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Possible causes of prolonged apnœa

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The starting point of this paper is the apparently simple question, which I have often discussed with anæsthetic friends, 'Why was this patient so slow in recovering his normal breathing? Was it because . . .?' Discussions of this kind have usually focussed on the properties of muscle relaxants; and sometimes ideas are put forward best described by adapting Churchill's phrase, as hypothesis wrapped in a theory enshrined in a speculation. As one goes into the problems presented it seems possible that it may be wrong to concentrate exclusively on problems of neuromuscular block, and that there are a number of other causes for failure to breathe deserving more attention. In this paper, therefore, I have attempted simply to enumerate some possible mechanisms for prolonged apnœa such as occur to an experimental pharmacologist. We shall deal only with apnœa due to failure of respiratory muscular movement, and exclude conditions such as bronchial obstruction.

These cases appear to be unusual, in relation to the large number of uneventful anæsthesias, although they are none the less important or interesting for that. If this is true, then one is entitled, and indeed ought, to look for reasons which might not habitually operate; that is, one should enquire, necessarily rather speculatively, as to how *unusual* responses might come about. To justify the speculations in detail, would be a very lengthy proceeding; accordingly I will only indicate briefly the nature of the evidence which could be brought to bear on them.

MORIBUNDITY


In experimental work, if one has had bad luck or been sufficiently incompetent, one sometimes brings an animal, through asphyxia or circulatory shock or both, to a state where it is still breathing, but where any further insult, even one which is normally relatively trivial, will suspend respiration. A similar situation may occur clinically, for

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as anæsthesia has become increasingly skilful and increasingly safe, steadily poorer risk patients come under treatment. Under these circumstances, patients whose survival is in question, whatever is done or not done, must inevitably come to receive anæsthesia. Such cases are obviously very unsuitable for studying the normal risk of an anæsthetic procedure. In particular it seems unprofitable to use cases, whose survival is anyway in peril, as evidence about the nature of action of, say, muscle relaxants, just as no pharmacologist should use a moribund animal to analyse the normal action of drugs. Perhaps, indeed, one should take the question the other way; it might be worthwhile to use the reaction to the anæsthetic procedure in seriously ill patients as an indication of what the threat to their life is. But for our immediate point I wish simply to suggest that any patient whose survival was in question before the operation began should be set in a category by himself in analysing the causes of prolonged apnœa.

OVER-ANÆSTHETISATION

Next we must consider whether, even with ordinary practice, occasional patients might receive too much anæsthetic. Immediately one recalls that, with every drug, individuals vary in their response to it. For cardiac glycosides the range of doses which covers the majority of patients runs over a threefold range, say for digoxin, from 0.5mg in the sensitive to 1.5mg in the resistant for roughly equal effects. With sodium amytal anæsthesia, the range is wider – roughly from 5 to 25mg/kg, given by intravenous infusion¹². Studies on variability in response to drugs have shown that in the main the distribution of sensitivities has the properties of a normal distribution; if the proportion reacting to a dose is plotted against the dose or the logarithm of the dose, one obtains one of the characteristic distribution curves. The implications of a distribution of sensitivity are far-reaching. In the first place, we must expect similar differences with the common anæsthetics; and probably the range over which patients will distribute themselves in their reactions will be of the order of 3–4 fold. But there is a second point. The investigations of variability have usually been on groups of tens, possibly a hundred or so subjects. In relation to clinical practice these are tiny numbers. But if the groups are made much larger – say the sensitivity of one million subjects to thiopentone is studied – then we will expect to run into a number of extraordinary sensitivities, if the laws of distribution continue to operate. It is the same with tossing pennies; with any reasonable number of trials, say up to one hundred, more than six or seven heads in succession would be unlikely; but in 5,000 trials a series of fifteen heads could be expected – and have indeed been observed. Similarly, for the situation when ninety-five out of a hundred patients come into a range of



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dosage of one half to two times of the average dose, one in about 15,000 will react to one quarter of the average dose.

One may ask, naturally, as to what the causes of such variation may be. There is no lack of causes, although it is unlikely that we can name them all; variations in the speed of administration, in the magnitude of the volume in which the anæsthetic is dispersed (*i.e.* fluid and fat volumes), in the rate of elimination or metabolism, in the efficiency of the circulation which distributes the drug. In addition, we have to take into account subtler variations in sensitivity of the neuronal cells themselves, which may rest on metabolic differences or the previous history of the patient.

These and other sources of variability will be important where the dose of a drug is adjusted by common practice rather than by the immediate requirements of the patient. In practice it must be impossible to ensure that the dose given is exactly what a particular patient needs; I imagine that, as with animal experiment, one first gives a dose which is related to the normal average dose, and thereafter the dosage is supplemented as required. This would obviously be the method most economical of time; but, by the same token, if the patient is exceptional, with a susceptibility widely different from normal, he will be liable to serious overdosage.

UNDERVENTILATION

For normal anæsthetic practice in which oxygen mixtures are breathed, carbon dioxide retention must be the main danger of under ventilation. Can this ever itself depress respiration? It is well known, chiefly, so far as man is concerned, from work in diving and submarine physiology, that 10 per cent carbon dioxide or more produces unconsciousness. It is also known that very high concentrations can be lethal to animals. But loss of consciousness is not the primary issue; and the concentrations required to kill an animal are probably higher than could be reasonably expected to occur even with the grossest underventilation clinically. Is there any evidence as to the effects of carbon dioxide excess on the respiration?

Recently Dr Payne and I have been examining on cats the factors controlling the normal respiratory response to carbon dioxide. This work is still in progress and is not entirely easy to summarise. But one point has emerged from these animal studies. With thiopentone anæsthesia, even carried to the deepest levels, carbon dioxide seems always to be a stimulant to respiration. With deep anæsthesia, the respiratory response is much reduced and is transient, so that in a few minutes the respiration returns to its central level. But even with 20 per cent carbon dioxide, no depression of the respiration could be obtained. With ether, on the other hand, the response to carbon

dioxide is rather readily abolished; and with fairly deep anæsthesia, but not so deep as to itself threaten life, the administration of 5 per cent carbon dioxide may actually stop the animal breathing.

The implication of this, bearing in mind that one always has to extrapolate from animals to man with some degree of caution, is that one ought to take seriously the danger, not merely of unconsciousness or of a reduced response to carbon dioxide, but of frank respiratory depression by this gas. Many anæsthetists of course, are aware of this. But it also seems to be important that the effect of a given underventilation may vary appreciably with the anæsthetic, and no doubt also with the other ancillary agents which are used.

Oxygen lack, one imagines, could only occur when the anæsthetic apparatus has been removed from the patient in the post-anæsthetic period. Then, perhaps, a depressed minute volume while inhaling air could give rise to anoxæmia. Under these conditions of course, damage to the respiratory centre can take place, and the patient would be reduced to that state of moribundity discussed above.

OVERVENTILATION

This is a familiar possible cause of apnœa. The mechanism usually invoked is that with overbreathing carbon dioxide is washed out from the blood so that the respiratory centre and chemoreceptors are driven only by the stimulus of anoxæmia. So long as oxygen continues to be breathed the apnœa may tend to be somewhat persistent. One might have thought that there would be little difficulty in determining whether continuing overventilation is the cause of an apnœa, and that merely suspending the respiration for one or two minutes would be enough to restore normal breathing if this was the cause. I think it is worth noting, however, that there seems to be quite an important variation in individual susceptibility to the effects of overventilation. Mills⁸ made some interesting studies on voluntary hyperventilation in conscious volunteers. In some subjects apnœa could not be produced; when the test over-breathing period was completed, they continued to overbreathe. For some of this group he attributed the continuance of overbreathing to a reflex response to reflex of blood into the thorax, blood which had been driven out by the previous hyperpnœic effort. In others of these cases no satisfactory cause of the hyperpnœa was identified. Now this is a different point from our present concern. But it shows that individuals can vary considerably and that some are more prone to apnœa following hyperventilation than others. I would also say from animal experience, that it is easy to be seriously deceived by an animal in whom a slight but persistent overventilation has occurred; the apnœa which follows the overventilation before normal breathing returns is often so long as to make one hesitate to allow it to

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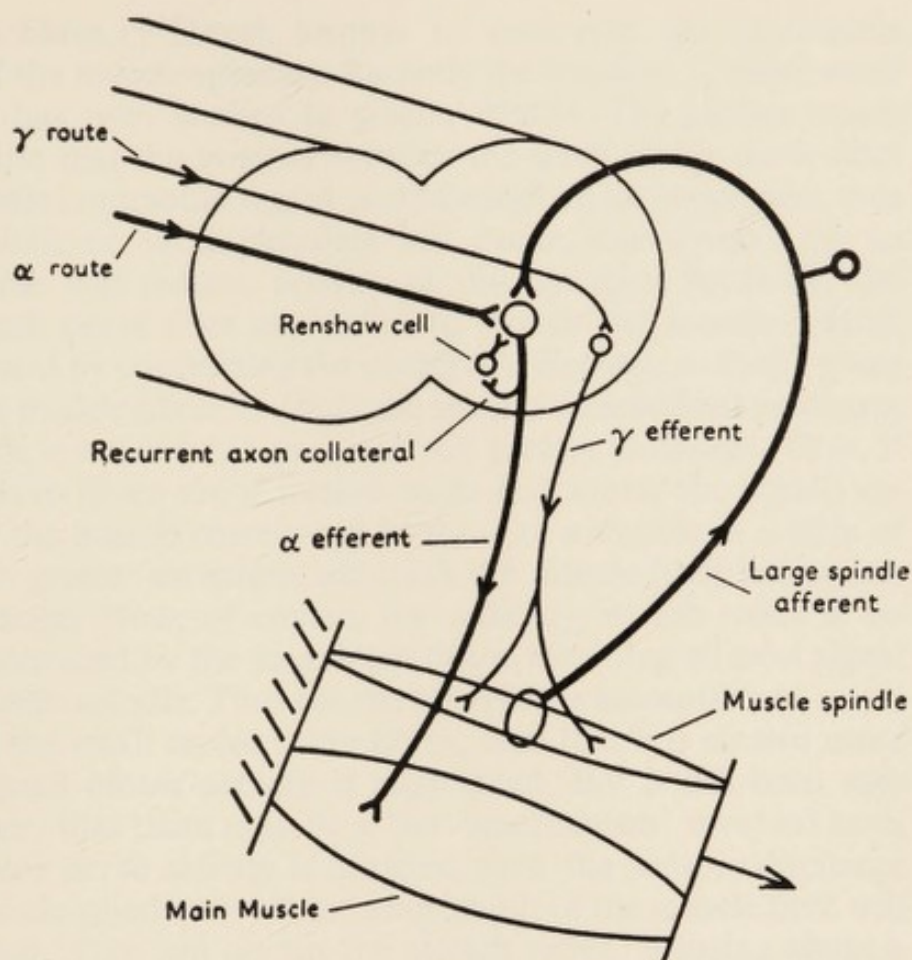
continue. One wonders if there is not a field for investigation here. It might be worthwhile to study the duration of apnœa which is produced by varying degrees of overventilation in patients anæsthetised with standard procedures. If one knew what the usual range of variation was it would help considerably in assessing the odds that a given patient was apnœic from this particular cause; and it would help in laying down a standard test period during which ventilation could be suspended in order to test whether overventilation was involved.

AFFERENT STIMULATION

It is possible to suspend respiration temporarily by various forms of sensory stimulation. The apnœa of getting into a cold bath is one example. Excitation of the vagus nerve or sensory nerves in animals can produce the same effect, and there are chemical compounds, active on chemoreceptors, which can amongst other effects depress the respiration temporarily. One would have thought these observations too far removed from clinical practice to have much relevance, were it not for such reports as that a patient, following an operation, would fail to breathe properly despite all usual measures until the cuff on an indwelling tracheal tube was deflated⁹. The significance of this is certainly arguable. It may be that the act of deflation of the cuff constituted a stimulus to the trachea. Alternatively, it may be that the continued inflation of the cuff produced a sustained excitation of an unusual kind to vagal afferent fibres in the wall of the trachea, and that its removal allowed normal respiratory rhythm to reoccur. At all events, it raises the possibility that forms of afferent sensory stimulation, which might not necessarily have to reach consciousness, might suppress breathing or simply disorganise the normal, rhythmically synchronised, respiratory activity. One wonders in this connection what effect those sensory stimuli have during the immediate post-operative period, which later constitute post-operative pain. The fact that sensation is not reaching consciousness does not necessarily mean that it is devoid of physiological effect in the body.

AFFERENT PARALYSIS

At the risk of appearing to wish to ride two horses simultaneously, I must also raise the converse point to the one just mentioned. There is good evidence that normal respiration is often driven by central nervous influences other than those arriving from chemoreceptor excitation. For instance, the hyperpnœa seen in muscular exercise starts sooner, and may be greater, than would be accounted for by blood gas exchanges. Reflexes from muscles and joints have been proposed to account for these results. This implies that interference with the



THE STRETCH-REFLEX AND RELATED MECHANISMS

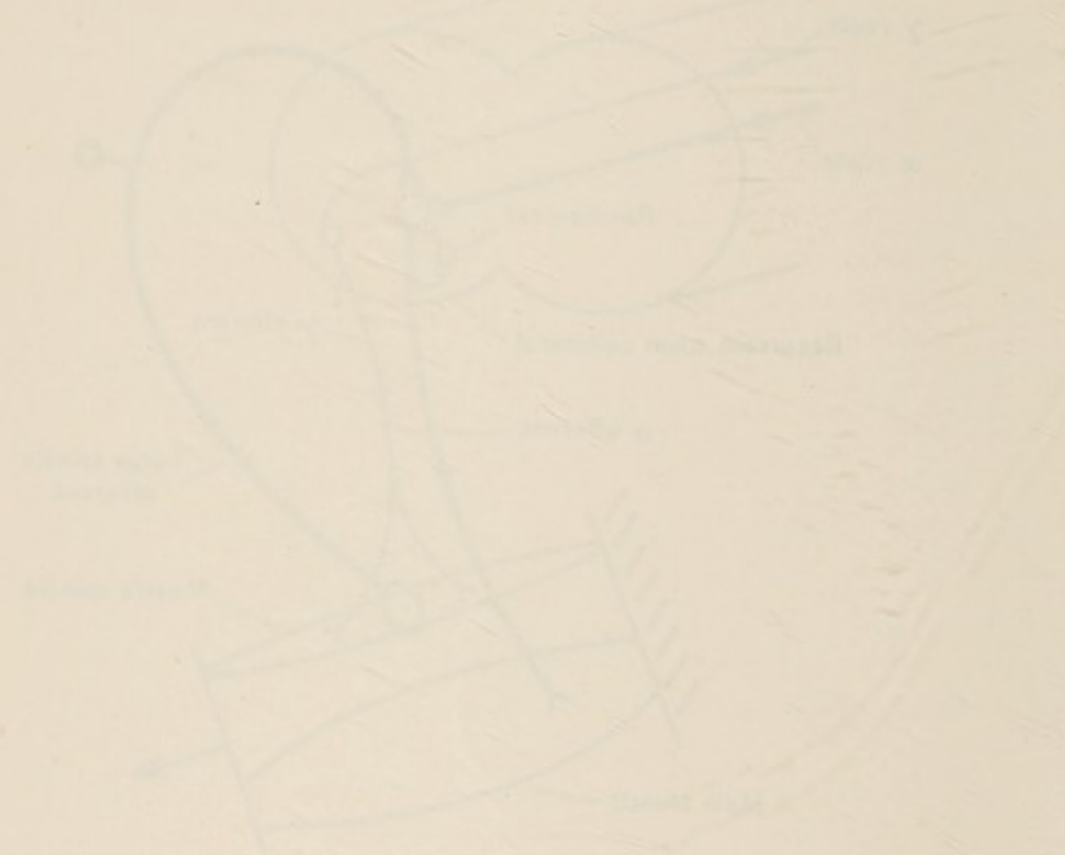
The muscle spindle lies in parallel with the main muscle and its fast conducting afferent is in synaptic connexion with the large α motoneurone supplying the main muscle fibres. A slow conducting γ motor efferent (thin line) supplies the contractile poles of the spindle and thus can alter the bias on the spindle sensory ending.

The muscle can be made to contract either by impulses from higher centres exciting the α motoneurone direct (the α route) or by impulses in the γ efferents (the γ route) which activate the muscle indirectly via the stretch-reflex arc (the 'follow-up' servo).

A subsidiary feedback loop via the recurrent axon collateral and an inhibitory Renshaw interneurone may be concerned in stabilizing the response of the α motoneurone to its excitatory input.

Hammond, *et al.* 1956; by permission of the Editor, British Medical Bulletin.

normal pattern of afferent inflow to the central nervous system may reduce the respiratory drive. Here a rather interesting connection with some recent neurophysiology arises. For a long time we have usually thought of the voluntary muscles in rather simple terms as receiving innervation simply by way of the large cholinergic motor nerve fibres (often called α fibres). But it has been known for a long time that there are also in the ventral roots a surprising number of



THE RESULTS OF THE EXPERIMENTAL INVESTIGATION OF THE EFFECTS OF THE VARIATION OF THE TEMPERATURE OF THE MEDIUM ON THE RATE OF GROWTH OF THE CULTURE OF THE BACTERIA...

The results of the experiment show that the rate of growth of the culture of the bacteria is affected by the temperature of the medium. The rate of growth is highest at a temperature of 37°C and lowest at a temperature of 15°C. The results also show that the rate of growth is affected by the pH of the medium. The rate of growth is highest at a pH of 7.0 and lowest at a pH of 5.0. The results also show that the rate of growth is affected by the concentration of the medium. The rate of growth is highest at a concentration of 1.0% and lowest at a concentration of 0.1%.

It is concluded that the rate of growth of the culture of the bacteria is affected by the temperature of the medium, the pH of the medium, and the concentration of the medium. The rate of growth is highest at a temperature of 37°C, a pH of 7.0, and a concentration of 1.0%.

small nerve fibres (γ -fibres), known to innervate the contractile substance of the muscle spindles. Recently the function of these small nerve fibres has been studied in greater detail⁴. The picture which emerges is first that the synapse between the small motor nerve fibre and the spindle contractile region is cholinergic in its properties; thus decamethonium or succinylcholine will excite, and drugs such as d-tubocurarine will reduce, activity at this synapse. Secondly, the effect of small nerve fibre activity is to stretch the muscle spindle sensory element by contracting the contractile element, so that a given length of the muscle fibres in which the spindle is embedded produces, as the spindle is activated, a progressively greater discharge. Thus, if the small nerve fibres are activated more and more, the signals received from the muscle correspond to those of a muscle in a state of progressively greater extension, although the muscle itself has undergone no change. Now, of course, the ordinary stretch reflex is essentially determined by the magnitude of the incoming afferent signal from the muscle spindle. Thus the stretch reflex is susceptible to a sort of 'bias' by the small motor nerve fibres, such that it is elicited more readily as small motor activity is augmented. But it has been suggested further, that there may be a 'servomechanism' involved here. If small motor nerve activity is initiated, then the sensory discharge from the muscle spindle for the existing length of the muscle fibre will be augmented. This will set up the stretch reflex, bringing about a shortening of the muscle. Thus muscular movement can be mediated in two ways. It might be by a direct discharge down the large motor nerve fibres, which will yield a tension in the muscle directly dependent on the frequency of discharge in the large motor nerve fibres; such a method of control yields gradations of *tension* and may be a little difficult to modulate. But if on the other hand, activity is initiated down the small motor fibres, the muscle will change its *length* until it reaches a length matching the length of the muscle spindles; in other words with contractions initiated through the small fibre system, the muscle will come to take up a new length rather than a new tension, a type of movement which is obviously much more useful for a large variety of the body's activities. For many purposes it is more important to have the limbs in a known position and for power to be supplied to retain that position than for a known tension to be applied to a limb and for the position to vary according to the resistance offered to the force of the muscle.

This is something of an excursion. But it may serve to illustrate how, if a muscle relaxant is administered, it is only too probable that the proprioceptor inflow to a patient will be changed. With a supine anæsthetized patient it may well be that sometimes the proprioceptor inflow will constitute the main sensory afferent activity. If this is then

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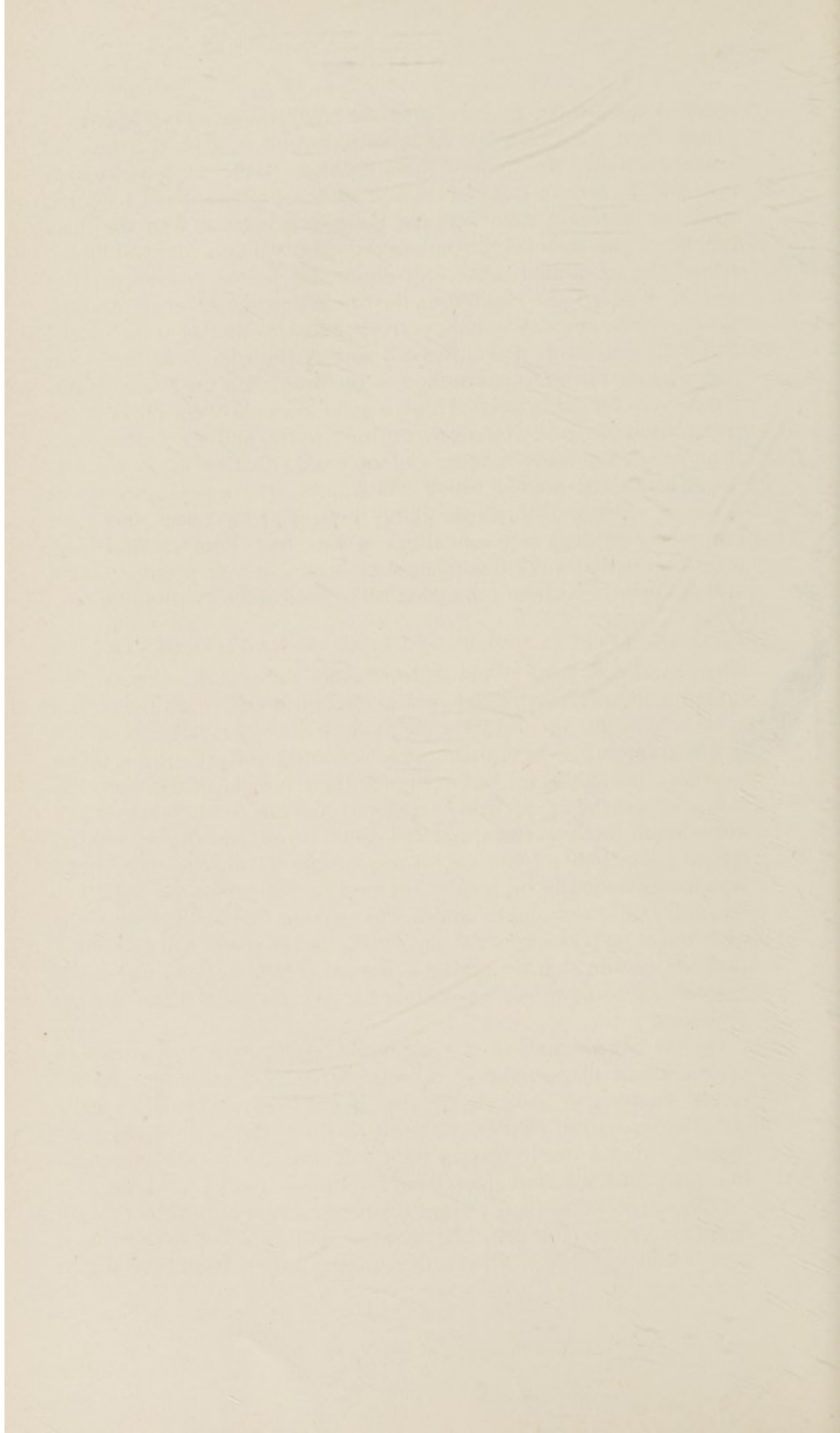
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reduced still further by curarising the small motor nerve fibre end-plates, there may be a considerable reduction of even this residual sensory activity. We can now recall Bremer's studies on the *encéphale isolé* and the *cerveau isolé*. In the first of these preparations a section is made in the brain stem between the mesencephalon and the diencephalon. This removes the bulk of the sensory inflow to the brain but leaves the trigeminal nerve still connected to the central nervous system. Under these conditions the animal, in the absence of anæsthesia, shows cortical activity corresponding to that of wakefulness. But if the section is now advanced so that the trigeminal nucleus is now excluded from its connection to the brain then the animal enters a state very similar to sleep. This is a good example of the effect of the deprivation of sensory inflow on central nervous activity. One can put it alongside the fairly familiar experimental situation where one has an anæsthetized animal which will not breathe unless its chest is squeezed, or even sometimes lightly pressed. I have seen this most commonly in dogs but sometimes in cats; and I understand from anæsthetists that a not dissimilar state occurs in man when a patient will not breathe without some physical or even auditory stimulus.

CENTRAL EFFECTS OF DRUGS USUALLY INACTIVE CENTRALLY

There is always some doubt as to whether drugs such as muscle relaxants can, under particular clinical circumstances, reach the central nervous system. In normal animals it is clear that substances like d-tubocurarine or hexamethonium penetrate only in the smallest amounts through to the brain. In man there is a classical demonstration of this in the unique and courageous study by S. M. Smith, *et al.*¹¹ Here Smith received three times as much d-tubocurarine as was required completely to paralyse his respiration; during the experiment, which was naturally prolonged, many observations on his ability to feel and think were made; and it was striking that at the end of the experiment he remembered things which the observers had forgotten. It seems certain that no central action of d-tubocurarine had taken place which could in any way reduce the efficiency of ordinary mental processes.

On the other hand, during operation, particularly in patients in peripheral circulatory shock, or with intestinal obstruction and resultant changes in body electrolytes, it has been suggested that the blood/brain barrier changes its properties. In particular it has been proposed that a rise in plasma potassium may allow d-tubocurarine to exert a central action, depressing respiration. Now I think the idea that these conditions may change the permeability of the blood/brain barrier is a reasonable one. The literature on this barrier in so far as it is relevant to clinical work is rather unsatisfactory. But taking it as it



stands, one can point to evidence that conditions like circulatory shock, dehydration, asphyxia, or even anæsthesia itself, will all predispose to the entry of drugs into the brain. So that *prima facie* it is not unreasonable to suggest that drugs normally excluded might come to enter. But in the case of d-tubocurarine perhaps one should be a little hesitant. In the first place the central effects of d-tubocurarine are primarily epileptogenic. It has recently been shown that it is, applied centrally, a good antagonist to barbiturate anæsthesia. It is possible by giving it into the ventricles to produce a centrencephalic seizure not at all unlike ordinary epilepsy². To depress respiration relatively large doses have to be given, and then the depression only occurs after an initial stimulant period¹⁰. One would therefore expect to see a stimulant effect on respiration if anything. Further if you make the rather large assumption that the blood/brain barrier becomes completely permeable, it is doubtful whether the amount which would appear in the brain from a dose generally dispersed to the body would be enough to have any major effect at all. For instance, with a dose of 30mg in man perhaps one or two milligrammes of this might be assumed to enter the whole brain; of this presumably only a fraction could be acting at the important sites. Yet with local intracisternal or intraventricular injections in the cat, a far smaller target, a total dose of this kind is needed to produce any substantial effect. Since it is doubtful whether the blood/brain barrier would be completely broken down under these conditions, my own feeling is that such activity is improbable on quantitative grounds.

One might also enquire, if a central effect of muscle relaxant is postulated, why it is not more common. We have to suppose that some predisposing factor allowing the drug to enter the brain should be present; yet cases subject, through disease, to the factors which I have already mentioned, such as anæsthesia, shock, anoxia, dehydration, are, I think, more common than the prolonged apnœa which we are discussing. If a central action of d-tubocurarine mediated thus were really significant, then prolonged apnœa should be one of the biggest problems and not one of moderate rarity.

PROLONGED RELAXANT ACTION

Finally we come to the problem of the mechanisms by which an ordinary dose of relaxant might come to exert an unusually prolonged effect peripherally. Perhaps we should straight away set on one side cases of abnormal sensitivity to relaxants such as are shown by myasthenics. It seems that the problem of prolonged apnœa after operation is commoner than the incidence of myasthenics; and one gathers that in many of the cases it was clear at the beginning of the

operation that the sensitivity of the patient to a relaxant was not abnormal. Sometimes, of course, an overdose of relaxant is given to a myasthenic patient unwittingly, with corresponding difficulties ensuing. But this is outside our present concern.

Four main possibilities suggest themselves: changes in blood flow during the operation, fall in body temperature, the accumulation of breakdown products, and peculiarities in the mechanism of action of relaxants.

Blood flow

Suppose a relaxant is injected while the circulation is vigorous; then it will be rapidly distributed and rapidly taken up by the various receptor areas. Suppose now that there is a severe hæmorrhage or some other state producing a defect of circulation; this will reduce the rate of blood flow through the muscles, on which will depend, at the end of the operation, the rinsing out of the muscle relaxant. The renal and liver blood flow will be cut down also, with corresponding reductions in elimination or metabolism. In an animal it is possible to produce an almost indefinite period of neuro-muscular block with d-tubocurarine or decamethonium if the renal vessels are tied and sufficient decamethonium is given to distribute itself at an adequate level in the extracellular spaces. Thus with a defect of circulation occurring in this way, a serious prolongation of the action of the drug could occur. It is worth noticing the requirements for such a situation. In the first place the worst case is certainly when the circulation is good to begin with and bad later on. If it is bad throughout, then the rate of take-up by the muscles of the relaxant will be correspondingly reduced and it is possible, although not certain, that even a sluggish rate of elimination might be able to keep pace more readily with the development of curarisation. It is probably also necessary, for this sort of process to occur, for the administration to be fairly prolonged. The passing off of the action of a single dose of an intravenously given drug is probably chiefly by dilution in the tissue fluids rather than by elimination. If one follows the course of injected material through the circulation, it first goes round in relatively concentrated form for one circulation; it is then considerably diluted for a second circulation time, and is hardly detectable as a localised concentration in circulating blood thereafter³. Thereafter, and more slowly, the drug in the blood diffuses into, equilibrates with, and is diluted by the extracellular spaces. When a drug is injected, therefore, a relatively concentrated 'slug' of the mixture first hits the tissues, followed by a prolonged exposure to a much lower and gradually diminishing concentration. It is probable that the effect of a given dose depends largely on the concentration of the initial 'slug'. If, then, the tissue

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REVIEWS

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fluids are free of relaxant, it will be able to dissociate from the receptors and to diffuse away; if, however, the tissue fluids have already taken up some of the relaxant, by reason of a more or less prolonged curarisation, this dissociation will be slowed.

What I have just said ought to apply to any drug; but in the case of depolarising agents we have to take account of ionic movements such as the leakage of potassium out of the endplates. It seems plausible to believe that the electrical inexcitability of the endplate region on which the neuromuscular block depends, may be of special significance here; for a reduction of blood flow will allow the local concentration of potassium to rise to higher levels and hence deepen the inexcitability more than if the blood flow is good. Whether such an explanation is correct or not, there seems no reason to doubt Churchill-Davidson and Richardson's observations¹ that ischæmia predisposes to intense prolonged block by decamethonium while vasodilatation achieves the reverse. This suggests that with depolarising drugs prolonged apnœa might be a sequence to circulatory failure to a more pronounced degree than with other relaxants.

It is worth noting, here, that simple measurements of blood pressure represent an extremely bad index of flow rates. The level of blood pressure is the resultant of changes in cardiac output and peripheral resistance summed over the whole body; and it is quite easy to get substantial changes in peripheral resistance with the blood pressure little changed.

The body temperature

Dr Zaimis recently showed that decamethonium and succinylcholine are much more effective in the chilled animal or chilled patient, but d-tubocurarine retains its normal potency. One could attribute this in part to a reduction of blood flow through muscles which would, as we have seen, potentiate the depolarising drugs. D-tubocurarine would be expected on such a basis to be if anything, perhaps antagonised, since cooling a muscle tends to increase the tension of the twitch recorded to nerve stimulation. In addition to these local muscular events, elimination and metabolism should be delayed. This means that it would be well worth while to check the body temperature in patients. On the whole the recording of body temperature seems somewhat neglected, no doubt chiefly because operating theatres tend to be warm places. But one may note that in anæsthesia the thermal regulating system may be considerably depressed; and ganglion blocking agents or equivalent procedures can themselves allow quite a lot of heat to escape from the body. For instance, a supine subject receiving 25mg of hexamethonium subcutaneously and covered by a blanket may lose 1° or 2°F in body

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temperature, chiefly by vasodilatation of the legs. In addition during an operation exposure of the tissues allows water to evaporate, providing another means of heat loss. It seems quite possible, therefore, that even in what would be for the normal individual quite warm surroundings, an anæsthetised paralysed patient could lose a significant amount of body heat. It would be an interesting study to discover what in fact is the usual temperature course of patients during and after an operation, to assess how often gross falls in temperature may occur. It is not impossible, indeed, that serious rises in temperature may occur too, although the consequences have been little explored.

Breakdown products

With succinylcholine it was hoped at first that the products formed from it following hydrolysis of it by cholinesterase, would be totally inactive. It is clear now, however, that from it is formed first of all the mono-choline ester, which is something between one tenth and one fortieth as active as the parent compound; that this ester is split considerably more slowly than succinylcholine itself; and that the final product, choline, is itself capable of neuromuscular action⁵. Choline is not at all potent, but extrapolating from the animal figures it seems that the total amount formed from one gramme of succinylcholine would be enough to have a significant effect in man. There is, therefore, some scope for the operation of individual susceptibilities in allowing these abnormal products, whether through a defect in cholinesterase or in choline disposal, to produce a prolonged apnoea themselves. One doubts whether in fact a failure to break down succinylcholine is of major importance, since the biggest reductions in cholinesterase so far described have not been much more than one tenth of normal levels. On simple reasoning this might allow one to predict an apnoea lasting something of the order of ten times as long as normal, so that a dose of 50mg or 100mg of succinylcholine might have an effect lasting twenty or thirty minutes. It seems rather unlikely that any apnoea lasting for two hours or more could be attributable to a defect of cholinesterase, but rather that there is always enough cholinesterase somewhere in the body to destroy succinylcholine within this period. Nevertheless, it is difficult to reject this possibility completely, particularly as we don't really know all we should about the fate of the metabolites in detail. In addition recent studies on the genetics of serum esterase suggest that in occasional patients the enzyme may be quite different from normal, not merely present in reduced amount^{6 7}; if enzymes elsewhere in the body were similarly abnormal, and all incapable of splitting succinylcholine, then a notable prolongation of succinylcholine action would indeed be expected.

Changes in the action of muscle relaxant

This is a subject which is developing considerably and opinions differ somewhat. To my mind there seem to be two types of change in action which can be broadly distinguished. First a frank change in the *type* of block, of which perhaps the action of nicotine on a ganglion is the most typical and best documented example. Here it is clear that at the start nicotine excites the ganglion and depolarises it, and that after a fairly brief interval the block is still present but the depolarisation vanishes, leaving a state comparable to ganglion block by hexamethonium or d-tubocurarine. Dr Zaimis has shown that in the monkey decamethonium produces what one can readily regard as a precisely analogous state, *i.e.* a block like that of decamethonium on the cat tibialis at the start, passing over after continued administration to a state similar in its properties to block by d-tubocurarine. Such a type of action has many analogies, especially in the sympathomimetic field; for instance, ergotamine precedes its adrenaline-blocking action by a period of powerful sympathomimetic action.

The second change in type of action can perhaps be briefly called the development of refractoriness. It is normal to see with successive doses of, say, a depolarising drug, that the depolarisation of an end-plate achieved by repetition of the same dose gets smaller with the repetition. This has been described for acetylcholine applied to frog muscle *in vitro*, for decamethonium on cat muscle, and for acetylcholine preserved by anticholinesterase in the whole animal. So far as my own experience goes, in the mammal the depolarisation persists but is simply reduced in magnitude, although in frog muscle Thesleff has shown that the depolarisation may disappear altogether. There are analogies here with a somewhat different phenomenon in pharmacology. Before the days of antihistamines, Barsoum and Gaddum showed that you could obtain a specific test for histamine by 'desensitising' the tissue to histamine through exposing it to a high concentration for some time. After this, histamine becomes ineffective while other stimulants in the intestine continue to be effective, giving a sort of specific antagonism to histamine or histamine-like substances. Then as a period of, say ten to thirty minutes elapses the structure would regain its normal sensitivity to histamine. This seems to be a phenomenon rather like the refractoriness developing to the natural transmitter.

These two mechanisms may be of some practical significance. My personal opinion is that both may operate, but that such mechanisms may not be as common as postulated. The often quoted fact that neostigmine may come to antagonise a block produced by succinylcholine when given after a period of apnœa, is not itself decisive for there being a neuromuscular block of competitive type. It is worth

remembering that in the earliest stages of the pharmacology of myanesin, it was suggested that myanesin was a neuromuscular blocking agent, because neostigmine increased the strength of animals paralysed with it. A judiciously chosen dose of an anticholinesterase can certainly potentiate single twitches of the muscle and might increase muscle strength if the incoming volleys to the muscle are not too frequent. But setting on one side how to view these new developments, I think it is worth noting that they do not necessarily offer any explanation for *prolonged* actions. Their significance is chiefly in relation to treatment. They imply that after waiting for a period during which cholinesterase had ample opportunity to act on the succinylcholine in the body, a dose of neostigmine might be tested. But they also indicate that administration of neostigmine is a dangerous thing not only for its side effects or its own curarising action, but also for the danger that it may, through accumulation of acetylcholine, cause refractoriness of the endplates itself. In relation to practice it may also be significant that sometimes difficulty occurs when the patient has received either a rather large amount of relaxant over a long period, or when relaxants of different types have been mixed. The pharmacological situation, obviously, becomes very complex. But perhaps a worthwhile precaution is to keep the dosage down as low as is feasible and to minimise mixing of different drugs as far as possible.

RECAPITULATION

We thus have as possible causes of failure of respiration after an operation: Moribundity; Overanæsthesia; Underventilation; Over-ventilation; Afferent stimulation; Afferent paralysis; Central action of drugs; Prolonged neuromuscular block.

With this selection of possible causes it seems clear that to treat an apnœa with drugs should not be done unless there are clear reasons for giving a drug, and the choice of drug is unambiguous. As soon as serious uncertainty arises, one feels as a pharmacologist that the wisest course would be to use conservative treatment and to avoid complicating an already difficult picture.

How far can this complicated list of possibilities be sorted out and reduced? It is obviously unsatisfactory to be confronted with this type of speculative uncertainty. There are, however, several investigations which would be feasible and which might help to clarify the situation.

(a) The collecting and sifting of the cases. Although a number of reports of the representative cases exist, I am not aware of any large-scale study, which would allow one, for instance, to say with confidence what the predisposing factors are to these prolonged apnœas. I am not, indeed, even clear as to whether there is general agreement as to what prolonged apnœa consists of, *i.e.* how long a

patient must experience difficulty in breathing before an anæsthetist gets worried. Obviously varying anæsthetic practice will give rise to varying criteria. Although the analysis of a heterogeneous collection of case histories is often not as rewarding as one had hoped, it is nevertheless a task which needs to be undertaken, if only because not infrequently such studies exclude otherwise plausible explanations.

(b) One of the remarkable facts is that in the bulk of cases of prolonged apnœa reported it is uncertain whether failure to breathe is of peripheral or central origin. As we have seen, one can point to a number of central causes which might operate. Clearly, too the therapeutic approach would be dictated by the nature of the apnœa. The required information could easily be obtained, if use was made of some small portable stimulator which was connected to an electrode applied to suitable motor nerves through the surface of the skin. The practice of faradisation therapy has developed a good deal of experience of points at which the motor nerve to a muscle can be stimulated fairly selectively; a re-examination of this experience by anæsthetists could furnish them with a useful weapon and allow them to test even a range of muscles for their response to motor nerve stimulation. It is probable that the mere presence or absence of some form of contraction would not be a sufficient test whether block was central or peripheral; in animals it is easy to see a contraction of a muscle when the tension it will develop is a very small fraction of the normal. On the other hand a little practice at seeing the response obtained normally would soon establish a baseline of experience. There is not much doubt between a muscle which is contracting vigorously and one which has a trivial response. It would, of course, be more elegant if a recording of muscle tension or of muscle action potential is obtained but perhaps this is hardly practicable for everyday anæsthetic use. A shrewd observer can make a reasonable estimate of the extent of paralysis of a standard muscle simply by eye. It is worth remembering that tubocurarine used to be assayed by the rabbit head drop test, which essentially consisted in a subjective decision as to when the muscles of the rabbit's neck were relaxed to a roughly standard degree. This assay method proved fully adequate for the close control of the potency of curare preparations.

(c) The possibility that d-tubocurarine, and perhaps other relaxants, has a central effect should be testable by electroencephalography. This would clearly not be possible on all patients. But it should be feasible to have a reasonable number of subjects under various operative conditions receiving typical relaxants and to test whether any convulsive or depressant effects attributable to the relaxant appears.

(d) A last possibility is that of analysing the excretory products in

the urine. If one wishes to suggest, for instance, that a prolonged action by d-tubocurarine is due to failure to eliminate the drug, then it should be possible to demonstrate that a smaller amount has appeared in the urine than normal. I am not aware that any such study of elimination under practical surgical conditions has been done but see no reason why it should not be. Methods for assaying d-tubocurarine biologically are quite straightforward; and the analysis could be extended to all the muscle relaxants now used. The converse situation would also be of great interest; if one could collect the urine from a patient with prolonged apnœa and show that the samples collected during and for some hours afterwards had most of the dose of curare in them, then a prolonged action by the relaxant would become a much less plausible cause for the prolongation of the apnœa. Studies of the pharmacodynamics of d-tubocurarine would be very valuable and would throw light on considerably more than simply the question of prolonged apnœa.

This talk has been essentially speculative and has attempted primarily to suggest that the problem of failure to breathe after an operation may have numerous causes and that these causes should be capable of analysis. Apart from the great objective of removing a dangerous and obscure difficulty in anæsthetic practice, such analysis would also be of considerable interest in the wider context of human physiology and pharmacology.

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