure; breathing and muscle strength were normal as soon as the acidosis had been corrected.

Although all these factors may have played a part, it is probable that hypoventilation (either absolute or relative) has been the major factor. A patient with metabolic acidosis should be hyperventilated to keep his pH normal. It is a common practice, at the end of an operation, to cut off the absorber, to stimulate respiration and to give the patient pure oxygen: this further raises the pCO_2 while masking the hypoventilation and the cyanosis.

2. Diagnosis. This condition should be suspected when, at the end of an operation, the patient fails to resume normal muscle tone and respiration in spite of adequate doses of neostigmine. It must be pointed out that neostigmine may be harmful in case of cardiovascular disorders induced by

the fall in pH. To establish the diagnosis, and lead the correct treatment, arterial blood should be drawn, and pH, pCO_2 and plasma bicarbonate measured.

Peripheral nerve stimulation (ulnar or median) is of little help and may lead to a faulty conclusion since acidosis is likely to depress neuromuscular conduction.

3. Treatment. Without waiting for the results of these laboratory investigations, the patient should be intubated and hyperventilated with air or oxygen; bicarbonate may eventually be used. ECG should be monitored. Uusually the condition improves in a matter of minutes (10–30). When muscle tone and consciousness are normal, the respirator is disconnected and the patient left to breathe on his own. He may then be extubated or further assisted if necessary. Arterial blood should then be taken again and the figures compared with the previous ones.

Summary.—Decompensated acidosis, usually mixed, metabolic and respiratory, may mimic residual curarization at the end of an operation and may lead to respiratory failure. It does not respond to neostigmine but to hyperventilation and eventually alkalinization.

Six cases are presented in which this complication occurred, was recognized through blood gas studies and successfully treated.

Baraka A.: The effect of carbon dioxide on the neuromuscular block caused by d-tubocurarine chloride in the human subject. Brit. J. Anaesth. *36*, 272–278 (1964).

Brooks D. K. and Feldman S. A.: A new approach to neostigmine resistant curarization. Anaesthesia *17*, 161–169 (1962).

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Cavellat M.: Interférence des troubles de l'équilibre acide-base sur l'anesthésie (à propos d'une observation). Cah. Anesth. *11*, 654–663 (1964).

Cohen E. N., Hood, N. and Canner P.: Blood pH and plasma level of d-tubocurarine. Anesthesiology *26*, 727–730 (1965).

Feldman S. A.: Neostigmine resistant curarization. Anaesthesia *18*, 106–108 (1963a).

Feldman S. A.: Effects of changes in electrolytes, hydration and pH upon the reactions to muscle relaxants. Brit. J. Anaesth. *35*, 547–551 (1963 b).

Jenkins I. R.: Three cases of apparent recurarization. Brit. J. Anaesth. *33*, 314–318 (1961).

Katz R. L. and Wolf C. E.: Neuromuscular and electromyographic studies in man: effects of hyperventilation, carbon dioxide inhalation and d-tubocurarine. Anesthesiology *25*, 781–787 (1964).

3. Foldes:

Thank you very much! I would like to ask Prof. Crul to continue with his observations on hyperventilation.

4. Crul:

After the very elegant presentation by Dr. Coleman, I like to mention the results of my study on hyperventilation in curarization. My experiments

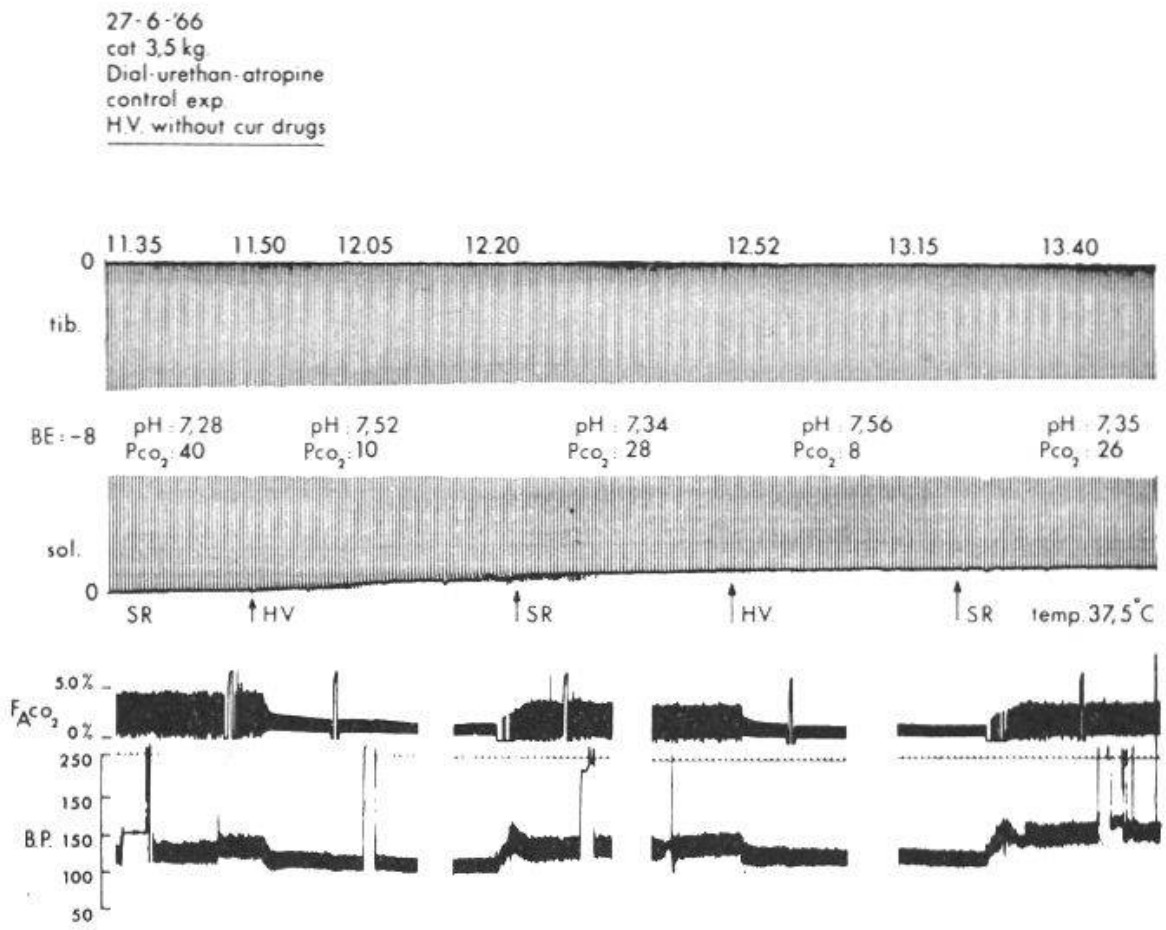


Fig. 1. Control experiment.—Contractions of tibialis anterior and soleus muscles of the cat stimulated indirectly via sciatic nerve. Between recordings of contraction, acid-base status of the cat, measured in arterial blood by micro-Astrup technique.—BE: base excess. Note that normal BE of awake cats is —6 to —8. SR: spontaneous respiration. HV: Hyperventilation. Core and muscle temperatures were kept constant.—F_ACO_2: infrared analysis curve of CO_2 concentration of in- and expiratory gases. Calibration for zero and 5% with test mixtures. BP: blood pressure by indwelling carotid catheter.

were first done on cats, and then continued on men. I used continuous infusion techniques for succinylcholine, d-tubocurarine and Alloferin (diallylnortoxiferine) and made the cats and men their own controls, by returning to the control level of muscular contraction after hyperventilation and after stopping of the infusion. I did not take the full range of respiratory alcalosis to acidosis but only from alcalosis to normal pH status.

Fig. 1 shows that in control cats changing respiration from spontaneous to artificial hyperventilation caused no change in contraction height of the soleus or the tibialis muscle over a long period of time. Infusions of d-tubocurarine (Fig. 2) produced a steady state of paralysis. Respiratory depression made artificial ventilation necessary (CR). Care was taken to avoid hyperventilation. After 20 min of steady curarization we changed to hyperventilation with pH-values of ± 7.53 and pCO_2 of ± 17 mm Hg. No significant changes in contraction height were seen in 10 experiments. Only after the end of the hyperventilation period was there a small insignificant increase

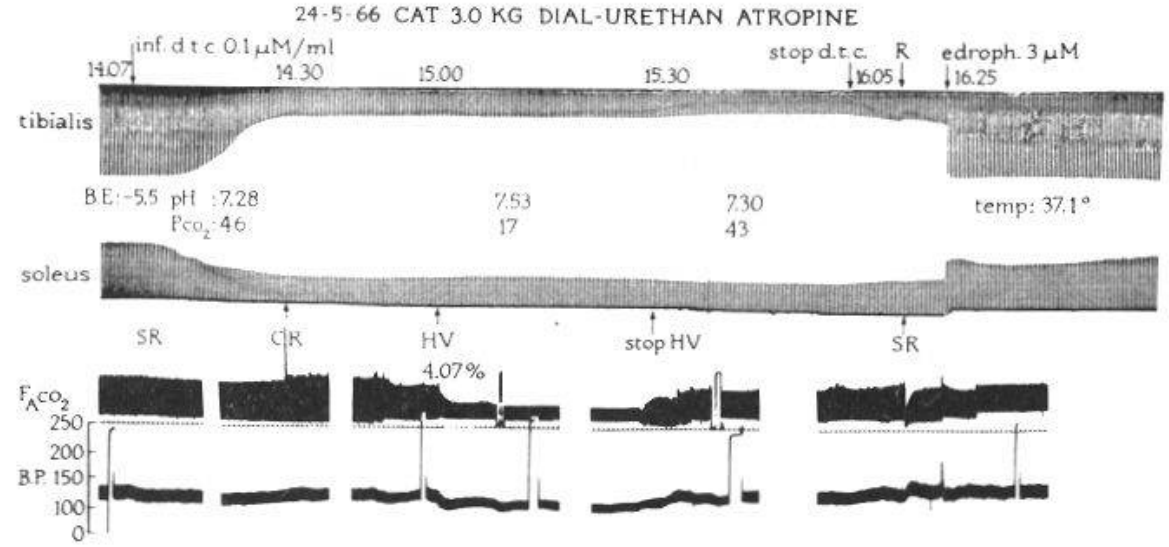


Fig. 2. Experiment with d-tubocurarine infusion 0.1 μMol/ml. Speed of infusion set at approximately 50% paralysis.—Explanation of signs see Fig. 1. R: flushing of infusion catheter with saline. No effect of hyperventilation on block by d-tubocurarine.

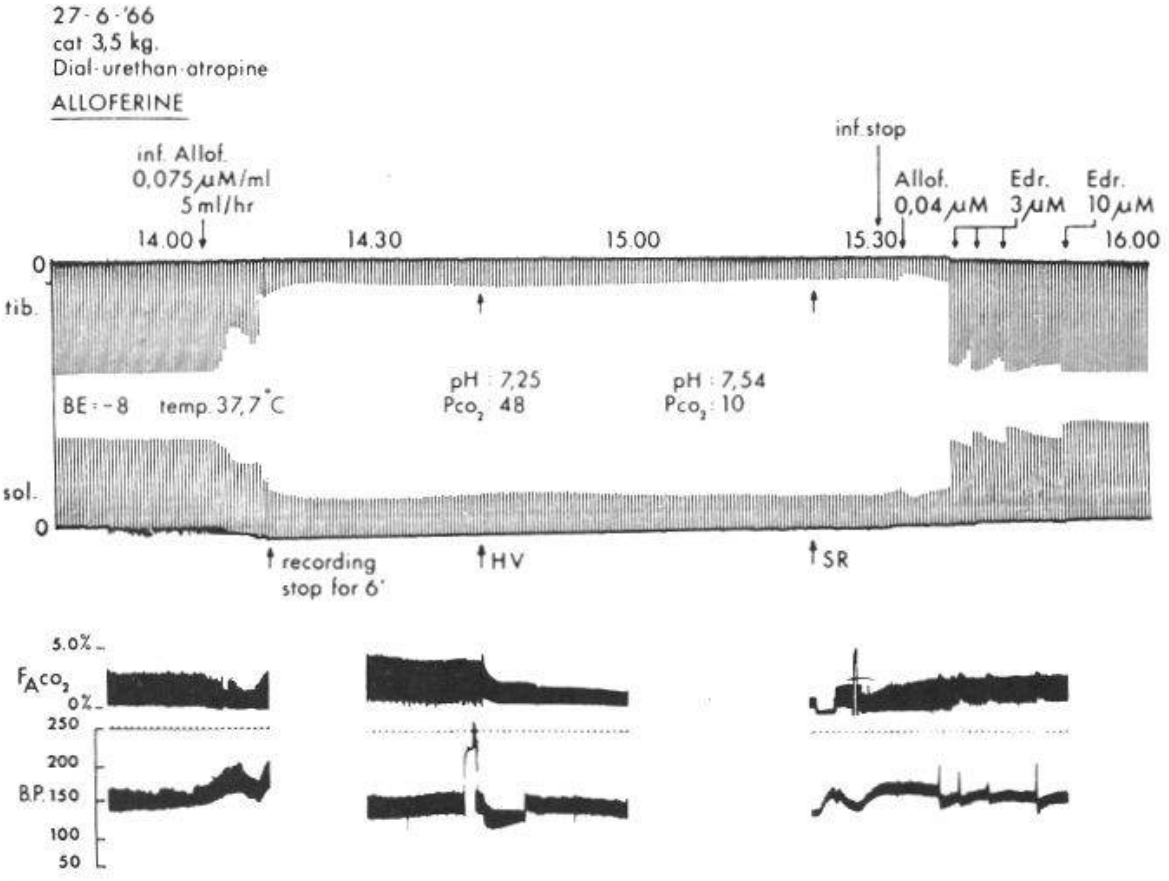


Fig. 3. Experiment with Alloferine infusion. For explanation of signs see Fig. 1. No change of sensitivity for Alloferine by hyperventilation.

of the block by d-tubocurarine. When at the end of the experiment we stopped the infusions, the contractions returned to the control level or almost to the control level; sometimes we helped this reversal by giving edrophonium.

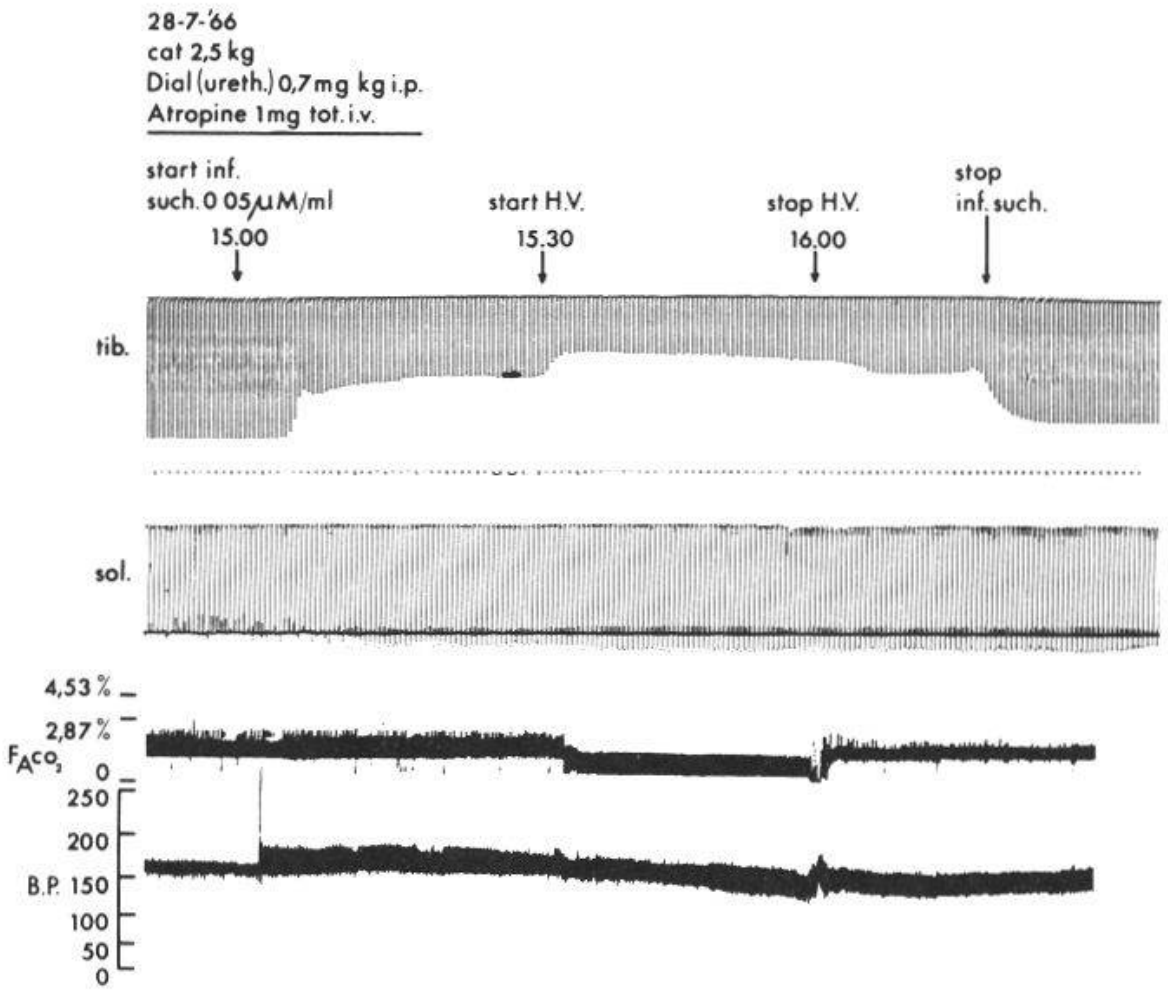


Fig. 4. Experiment with succinylcholine infusion. Note sudden decrease of contractions of tibialis after start of HV and return to normal values after it.

In Fig. 3 you see the same type of experiment with Alloferin. Here again, after a steady state of paralysis of the tibialis and soleus changing from normal ventilation to hyperventilation gave no significant alteration of the contraction height. Ten experiments were done with Alloferine, all with the same results.

Fig. 4, in contrast, shows that succinylcholine block of the tibialis muscle was increased by hyperventilation in 12 out of 13 cats. This increased block in 3 experiments reversed slightly and spontaneously before the ventilation was brought back to normal spontaneous ventilation. The soleus contractions were unaffected. In 3 other experiments, while continuing hyperventilation, we added CO_2 to the inspired gazes, so that we reached the same level of end-tidal CO_2 as before hyperventilation. In that case we got a quick return to the original contraction height as it was during spontaneous ventilation. In one of the experiments (Fig. 5) succinylcholine even for a prolonged period of hyperventilation did not give any change in contraction height.

May I close by giving the preliminary results of the same experiments in man briefly. Spontaneous contractions of the muscles without curariform

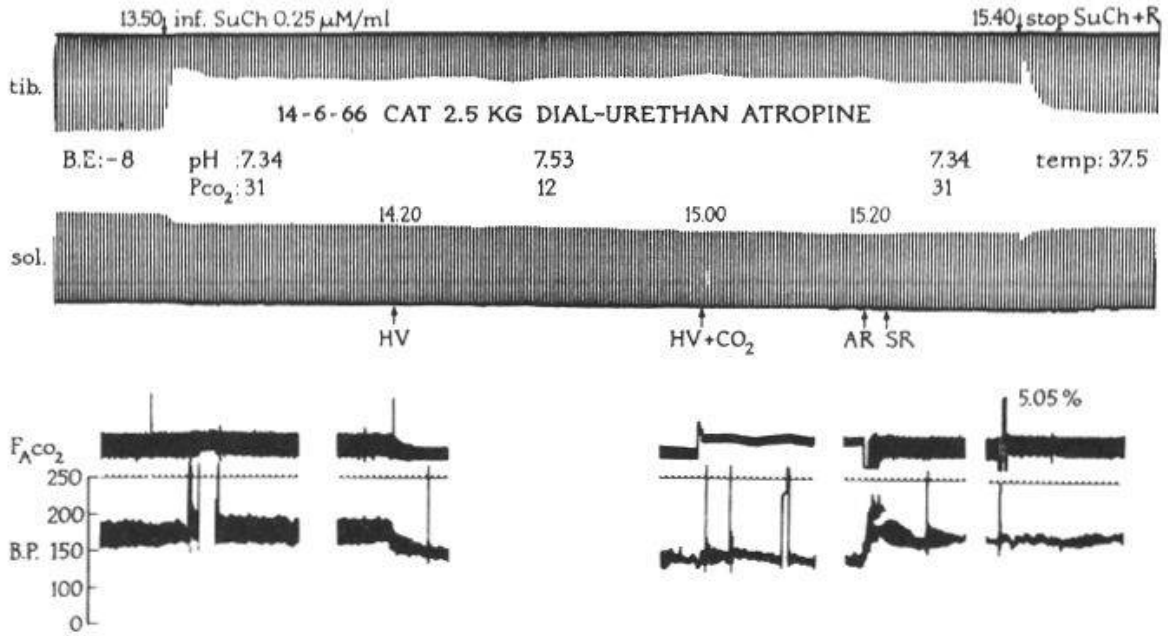


Fig. 5. Same experiment as in Fig. 4. No effect of HV on sensitivity for SuCh infusion.

drugs increased with hyperventilation (which was not seen in cats). Secondly, we did not see the marked decrease of contraction height of the muscles with hyperventilation during the infusion with succinylcholine. Therefore the changes were even less in men than in cats. We did not see significant changes in sensitivity to d-tubocurarine, succinylcholine or Alloferine in changing from spontaneous to controlled hyperventilation.

5. Foldes:

Thank you very much Dr. Crul. You have heard during the preceding lectures that the prolonged apnea observed at the termination of surgery may be caused by different mechanisms, not only by persistent neuromuscular block.

Before one attempts to treat prolonged apnea, it should be determined if it is due to persistent neuromuscular block or is caused by other factors. The various mechanisms which may cause prolonged apnea include reflex breath-holding, due to stimulation of the endotracheal tube, central respiratory depression caused by narcotics, general anesthetic agents, acidosis and fluid and electrolyt disturbances.

In this respect I would like to draw your attention to what we heard from Prof. Thesleff yesterday, namely, that calcium deficiency may result in the release of insufficient quantities of the transmitter substance (acetylcholine), and this in turn may produce a prolonged neuromuscular block. Calcium deficiency may occur under two sets of circumstances: (a) After excessive hyperventilation for prolonged periods, and (b) after multiple transfusions of citrated blood. In order to be sure that we are dealing with a neuromuscular block, we have to have some reliable method of diagnosis. Dr. Churchill-Davidson and his associates developed a simple practical

technique which can tell us with certainty whether the apnea is due to neuromuscular block or to some other factor. I would like to ask Dr. CHURCHILL-DAVIDSON to show us his film of this technique and to comment on it.

6. CHURCHILL-DAVIDSON: **The diagnosis of neuromuscular block**

Until recent years the clinician administering an anesthetic (including a muscle relaxant technique) had no reliable guide as to the exact degree of muscle paresis that was present at any precise moment. At the end of the operation, various signs such as the ability of the patient to put out his tongue or raise his head were used. None of these was satisfactory in the unconscious patient. Some anesthetists used the tidal volume as a visual guide to the adequacy of respiration, yet it is often forgotten that tidal volume is only one tenth of vital capacity. Theoretically, therefore, it is still possible for a patient to have a normal tidal volume but still be gravely at risk with 90% of the respiratory muscle fibres still paralysed.

This has now all changed, for today it is possible to measure neuromuscular transmission with a portable transistorized nerve stimulator (Fig. 1). Such an instrument is compact and easily held in one hand. The output is variable from 0 to 250 volts with a pulse width of 0.3 msec. An impulse can be

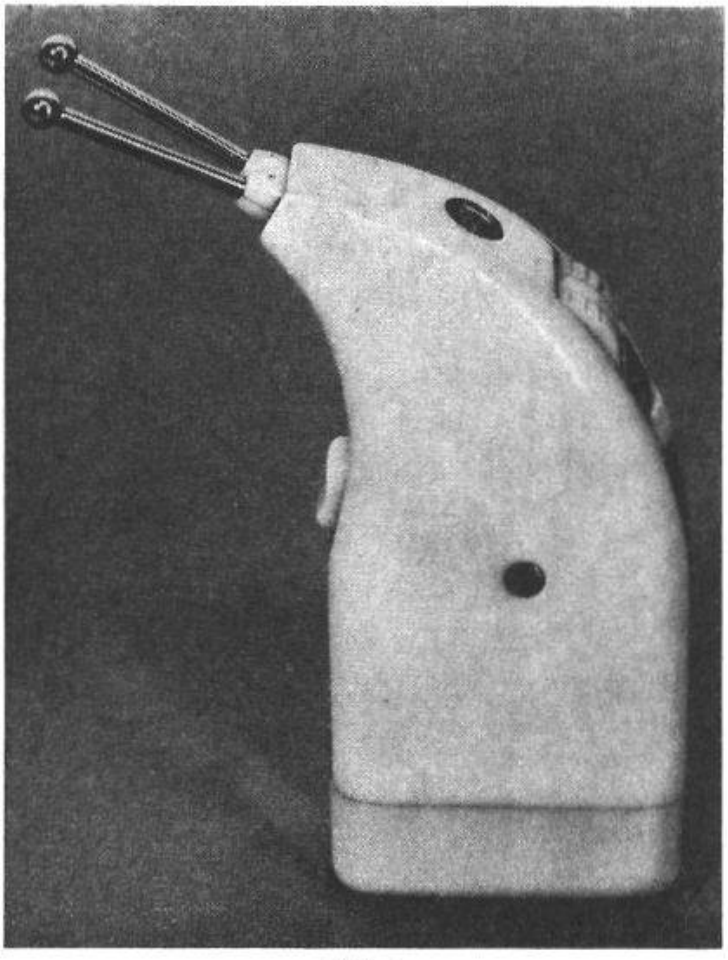


Fig. 1.

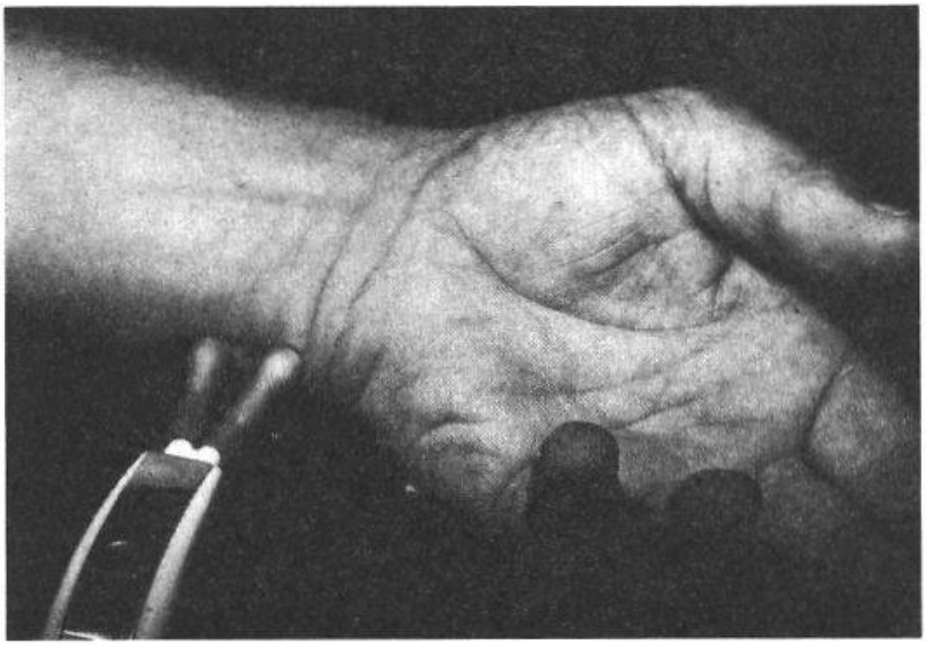


Fig. 2.

administered either singly at twitch rates or in a train of tetanic impulses at 50/sec. When applied to the ulnar nerve at the wrist (Fig. 2), the movements of the corresponding fingers will reveal useful information on the state of neuromuscular transmission.

The value of such a peripheral nerve stimulator in clinical practice is twofold. First, it reveals the exact amount of paresis that is present. The hand muscles have proved most useful in this respect as they appear to be much more sensitive to both types of muscle relaxants (i.e. depolarizers and non-depolarizers). Thus, if the hand muscles can be shown to have recovered from the effects of the relaxant drug the anaesthetist can confidently assume that full respiratory activity has been regained. Again, a peripheral nerve stimulator is most useful for monitoring neuromuscular transmission in the presence of a continuous infusion of succinylcholine in order to prevent an overdose. It can also be used to observe the efficacy of anticholinesterase therapy after d-tubocurarine in a severely ill patient so that only the minimum quantity of these drugs need be used.

The second principal value of a peripheral nerve stimulator in clinical practice is to demonstrate the exact type of neuromuscular block that is present. It has been shown electromyographically that the pure depolarizing block exhibits a characteristic set of features. First, both twitch and tetanic rates of nerve stimulation are well maintained. Secondly, there is no post-tetanic facilitation. Thirdly, following the injection of an anticholinesterase drug there is either no change or an increase in the neuromuscular block.

In direct contrast with the non-depolarizing group of drugs the characteristic features are: 1. The presence of a "fade" with both slow (twitch) and fast (tetanic) rates of nerve stimulation. 2. The presence of post-tetanic facilitation. 3. Improvement in neuromuscular transmission after the injection of an anticholinesterase drug.

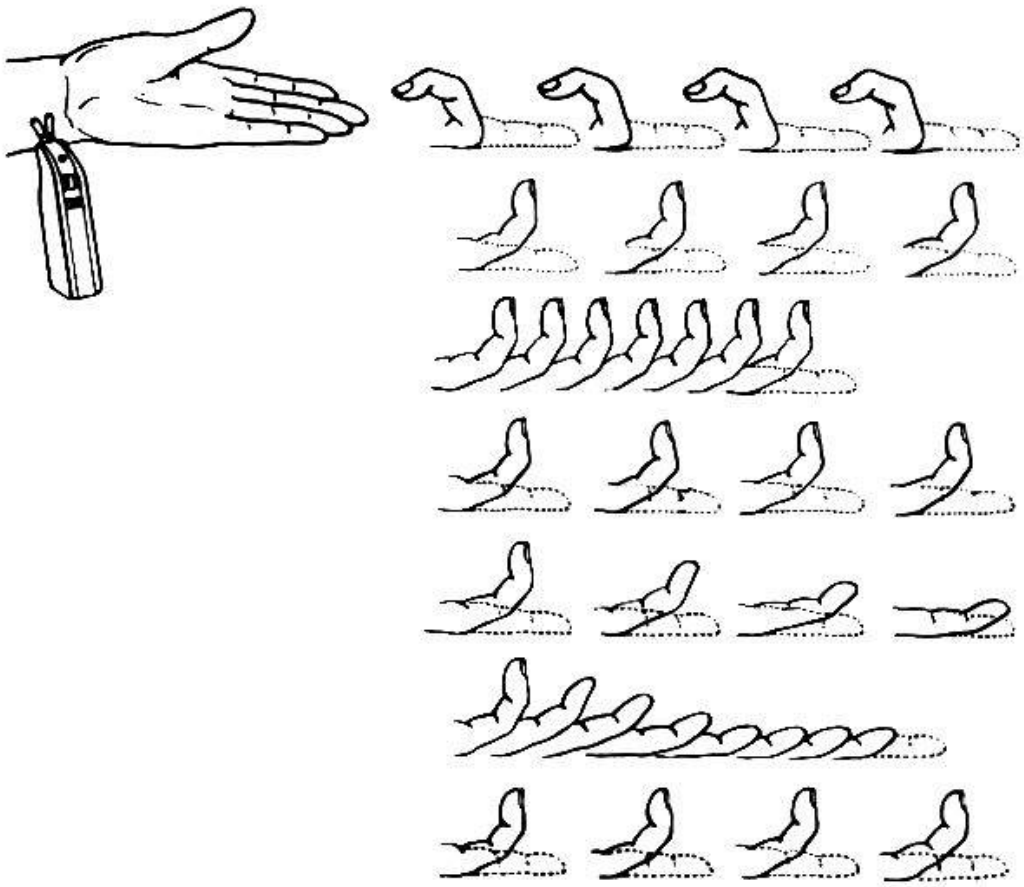


Fig. 3.

For teaching purposes, it is invaluable to be able to demonstrate not only the degree but also the characteristic of the particular type of neuromuscular block that is present. Furthermore, during an infusion of succinylcholine it is possible to demonstrate the gradual change in the type of block. In the early stages the finger movements are typical of depolarization but later both "fade" and "post-tetanic facilitation" become evident as the dual block becomes established (Fig. 3).

7. FOLDES:

Thank you very much for this really excellent and instructive film which demonstrates all the essential points very well. I would like to comment on the use of the antagonists of muscle relaxants. The first important decision to be made is when to use and when not to use them. When a patient is sufficiently awake at the end of surgery (and this is frequently the case with modern methods of balanced anesthesia), there are certain signs that can be used to determine the degree of residual neuromuscular block. One of them is the ability of the patient to lift his head as mentioned by Dr. STOVNER, and the other is the adequate power of the levator palpebra and external ocular muscles which are usually the last to recover. Without diagnostic aids, such as Dr. CHURCHILL-DAVIDSON's nerve stimulator, recognition of the need for antagonists may be difficult in unconscious patients.

Occasionally, patients who have received neuromuscular blocking agents may seem to breathe adequately at the end of anesthesia. Subsequently, however, because of this rapid fatigue of the partially curarized muscle (which Dr. CHURCHILL-DAVIDSON has shown us in his film), a phenomenon often referred to as "recurarization" can occur. This term is a misnomer since the gradually developing respiratory insufficiency after discontinuance of anesthesia is caused not by mobilization of relaxants from sites of inactive storage but by fatigue of the still partially curarized muscle. The reason for the initially adequate tidal volume is that during anesthesia the patient's respiration is assisted or controlled, and therefore his respiratory muscles are well rested. As he starts to breathe spontaneously, the partially curarized muscles become tired and the tidal volume becomes less and less. The patient tries to compensate for the decreasing tidal volume with an increased respiratory rate. This leads to a vicious circle and soon the patient may become completely apneic. Because of this danger, in any doubtful case, the degree of curarization should be determined with a nerve stimulator before deciding whether or not an antagonist is indicated.

Now we are going to turn to a slightly different topic. I would like to ask Dr. MAYRHOFER to tell us something about the advantages and disadvantages of the combined use of more than one relaxant on the same patient.

8. MAYRHOFER:

Ladies and Gentlemen, I am well aware of the fact that the mixing of depolarizing and non-depolarizing agents is frowned upon by our chairman and some members of our panel. Of course, I also do *not* advocate the indiscriminate use of combinations of relaxants. And I am in general agreement with Dr. FOLDES who in his book on muscle relaxants points out that an agent of one type should only be given after the effect of the agent of another type has worn off. However, there are, as I believe, a few indications in which a combination of different relaxants may be useful to some extent and reasonable to use.

When we first introduced succinylcholine chloride in Austria in 1951, we were so pleased with its short-lasting effect that we only used it for short procedures and for intubation and also for the closure of an abdominal wound. And we did not bother to use the long-lasting relaxants in between. And in fact, with this routine which we followed in the early fifties, we never saw anything wrong with mixing succinylcholine and curare, and we never encountered any difficulties clinically, except in one case towards the end of an operation for which d-tubocurarine was used as the main relaxant, when the anesthetist had started de-curarization with neostigmine; it was found all of a sudden that a swab had been forgotten in the belly and we had to reopen it. The girl giving the anaesthetic used succinylcholine to facilitate opening and reclosure of the abdominal wound. She had then to sit with the patient for 3 hours. At that time the potentiating effect of

acetylcholinesterase to depolarizing relaxants was well established. She just had not thought about it and thus she had to learn it the hard way.

As early as 1953, I observed that we hardly ever saw pains in our major abdominal and thoracic cases but that patients who had minor procedures, particularly bronchoscopies and such, complained bitterly of muscle pains the next day, lasting for one or two days. And I also remember that at that time, when having a medium dose of succinylcholine given to myself in a conscious state I experienced a rather severe short-lasting pain when the muscle fasciculation came upon following i.v. injection. You remember that CHURCHILL-DAVIDSON observed in 1954 lower incidents of muscle pains in patients who were lying in bed, as compared to the ambulatory patients, and also reported his attempts to use neostigmine as a prophylactic antidote. Already yesterday I briefly mentioned the studies which were also, just at that time, conducted at the Pharmacological Institute of Vienna, by KRAUPP, KLUPP and others, injecting relaxants into isolatedly perfused hind legs of dogs and cats. To me, the most striking finding of these experiments was the potassium release following intra-arterial injection of succinylcholine and other depolarizing relaxants, whereas following d-tubocurarine, there was not only no potassium release but also the succinylcholine potassium release was completely blocked by the pre-injection of d-tubocurarine. So we decided at that stage to conduct comparative clinical studies in our bronchoscopy patients. We studied three series of a hundred patients each. The first series served as controls, the second series received 0.5–1 mg of neostigmine half an hour after bronchoscopy intramuscularly as suggested by CHURCHILL-DAVIDSON, and the third series received—according to the size of the patient and his build—between 3 and 4 mg of d-tubocurarine about 2 min before the first dose of succinylcholine. d-tubocurarine prophylaxis was effective in reducing the degree of muscle pain to 0 or just slight muscle stiffness. In only one instance the patient complained about severe muscle ache but that was—as we later found out—a case in which the succinylcholine was given immediately after d-tubocurarine. We are now using Alloferine instead of this (1.5 mg), practically as a routine, in our bronchoscopy and bronchography cases. In a recent publication in Acta anaesthesiologica Scandinavica a report was given on similar studies with tubocurarine confirming this work of ours.

Now, because of the antagonistic effect which PATTON and ZAIMIS already established in 1949 for decamethonium and curare and which THESLEFF described for succinylcholine and curare in 1952, one needs about 30–50% more succinylcholine after this pre-injection of d-tubocurarine. But otherwise we have not seen anything untoward by using this sequence as a routine. On the contrary, we detected one case of latent myasthenia by pre-injecting this small curare dose which would otherwise probably have remained undetected and untreated. Personally, I am absolutely convinced that the blockade of potassium release from the muscle fibres is the key to the prevention of muscle pain. It just cannot be physiological to have

potassium deprived muscle cells and then an abnormally high extra-cellular level of the same ion. Some similarity and even confirmation I can see in the report of DOWDY and FABIAN, in 1963, on ventricular arrhythmias induced by succinylcholine in digitalized patients. In "Current Researches" they reported that they saw it in 17 patients and also did some studies on experimental animals. They pointed out that the intravenous succinylcholine can produce serious ventricular arrhythmias in a fully digitalized patient as well as in fully digitalized dogs and that these arrhythmias can be abolished by d-tubocurarine. They point out the similarity of the myocardial transmembranous influx of potassium, produced by digitalis, acetylcholine—and probably also by succinylcholine—which can be inhibited by d-tubocurarine.

Now, on the other hand, hardly anybody objects to using succinylcholine first for intubation and then turning to a non-depolarizing agent after the effect of the initial succinylcholine has worn off. But this is one thing I should like to stress particularly. I noticed this morning in one of the papers—I think it was Dr. TSCHIRREN's paper—when he mentioned that he was hyperventilating the patients after intubation under succinylcholine and went on to curarize them with Alloferine, keeping them on hyperventilation. I should like to draw your attention to a case being reported not long ago in the New York Journal of Medicine, of a 47-year-old man who had received a 100 mg dose of succinylcholine for intubation and a total of 42 mg of d-tubocurarine during a 5½ hours abdominal operation. In spite of several attempts at de-curarization with neostigmine, he failed to regain sufficient respiratory exchange for about 10 hours. The following day it was found that he had an unduly low dibucaine number indicating an abnormality in the plasma cholinesterase level. It then turned out that the anaesthetist had not waited for the effect of the intubation dose of succinylcholine to wear off.

Now, Dr. TSCHIRREN mentioned that they did 18,000 such cases, and Prof. FOLDES mentioned earlier this morning that abnormalities of the plasma cholinesterase would occur in about one of 2000–3000 cases. So it would seem to me that Dr. TSCHIRREN should have run across 6–10 such cases. I am therefore wondering whether he had made any such observations.

In conclusion, I should like to state that the combination of relaxants of different mode of action can be dangerous if one is not aware of their difference in action. Combination. however, is never useless, on the contrary, it can be very useful not only to detect abnormal plasmacholinesterase and also an occasional myasthenic patient, but mainly to prevent, as I pointed out, the annoying and rather unpleasant muscle pain following succinylcholine, even after very small and short procedures.

9. FOLDES:

I ask Dr. TSCHIRREN for his comment.

10. Tschirren:

Das Phänomen der prolongierten Apnoe nach Succinylcholin wegen atypischer Pseudocholinesterase ist uns natürlich gut bekannt, und wir sind auch auf mehrere derartige Fälle gestoßen, ungefähr entsprechend der von Prof. Mayrhofer angegebenen statistischen Verteilung. Diese Patienten sind aber in den 68 Fällen von verlängerter Alloferin-Wirkung nicht enthalten, genauso wenig wie die Fälle mit Pseudocholinesterasemangel bei Leberschäden, Verbrennungen usw. Hier wie dort war ja die Ursache der Apnoe zu ermitteln, bei den 68 Fällen mit prolongiertem Alloferin-Effekt dagegen nicht.

Meines Erachtens ist es nicht nötig, wegen der möglicherweise vorhandenen Pseudocholinesterasestörungen von der beschriebenen Routine abzugehen und vorerst mit Probedosen von d-Tubocurarin oder Alloferin zu operieren. Wenn eine Pseudocholinesterasestörung vorliegt, so wird die Apnoe durch das Succinylcholin bewirkt, und es ist dann ziemlich gleichgültig, ob noch eine zusätzliche Relaxation durch ein depolarisationshemmendes Agens dazu kommt oder nicht. Theoretisch wäre es natürlich wünschenswert, von allen Patienten einen Enzymstatus zu haben, aber dieser ist recht umständlich zu erhalten, so daß es einfacher ist, das Risiko einer prolongierten Apnoe einmal auf 3000–5000 Patienten auf sich zu nehmen, um so mehr als der Effekt ja *nie* irreversibel bleibt.

11. Foldes:

I would like to clarify something. According to Kalow, the incidence of atypical homozygotes of plasmacholinesterase are encountered in about 1 of 2300 patients. But there are heterozygotes who have one typical and one atypical gene. The incidence of this anomality is about 1:200. Heterozygotes may also have prolonged apnea of lesser duration.

Now I would like to comment on what Dr. Mayrhofer said about my views on the combined use of relaxants. I feel that there are indications for it, but I don't think that I would subscribe to all his indications. In our experience with many thousand cases, if one injects a small dose (0.6 mg/kg) of succinylcholine slowly, in 30 sec, taking about 15 sec to inject one third of the dose, and the second two thirds in the following 15 sec, then the incidence of muscle pain in hospitalized patients is negligible. With outpatients, however, the situation is different, and muscle pain after succinylcholine is encountered with considerable frequency in this group. I think it is alright to intubate with succinylcholine and to maintain relaxation subsequently with a non-depolarizing relaxant. I believe it is also permissible to start out with a continuous intravenous infusion of succinylcholine, and if tachyphylaxis, manifested by a need for progressively increased infusion rates, develops to stop the succinylcholine and to continue with small doses of a non-depolarizing relaxant. It is pharmacologically unsound and therefore not justified to use succinylcholine for peritoneal closure in patients

who received non-depolarizing relaxants for the maintenance of relaxation during surgery. Under these circumstances, as much as 300 mg succinylcholine may be needed to overcome the residual non-depolarization block and then to produce adequate relaxation for peritoneal closure. Because of the large doses of succinylcholine required, this sequence of administration of non-depolarizing and depolarizing relaxants is potentially dangerous and may lead to prolonged apnea or even "irreversible curarization".

Now, Dr. CRUL wants to show on a slide the characteristics of the block obtained when succinylcholine is administered after Alloferin.

12. CRUL:

After having got some experience with a nerve-stimulator (Block-Aid monitor, Burroughs Welcome) somewhat like the method Dr. CHURCHILL-DAVIDSON described, we tried to find out what type of block would occur with a small dose of succinylcholine following an anesthesia done under Alloferin. It turned out, now in over 50 cases already, that even though the Alloferin effect had almost completely worn off, the first small dose of succinylcholine caused a non-depolarization block with fading tetanus and post-tetanic facilitation. So there was immediately a phase II block. This may contribute to the prolonged action of succinylcholine sometimes seen when it is used for the closure of the abdomen at the end of an operation done under non-depolarizing curariform drugs.

13. FOLDES:

Tank you Dr. CRUL. Next I would like to ask Dr. VOURC'H to show us briefly his method of preventing disturbing movements during electroencephalography in comatose patients.

14. VOURC'H and ARFEL: **Electroencephalography under suxamethonium, its use on comatose patients**

There is no need to stress the interest of electroencephalogram (EEG) on comatose patients. Whether the coma is of anoxic, neurologic, toxic, or metabolic origin, the comparison between clinical datas and the EEG enables to assess the effect of treatment, and may help to establish a prognosis. The acute problem of organ transplantation requires extreme precautions to determine the state of irreversible coma.

EEG recording of comatose patients meets with some difficulties, due to muscular artefacts (convulsions, ocular movements, etc.) which may blur the tracing to the point of making it unreadable.

For the past few years, we have used suxamethonium to abolish the patient's muscular activity and to clear the EEG from these artefacts.

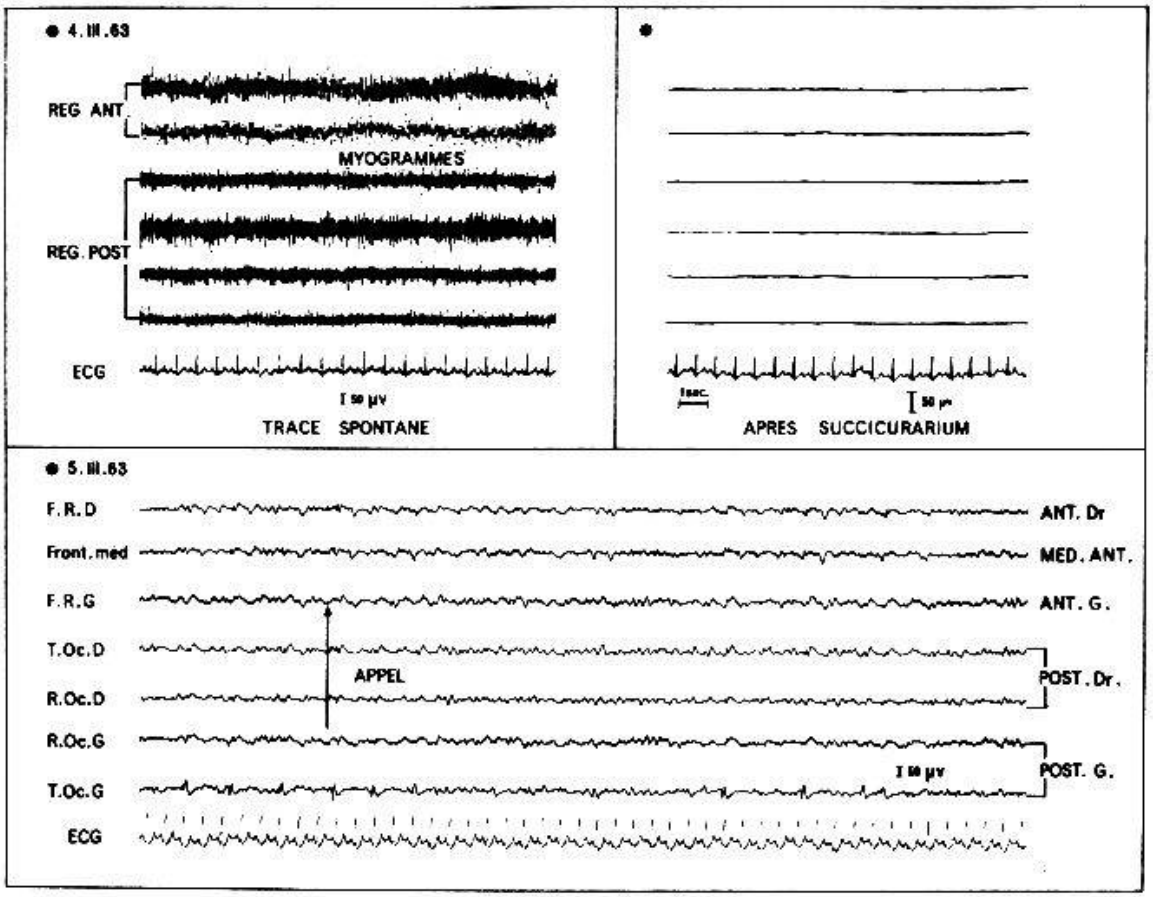


Fig. 1. F. M., 64 years old. Anoxic encephalopathy.—Disturbance of cerebral rhythm: by myogram.—Derivations (4th March 1963) on each specimen (from top to bottom): Anterior regions: right fronto-rolandic; left fronto-rolandic. Posterior regions: right temporo-occipital; right rolando-occipital; left rolando-occipital; left temporo-occipital.—ECG: DI.—*Interpretation:* Spontaneous recording on 4th March 1963 is flooded with very active myogram. After injection of suxamethonium, cerebral activity is nearly nil. However, on 5th March, EEG shows a recovery of varied activity, in which some spike-waves can be seen in left temporo-occipital derivation.

Suxamethonium has no action on the central nervous system; it is short-acting, has little action on the circulation in most cases and does not interfere with the patient's condition as long as respiration is controlled. This requirement is usually easily dealt with: most patients have a tracheostomy and are already ventilated; if not, they should be intubated, since a mask would interfere with the electrodes and correct EEG recording.

Our technique is simple: once the electrodes have been inserted, an intravenous dose of 0.5-1 mg/kg of suxamethonium is administered; this dose can be repeated if required. Since patients are in coma, there is no need for any anaesthetic drug, which would alter the EEG.

We present five cases which show the results thus achieved.

Obs. 1. Mr. F., 64-year-old patient, was admitted on 16th January 1963 in the Neurosurgical Department for a cordotomy (intractable post zosterian pain). The operation was performed without any complication, but was unsuccessful.

Operated again on 4th March 1963. At the end of the procedure, respiratory and circulatory arrest, cyanosis, bilateral pupillary dilatation, due either to air embolism or to circulatory failure in a hypertensive patient, who had already suffered from angina pectoris and two episodes of cerebral ischaemia.

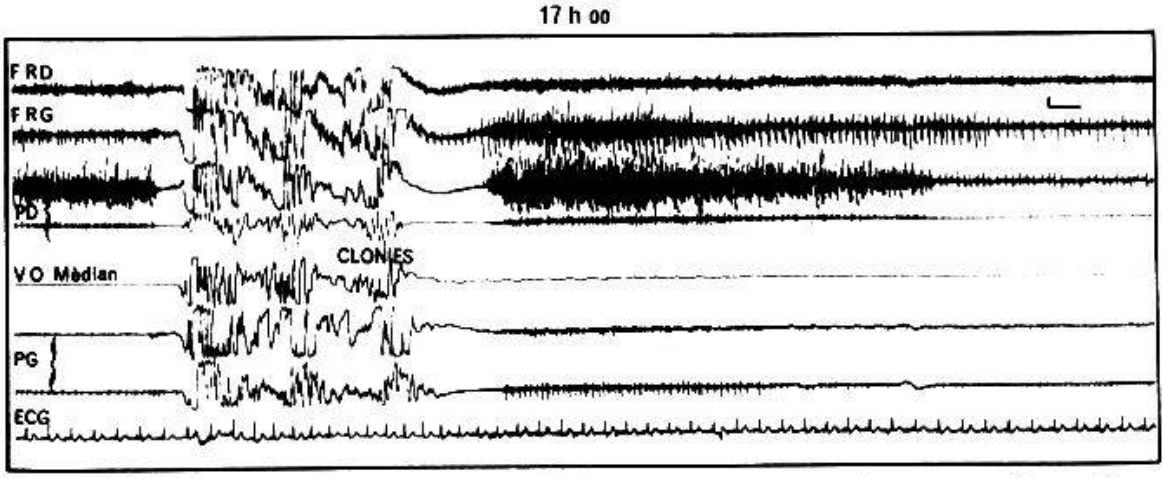
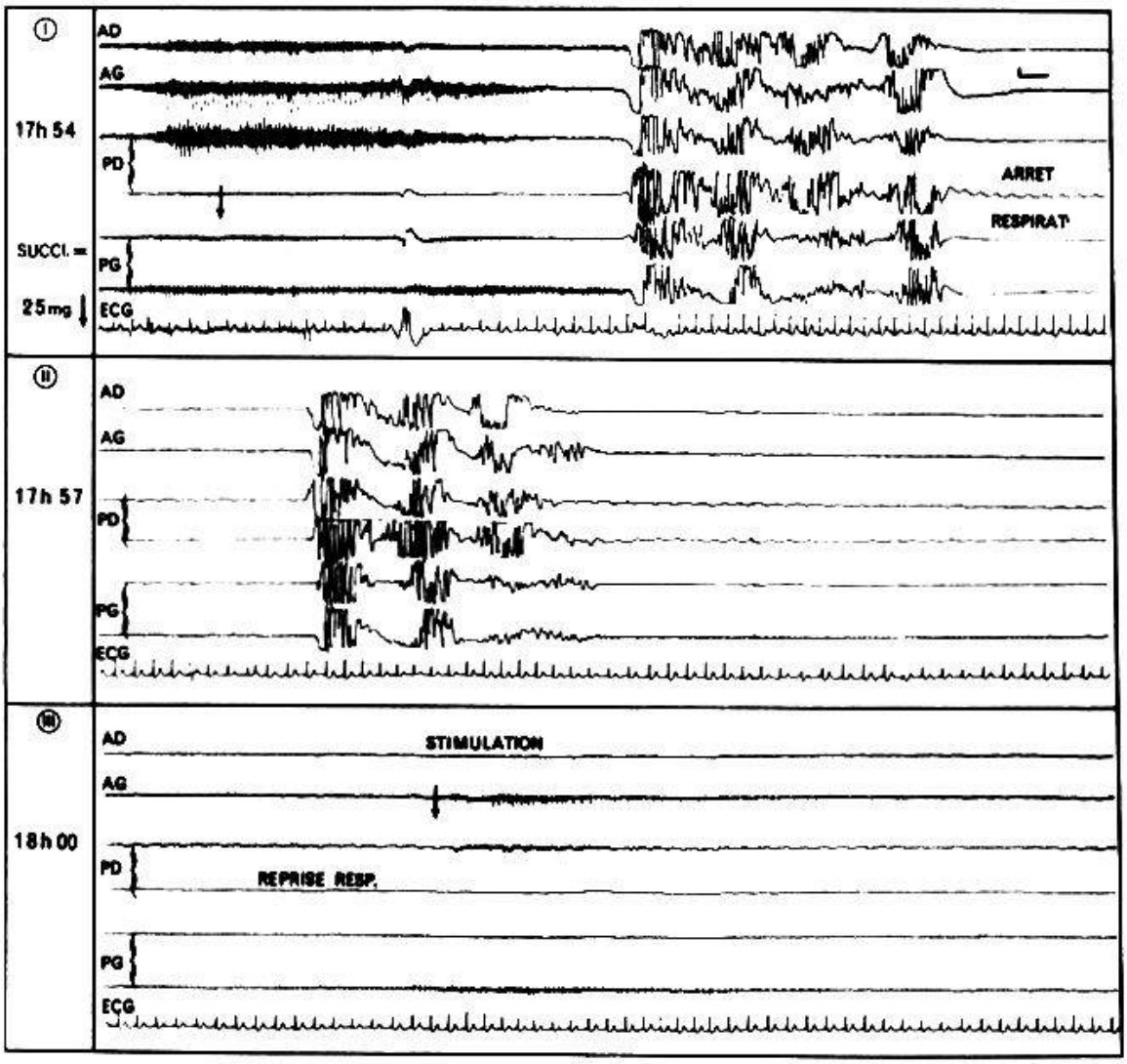


Fig. 2. N. O., 61 years old. Anoxic encephalopathy.—Problem of assessing the authenticity of paroxistic bursts.

a) *17.00 hour.* Tracings (27th September 1965): FRD: right fronto-rolandic. FRG left fronto-rolandic. PD: 3rd and 4th lines: right temporo-occipital; right rolando-occipital. VO median: vertex-occiput, mid-line. PG: 6th and 7th lines: left rolando-occipital; left temporo-occipital.—ECG: DI.—*Interpretation:* On a very flat background appear periodically paroxystic bursts of high amplitude, synchroneous with myoclonies; these are of palpebral and peri-oral origin, irradiating towards the chin. An intense myogram, particularly on the temporo-frontal areas, precedes and follows them.



b) Same tracings: *At 17.54:* injection of 25 mg of suxamethonium (arrow). About 20 sec later, long paroxystic burst, but without myoclonies. Respiratory arrest. *At 17.57:* on a very flat background appear again paroxystic figures without any simultaneous clinical manifestation. *At 18.00* (6 min after injection): respiration comes back; nociceptive stimuli induce again a response, with myogram.

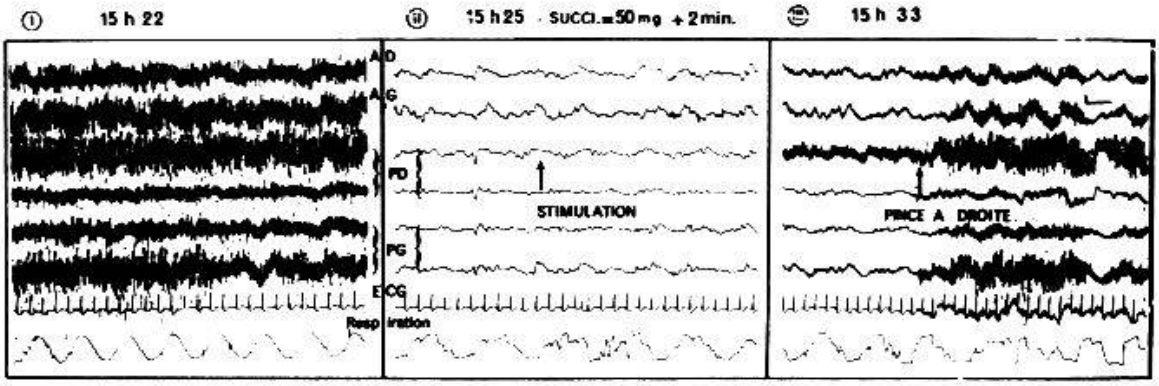


Fig. 3. D. G., 79 years old. Pulmonary embolism.—Disturbance of cerebral rhythm by intense myogram.—Tracings (22nd April 1965): 1st line (AD): right fronto-rolandic. 2nd line (AG): left fronto-rolandic. 3rd and 4th lines (PD): right temporo-occipital; right rolando-occipital. 5th and 6th lines (PG): left rolando-occipital; left temporo-occipital.—7th line: ECG = DI. 8th line: respiration.— *Interpretation: At 15.22:* tracing is full of myograms which blur completely cerebral rhythm. *At 15.25,* 2 min after injection of 50 mg of suxamethonium: myograms have completely vanished, showing a slowed and non-reactive cerebral rhythm. *At 15.33,* 10 min after the injection: myograms reappear, induced mainly by nociceptive stimuli.

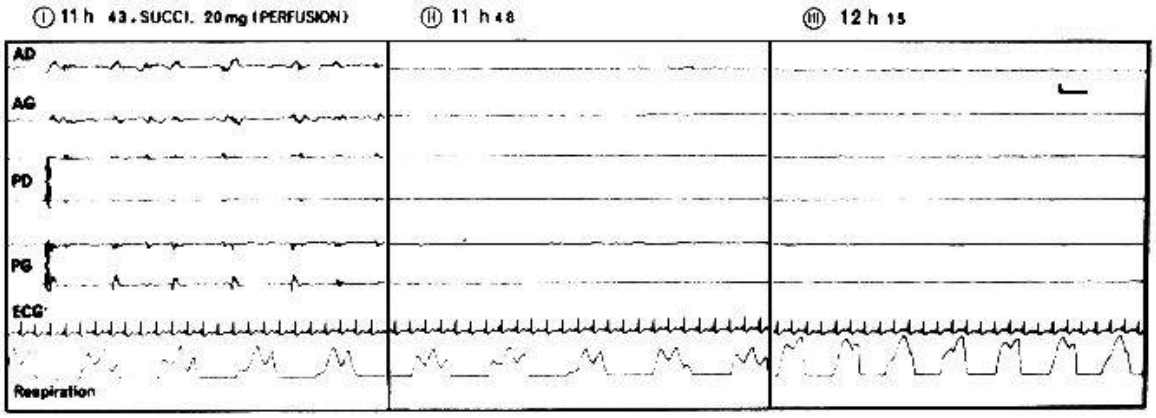


Fig. 4. P. F., 53 years old. Hepatic coma.—Problem of ocular muscle fasciculations inducing artefacts which make accurate appreciation of cerebral rhythm difficult.—Tracings (19th April 1966): same as Fig. 3.—*Interpretation: At 11.43:* small discharges, more or less periodical, synchroneous with orbicular fasciculations. 20 mg of suxamethonium are administered in an intravenous infusion. *At 11.48:* the fasciculations have stopped; artefacts have disappeared, revealing a nearly complete disappearance of cerebral rhythm. This is still seen *at 12.15* and has been irreversible. Note that injection of 20 mg of suxamethonium in this cirrhotic patient has been followed by prolonged action.

The patient was put in recumbent position, ventilated with oxygen; an ECG showed ventricular tachycardia, reverted to normal rhythm with procaïne amide. Spontaneous respiration was restored, and the patient was opening his eyes. He was sent to the Intensive Care Unit, still intubated, and found to be in stage II coma with bilateral pupillary dilatation, and sluggish corneal and tendinous reflexes. Blood pressure was low (70 mm Hg) and was adjusted with a vasopressor to preoperative level.

An EEG (Fig. 1) was distorted by myogram; after suxamethonium, it was found to be nearly flat.

The following day, it had improved and the patient was in better physical condition. He was discharged on 28th March; his EEG was similar to the preoperative one.

Obs. 2. Mrs. N., 61-year-old patient, was admitted into the Intensive Care Unit on 27th November 1965 from another hospital after a cardiac arrest. She had been operated some time before for carcinoma of the cervix; a recurrent growth had involved the bladder. The accident occurred at the end of a cystoscopy and coagulation for bleeding.

The patient, who was intubated, was tracheostomized; respiration was spontaneous. Muscular contractions and clonic movements made the EEG tracings difficult to read (Fig. 2a), in particular it was impossible to determine the nature of large bursts of sharp waves, synchronous with clonic movements of the eye-lids and oral muscles; myogram was extensive. 25 mg of suxamethonium were injected, and these artefacts eliminated (Fig. 2b).

This stage III coma progressed to stage IV and the patient died on 30th November.

Obs. 3. Mrs. D., 79-year-old patient, was admitted on 6th April 1966 for fracture of the tibia. She was found to have a raised temperature and was put on antibiotics. Though her fever did not recede, she was operated in the morning of 14th April, under Esmarch band, general anaesthesia and intubation. At the end of the procedure, respiratory and circulatory arrest occurred, treated by ventilation and external massage. ECG showed signs of acute cor pulmonale; an angiography confirmed a massive pulmonary embolism. Embolectomy was considered, but turned down in view of the patient's age and condition; inferior vena cava was ligated.

The patient was taken to the Intensive Care Unit; her condition had improved (stage II coma, with spontaneous respiration, coordinated responses, corneal reflexes present, with corneal mandibular reflex); a tracheostomy was performed (Fig. 3).

On 16th April, she was conscious, could answer orders but was anuric and put under peritoneal dialysis. Gastrointestinal bleeding appeared on 20th. She died on 23rd April.

Obs. 4. Mrs. P., 53-year-old patient with known advanced liver cirrhosis, was operated on 15th April 1966 for wound disruption. She had been operated some years before (hysterectomy, wound disruption) without complications.

After the procedure, she fell into hepatic coma: stage II, then III, with pupillary dilatation, hypertony, followed by flaccidity, gastro-intestinal bleeding, oliguria. An EEG taken on 19th April (Fig. 4) was distorted by palpebral fasciculations and respira-

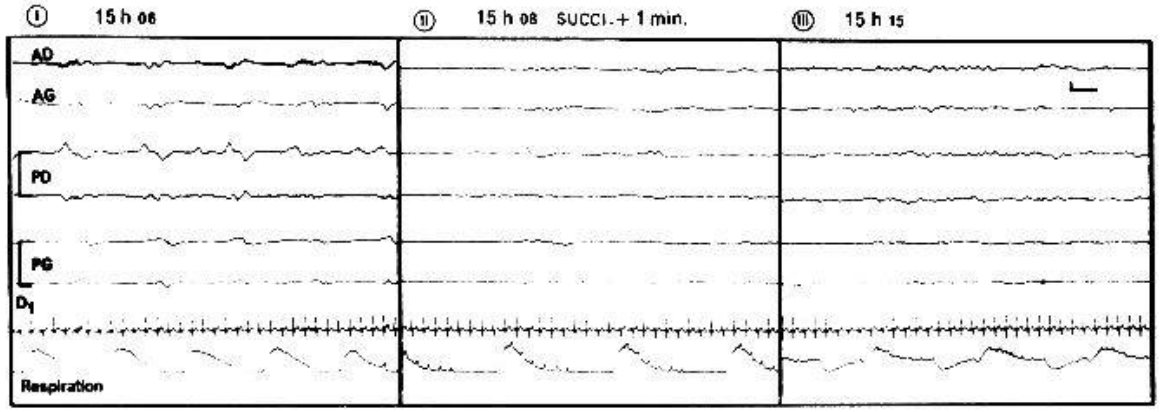
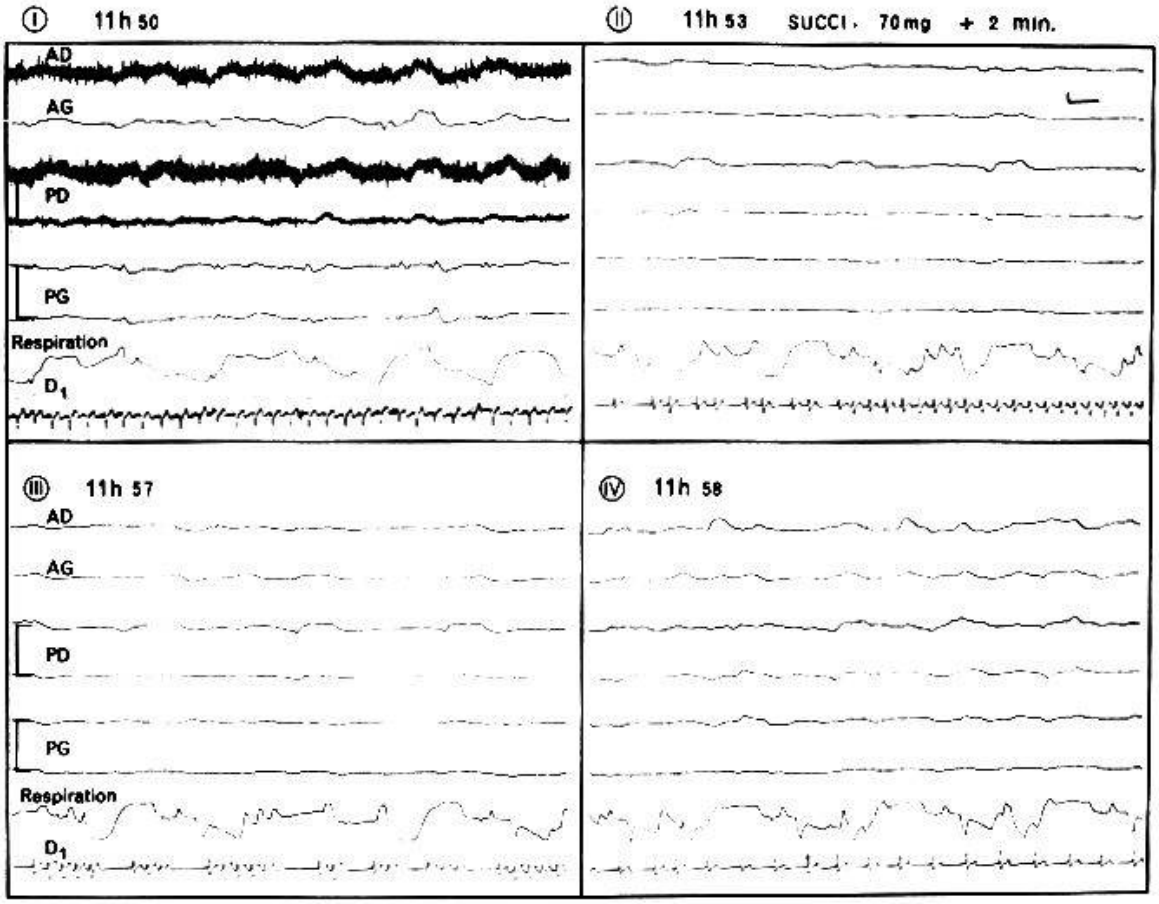


Fig. 5. D. H., 23 years old. Neurological coma (glioma of the brain stem). Problem of authenticity of periodic slow waves.

a) 18th April 1966.—Tracings: on this and the following figures, same as in Fig. 4.—*Interpretation: At 15.06:* EEG shows slow waves (which had appeared 48 hours earlier) and are marked with some periodicity, linked apparently to respiratory movements. Gasps and head movements occur with each inspiration. *At 15.08*, 1 minute after injection of 50 mg of suxamethonium: respiratory arrest. The tracing then becomes much less active; it consists only of intermittent bursts of theta and delta waves, occurring mainly on the right side. *At 15.15:* the cerebral rhythm becomes slightly more active; theta waves appear on the right hemisphere but without any periodicity. No modifications of the ECG.



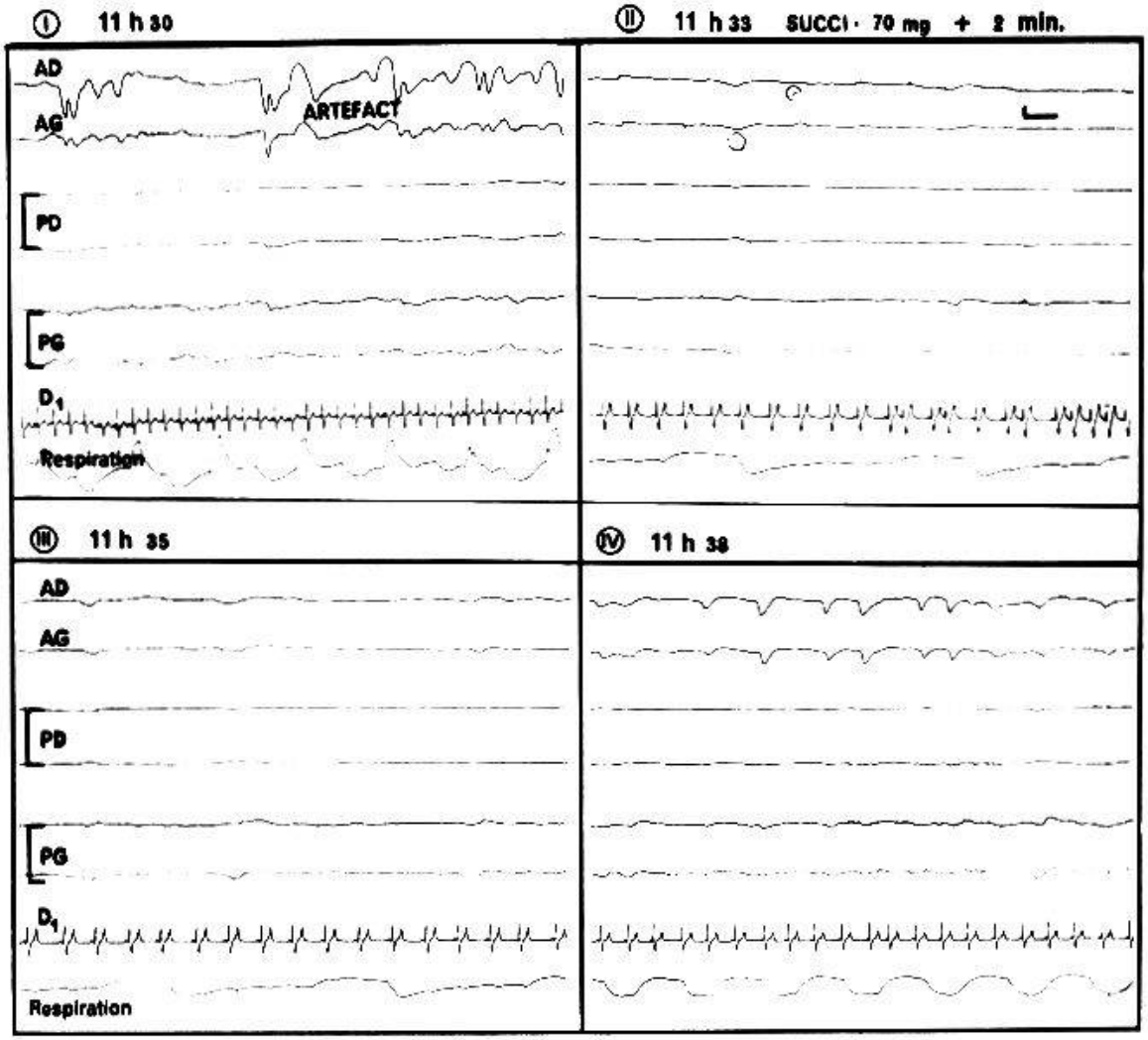
b) 20th April 1966: *Problem of assessing cerebral rhythm under numerous artefacts.*—Tracings: same as in Fig. 5 a.—*Interpretation: At 11.50:* marked myogram and various mechanical artefacts. *At 11.53*, 2 min after injection of 70 mg of suxamethonium: the tracing is cleared of artefacts and shows a very poor, much deteriorated activity with intermittent increase of slow figures on the right. Beginning of ECG modifications. *At 11.57:* same aspect, but poorer; heart rate shows some 1- or 2-seconds pauses. *At 11.58:* obvious improvement of cerebral activities, though they are still extremely slow and completely non-reactive. This improvement coïncides with the regularization of the heart rate. ECG shows vagal stimulation (acetylcholine-like action of suxamethonium).

tory movements. An infusion of minimal doses of suxamethonium (20 mg) abolished these artefacts but had a prolonged action on the patient in terminal liver failure.

Obs. 5. M. D., 23-year-old patient, was admitted in March 1965 for headache, vomiting, right hemiparesis. Pre-operative EEG was consistant with posterior fossa tumor, with bilateral cerebellum involvement.

Operation (1st April 1966) showed a glioma of the brain stem. Next day, the patient was conscious, but with Cheyne-Stokes rhythm and swallowing difficulties; a tracheostomy was performed. On 4th April, gastric hemorrhage, fever; consciousness was normal. On 6th April, cardiac and respiratory arrest, treated by ventilation and external massage. The patient was put under respirator. From then on, until his death (28th April 1966, due to intratracheal haemorrhage), the patient was in coma (stage II–III) with spasticity, corneal mandibular reflex, status epilepticus, spontaneous respiration.

Many EEGs under suxamethonium have been recorded (Fig. 5a–c). On the last two, ECG showed marked cardiac disturbances, consistant with vagal stimulation due to the acetylcholine-like activity of suxamethonium (atrio-ventricular block, cardiac slowing) –the only instance in which such disturbance was found. The problem here



c) 25th April 1966. —Tracings: same as in Fig. 5 a.—*Interpretation: At 11.30:* patient has continuous palpebral winking, recorded as artefacts on anterior regions (AD and AG). *At 11.33*, 2 min after injection of 70 mg of suxamethonium: the palpebral artefact disappears; the cerebral rhythm is markedly depressed, with only an occasional slow wave. Same pattern *at 11.36*. *At 11.38:* the action of suxamethonium wears off: palpebral movement is again recorded on two upper lines. ECG alterations comparable to those of previous tracing. —On these three recordings, respiration was spontaneous before injection and was controlled manually or through a respirator during the muscular paralysis.

was to eliminate the muscular artefacts induced by respiratory movements and muscular artefacts.

Summary.—We have used suxamethonium to induce muscular paralysis of short duration in order to provide adequate recording conditions for EEG of comatose patients. These tracings are often perturbed by myograms or muscular activity, which make their interpretation difficult. Suxamethonium deletes these artefacts and makes the lecture possible. This technique is innocuous as long as respiration is controlled during the period of muscular paralysis. Special attention should be paid to possible disturbances of cardiac activity, due to the acetylcholine-like action of suxamethonium.

15. FOLDES:

Thank you very much. There are two gentlemen in the audience whom we have invited to make comments. One of them is Prof. ECKMANN who is the Chief of the Tetanus Treatment Centre in Berne who will comment on the use of muscle relaxants in the treatment of tetanus.

16. ECKMANN:

I would like to draw your attention to the fact that the number of tetanus casualties in the world is about 200,000 per year, according to WHO.

Another comment I would like to make: From the purely medical point of view, there is no reason to treat severe tetanus with other means than with continuous muscle relaxation. The only reason not to do this in severe cases is the incredible amount of nursing which is needed for these patients and which is not always available, especially in countries with high tetanus incidence. Until very recently, there was not much choice left between the treatment with continuous muscle relaxation and other treatment. The use of high doses of Valium, however, now seems to offer the possibility to treat some of those patients with much less nursing care.

17. FOLDES:

Thank you. I think that Dr. DOENICKE would like to make a brief comment on the use of a drug combination for endotracheal intubation with Alloferin.

18. DOENICKE:

Es ist zwar einiges zu der Frage gesagt worden, ob die Succinylwirkung bei der Intubation abzuwarten sei. Doch, wie wir heute gehört haben, tun dies viele Kollegen nicht. Herr TSCHIRREN hat darauf hingewiesen, daß meist sofort nach der Intubation die Relaxation mit Curare fortgesetzt wird. Da können natürlich Komplikationen auftreten. Wir wissen, daß nach Succinylcholin auch Herzrhythmusstörungen vorkommen. Vor allem ist die Gefahr einer verlängerten Apnoe beim Vorliegen einer atypischen Cholinesterase zu berücksichtigen. AHNEFELD und FREY haben empfohlen, auch mit Alloferin zu intubieren. Diese Methode wurde von uns vor einigen Tagen geprüft, und wir erlebten ziemliche Schwierigkeiten. Wir haben nun eine Kombination versucht, dergestalt, daß wir zuerst Alloferin geben, dann 1-2 min später Epontol. Epontol hat eine Hyperventilationsphase und eine kurze apnoische Phase, in der wir intubieren. Wir haben dabei folgenden Vorteil: Das Succinylcholin wird ausgeschaltet, und wir haben es so nur mit einem Relaxans zu tun. Am Ende der Operation kann man sofort mit Neostigmin antagonisieren. Damit werden überflüssig: die relaxometrische Prüfung und auch die prophylaktische Aktivitätsbestimmung der Cholinesterase. Wir bestimmen allerdings vor jeder Intubation die Cholinesteraseaktivität und die Dibucainzahl. Ich glaube, daß die angegebene Kombinationsmethode in

Ausnahmefällen, z. B. bei Risikopatienten, dann einen Vorteil bietet, wenn eine Bestimmung der Cholinesteraseaktivität einschließlich der atypischen Esterase nicht möglich ist.

19. FOLDES:

Thank you very much. I would like to ask the remaining three members of the panel if they would like to make a comment at this time. If not, then I shall open the floor for questions and comments. Dr. STOVNER, do you want to make any comment at this time?

20. STOVNER:

I agree with Dr. ECKMANN regarding the use of Valium in the treatment of tetanus. In Norway, we have very severe cases of tetanus. I have treated two of them with Valium with very good results.

21. FOLDES:

Prof. HUGIN, would you care to make any comment? No. Prof. WASER? Nothing at this time. Then I would like to ask the audience if anybody would like to ask any questions or make any comments. Please state your name and to whom the question is addressed.

22. GOZON:

May I ask Professor FOLDES a question? You mention administering relaxants to myasthenic patients. This problem has been discussed frequently in the course of the past ten years, if I remember correctly, also in Vienna in 1962. In my opinion abdominal surgery can be easily performed in myasthenia gravis without the use of relaxants. Surely adequate relaxation can be achieved by using either ether or cyclopropane, although of course in these rare instances the surgeon would have to do without diathermia. I should be interested to hear Professor FOLDES' opinion on this problem.

Anfrage an Dr. TSCHIRREN: Waren bei den erwähnten 68 Fällen, welche nach Alloferinverabreichung eine postoperative Ateminsuffizienz zeigten, keine pH- oder Elektrolytverschiebungen vorhanden?

23. FOLDES:

With regard to myasthenia: if the abdominal muscles are involved in the myasthenic process, then naturally no muscle relaxants are required for intraperitoneal surgery. If, however, myasthenic involvement is limited to the ocular muscles, to the extremities, or to the bulbar area, then muscular relaxation must be provided for intraperitoneal surgery. My first choice in

these cases is regional anesthesia with adequate sedation. If regional anesthesia is not applicable, I prefer light general anesthesia combined with small doses of muscle relaxants to deep anesthesia with agents like ether, halothane or methoxyflurene. I would like to emphasize, however, the extreme care that must be taken with the use of muscle relaxants in myasthenic patients. Each patient must be carefully titrated for his relaxant needs. Depending on the severity of the disease, one should start out with 0.5 to 2.0 mg d-tubocurarine or the corresponding dose of Alloferine or gallamine. After observing the effects of the first dose 5 min later, small (0.5 mg) increments can be administered about 3 min apart until the desired effect is obtained. When this procedure is followed, the residual neuromuscular block can be reversed at the end of anesthesia by anticholinesterase just as in non-myasthenic subjects.

Perhaps Dr. MAYRHOFER has some comment to make?

24. MAYRHOFER:

I remember one case we did at home for a cesarean section in a myasthenic lady and the collegue who gave her the anesthetic just followed what Dr. GOZON suggested, to simply leave out all the anticholinesterases for a few hours, induce anesthesia with a small dose of thiopental, maintain the patient on nitrous oxide-oxygen and then afterwards, go back to the anticholinesterase treatment.

The last few cases of thymectomy, we have done five or six within the last year, were also done without any relaxant. But, of course, in abdominal operations (as Dr. FOLDES pointed out) the severeness of the disease makes some difference. If you are faced with a mildly myasthenic patient, you may have to use something stronger; you wouldn't get away for an abdominal procedure by just leaving out the anticholinesterase.

25. FOLDES:

I think Dr. CHURCHILL-DAVIDSON would like to comment.

26. CHURCHILL-DAVIDSON:

I would support Dr. GOZON in this very strongly; I have myself anaesthetized some 18 myasthenics for various operations like partial gastrectomy, cholecystectomy, etc., and I think, at my hospital in London, we have anaesthetized about 30 cases for thymectomy. In none of these cases have I been forced into having to use a muscle relaxant. I take the view that if I know that pathological changes are present at a certain specific site, I avoid the use of a drug which acts at that site. The only time I have been compelled to use muscle relaxants in my practice has been for diagnostic purposes. However, on one occasion I have used succinylcholine when the patient was 'in extremis' and needed rapid intubation to improve the airway.

In principle, I keep well away from the muscle relaxants whilst anaesthetizing myasthenic patients. There are many ways of giving an anaesthetic and this is surely one of the times when the anaesthetist can use some of the variety of techniques he has learnt. I would support the idea of using regional anaesthesia whenever necessary. If general anaesthesia is required then halothane will be found to be particularly useful in the management of anaesthesia for the myasthenic patient.

27. FOLDES:

I think the views expressed by Drs. MAYRHOFER and CHURCHILL-DAVIDSON are sound, but I would like to assure you that non-depolarizing relaxants can be used in myasthenic patients with the described technique quite safely. If one can obtain good relaxation in a myasthenic subject in light planes of general anesthesia so much the better. If, however, this is not the case, it is by far preferable to use a small dose of a non-depolarizing relaxant than to use deep planes of general anesthesia, or to watch the surgeon struggle in an inadequately relaxed abdomen.

28. TSCHIRREN:

Ich möchte hier wiederholen, was ich schon im Referat gesagt habe: Bei allen 68 Patienten waren keine anderen Ursachen zu finden, weder pulmonale noch stoffwechselbedingte noch cerebrale. Diese waren alle sorgfältig ausgeschlossen worden. Es handelte sich also ausnahmslos um Patienten, die eine normale Dosierung von Alloferin erhalten hatten, keine sonstigen Besonderheiten aufwiesen und doch eine prolongierte Apnoe zeigten. Deshalb haben wir auch keine Erklärung dafür und müssen uns mit der bloßen Feststellung beniigen.

29. FOLDES:

Thank you very much. I think that Prof. ZAIMIS would like to make some comments.

30. ZAIMIS:

Dr. FOLDES this morning emphasized that careful pharmacology for the correct use of muscle relaxants is important. I could not agree more with him. However, what he said about the pharmacology of neuromuscular drugs sounded to me to be in complete disagreement with pharmacologists who work with neuromuscular blocking agents in living animals. What really amazes me is that he has chosen to portray the pharmacology of these drugs only in isolated preparations. I refer especially to Prof. TAYLOR's

experiments which are very interesting in relation to an isolated muscle kept in a bathing solution for 18 hours. Such a muscle may show all sorts of interesting changes, but this has nothing to do with a skeletal muscle in vivo which has normal circulation. We have shown again and again that if you take a muscle, isolate it from the body and immerse it in a so-called "physiological solution", that this solution is not physiological for the muscle. The muscle starts changing in its responses to the various neuromuscular blocking drugs 20 min after its immersion in such a solution. Now, what will happen in 18 hours? I even refuse to think about it. The phase II block of Dr. TAYLOR's you will never see in vivo. In vitro you can produce all sorts of phases. It depends on how much drug you give, how long the in vitro experiment goes on and what time you make measurements. This phase II block where the muscle recovers and then after partial recovery goes into blockade again and stays blocked as long as you like, this is a phenomenon which appears only in the muscle in vitro. Now, one point regarding Dr. CHURCHILL-DAVIDSON's presentation. I think his results are very interesting. Again, I would like to point out (she goes to the blackboard) that we have a muscle and a nerve ending. If we give a dose of succinylcholine or decamethonium to produce a 90 to 100% blockade, a depolarization block with stable characteristics will develop. We have measured directly the depolarization and there is a perfect parallelism between the depolarization and the block. The phenomenon referred to as phase II block only develops after a very long time and large doses. The question occurs, is it not possible that the phase II block is caused by the action of the neuromuscular blocking agents on the nerve terminal? We have evidence today, that if you give a lot of these drugs it will affect the nerve ending. I think Prof. MAYRHOFER's suggestion of a potassium release is a very important one. Depolarizing drugs do release a lot of potassium and that potassium can produce, if you prolong the paralysis or give large doses, all sorts of complications either at the endplate or at the nerve ending.

31. FOLDES:

Thank you very much, Prof. ZAIMIS. I don't think I can answer your comments since this discussion has gone on for too long already. I was very sorry to learn that, according to you, none of the pharmacologists agree with me. I would only like to say that the effects I have described in my formal presentation earlier today can be readily observed in man. For example, tachyphylaxis to repeat doses of succinylcholine, increased sensitivity to non-depolarizing drugs after 15–20 min of succinylcholine administration, the occasional reversibility of the prolonged succinylcholine block by an anticholinesterase. The rest we can perhaps discuss privately. We have tried it many times before, but we could never agree.

Any other comments?

32. MAYRHOFER:

While we are disagreeing with your views, Dr. FOLDES, may I disagree with you also on another point you made during this panel? Namely, the influence of the speed of injection of succinylcholine on postanesthetic muscle pain. In our experience it has made almost no difference in the occurrence of muscle pains following succinylcholine. And also in the experiments that were conducted in the Pharmacological Institute of Vienna, they found, no matter how fast or how slow they injected the succinylcholine, about the same amount of potassium ions in the blood coming from the perfused limb. I am sure you are right that hexafluorenium, given beforehand, is perhaps safer than using d-tubocurarine. However, we have not had any hexafluorenium at our disposal and the small doses of d-tubocurarine (0.02 mg/kg), 1.5 mg for a 70 kg patient, had been sufficient to avoid muscle twitching as well as muscle pain.

I was wondering about Dr. CRUL's findings. He gave succinylcholine after prolonged Alloferin relaxation and found that succinylcholine did not show any change in its potency. In our clinical cases, even after the small 0.02 mg per kg body weight doses of Alloferin we needed higher doses of succinylcholine. We usually use 0.6 mg/kg body weight for intubation, but we need 0.8–1 mg/kg body weight after this prophylactic dose of Alloferin.

33. FOLDES:

Would you like to comment on this, Dr. CRUL?

34. CRUL:

Yes, Mr. Chairman. It depends on the time of injection of the succinylcholine and the degree of wearing off of the Alloferin block, whether you get a prolongation of the effect or not. But it is not obligatory for a phase II succinylcholine block to show a prolonged action. There are two different stages of recovery of a succinylcholine block, the second one of which may be prolonged in phase II block.

35. MAYRHOFER:

Would you, therefore, mean that succinylcholine can be given for the closure of an abdominal wound after having used Alloferin for the main part of the procedure, as opposed to d-tubocurarine?

36. CRUL:

No, I think that so far as we don't know the correlation between prolongation of action of succinylcholine and the change in the phase of block, it is wise not to use it.

37. FOLDES:

I would like to comment on one of Dr. MAYRHOFER's remarks. I repeat that with the dose and mode of administration of succinylcholine we use we have seen practically no muscle pain in hospitalized patients. Since he sees so many, the discrepancy can only be explained by a species difference between the aborigines of Vienna and New York. Now, I would like to ask Prof. WASER to make his closing remarks.

38. WASER:

Ladies and gentlemen, I have the honour to close this symposium which has brought us together for one and a half days. I think we have heard many interesting new facts, and the best of it was that we have gathered together basic scientists and clinicians. And this is very important. I would say from my standpoint that it is gratifying to see that what we have been doing for years in the pharmacology laboratory had some effect on clinical practices. This makes me happy, and I presume that all the other physiologists and chemists who participated in this symposium share my sentiments. On the other hand, we learned much from the clinicians, and we know now that we must go on trying to find even better drugs for anesthesia and muscle relaxation.

So, I want to give my thanks to all the speakers and especially to the foreign ones who came from far away countries to join us in this meeting. Naturally, I owe many thanks to the Swiss Academy of Medical Sciences, especially to Prof. FRANCESCHETTI who was a very fair president, to Prof. GIGON who worked so hard to assemble all of you here, and to Miss Dr. GRAF who was the efficient secretary of this Symposium. Finally, I have to mention again our sponsors, Hoffmann-La Roche and ask Dr. KUNZ to tell his associates that we are very grateful to them, that they made it possible for us to assemble here and discuss all these interesting facts. Thank you all again.

39. GIGON:

Es bleibt auch mir noch, allen unseren Vortragenden, den Zuhörern und unseren lieben und großherzigen Spendern, den Herren F. Hoffmann-La Roche & Cie. AG, auf das herzlichste zu danken. Mein Dank gebührt insbesondere auch Herrn Prof. KARRER für die Anregung zu diesem Symposium und Herrn Prof. WASER für seine so wertvollen Ratschläge bei der Organisation.

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