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THE EFFECTS OF MUSCLE RELAXANTS OTHER THAN MUSCULAR RELAXATION

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A MUSCLE relaxant may effect actions other than simple neuromuscular block in at least three ways. First, the depolarizing stimulant drugs display an excitatory stage as an intrinsic element in the development of the block, from which may flow additional actions. Second, the relaxants owe their activity to a chemical relationship to acetylcholine; if they are able to compete with or imitate acetylcholine at one synapse then they are liable to have activity at some other cholinergic synapse, or to react in some way with the enzymes which destroy acetylcholine. Third, the muscle relaxants in general use are all basic compounds, and hence need to be scrutinized for a number of reactions liable to occur, sometimes rather nonspecifically, among organic bases.

These three headings will be discussed first; finally, the problem of the assessment of such additional actions will be briefly treated. A number of special references will be given; others will be found in the valuable monograph on muscle relaxants by Foldes.[1]

THE CONSEQUENCES OF END-PLATE DEPOLARIZATION

Muscle Pains. It was early recognized that the first action of decamethonium or succinylcholine (suxamethonium) is to augment the response of a muscle to excitation of its motor nerve (by rendering the response to a single nerve volley repetitive), and to elicit incoordinate fasciculations in a muscle, independent of nervous excitation, and present after section of the nerve trunk.[2] These fasciculations seem to be most prominent in the deeper muscles of the body. They are earlier and most vigorous in shoulder girdle, face and arm; they then appear in the trunk and are less striking though still demonstrable in the lower limbs. They are most noticeable, in animals, when a full paralyzing dose is injected fairly rapidly, and can be reduced by slow injection. With very large doses they appear but rapidly disappear as block ensues. Such observations suggest that the rate of onset of the end-plate depolarization determines the vigor of the excitation; this conforms with the fact that succinylcholine produces fasciculations more readily than decamethonium, just as its depolarizing influence is more rapidly exerted. The total duration of fasciculation probably depends on the time taken to pass from the threshold stimulant action to full block.

These fasciculations may be associated with the deep muscle ache sometimes evident after the use of stimulant relaxants, and hence are of more than academic significance. It seems clear that they do not represent excitation of individual muscle fibers, for the movements elicited may be quite powerful; further, the electromyographic records obtained represent motor-unit activity, and do not conform with fibrillary responses.[3] How may synchronous responses of whole units be elicited by end-plate depolarization? One suggestion made by Masland and Wigton [4] to explain the centripetal discharges in a motor nerve of a muscle treated with neostigmine is that an axone reflex is set up. Such retrograde activation of one nerve termination by a depolarized end-plate leads to activity of the whole unit, as well as to centripetal impulses recorded in the nerve trunk.

A second possibility is raised by recent work on the muscle spindles. It is known that the junction of the small motor nerve fibers (γ fibers) with the contractile part of the spindle is a cholinergic synapse, and that its activation can lead to a discharge in the afferent nerves.[5] Such an afferent discharge is normally the basis of the stretch reflex. Consequently, the administration of a depolarizing drug would be expected to elicit reflex motor activity. It must

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be admitted that we have no clear knowledge of what the pattern of this motor activity would be and, in particular, whether it would conform to the fasciculations actually seen. One could expect that it would not be any normal movement, for the spindle excitation would be abnormal. Whereas normal γ fiber activity supplies a series of transient pulses to the spindles, a depolarizing drug would give sustained activation, with distribution through the muscle determined not by physiological nervous pathways but by factors such as blood flow.

These two possible mechanisms seem the most plausible causes for activation of motor units. The depolarizing drugs are not, in clinically used doses, stimulants of sensory endings; nor can any central excitatory action be plausibly assumed for quaternary salts. But it is still to be considered how activation of motor units and muscle spindles causes pain, and this (to judge from experience in unanesthetized subjects) not during the main action of the drug, but in the recovery period.[6, 7] With succinylcholine especially the pain outlasts the period for which the drug is known to be still present in the body. This "over-time" pain period and the character of the pain itself, an ache like the stiffness produced by muscle exercise, make it possible to suggest that some local trauma is done to the muscle. This is not incompatible with the fact that the fasciculations are mechanically feeble compared with the voluntary movements of physical exercise. For in exercise a whole muscle contracts, but in fasciculations it is only bundles of muscle fibers which contract, unsupported by tension development in the muscle as a whole and unlimited by any approximation of the points of attachment of the muscle fibers (such as occurs as in many ordinary movements). It seems reasonable to suppose that a vigorous contraction by a muscle bundle (or perhaps even a muscle spindle), with no possibility of shortening and without synchronous activity in adjacent bundles, may produce fiber rupture or damage; and that it is this damage which causes the pain.

A third possibility is that the pain and the fasciculations are not directly related: that the pain is due not to the arousing of propagated action potentials in muscles but to the development of a "contracture" similar to that known to occur in the extraocular muscles, causing a rise in intraocular pressure.[8] Such a contracture might be limited to the muscle fiber near the end-plate, and produce a damaging extension of the rest of the fiber. In animals it is common to see a significant increase in resting tone of skeletal muscle after giving decamethonium or succinylcholine if sensitive levers are used. With avian or amphibian muscle the effect is striking. A sustained contracture of, say, the deeper muscles of the trunk, deserves serious consideration, especially in view of recorded opinions that the incidence of pain and the incidence of fasciculation do not correspond closely. The main weakness in the theory is that we have no direct evidence in man as to whether such a contracture, of sufficient intensity to cause discomfort, can occur; and it leaves the superficial fasciculations unexplained.

Although we cannot be certain of the cause of the pain, the most plausible theories all associate it in one way or another with muscle depolarization. If this is true, muscle pains will be inseparable from the use of depolarizing muscle relaxants. It may be, however, that they could be mitigated if the rate of onset of the depolarization is slowed, just as that of decamethonium is, compared to succinylcholine.

Potassium Release. Depolarization of excitable membranes generally leads to potassium loss from the cell concerned. In the cat, end-plate depolarization produced by succinylcholine, decamethonium, and other depolarizing drugs, may be sufficient to raise the plasma potassium. The question arises whether a similar process is significant in human practice. It is clear that it must have a much smaller effect in man or it would have been rapidly recognized; but one would expect some effect of this kind, in view of the well established muscle stimulant effect. A systematic trial (Paton and Werner, unpublished), comparing changes of plasma potassium after the administration of succinylcholine with those after gallamine, in a series of patients undergoing dental extraction under thiopentone, treated in a random order with one or the other drug, showed that in fact succinylcholine produces a small but significant rise in plasma potassium (average 0.5 mEq. maximum about 30 minutes after

the first dose), whereas gallamine produces a small fall.

This result may serve to allay fears that a widespread depolarization of muscles may be harmful. The health-giving properties of muscular exercise reduce the significance of such fears; but it could still be maintained that the final result of a sustained depolarization localized to the end-plate region is different from that of repeated brief depolarizations of whole muscle fibers. Generalized potassium release can be taken as a possible index of the postulated harmful effect; and it is reassuring that it is so slight. It may still be valuable, however, to repeat these observations with patients whose ionic balance is disturbed.

Side Actions Related to Cholinergic Synapses

Actions Connected with the Parasympathetic Nervous System. The relatively cumbersome molecules of some relaxants may produce activity of an atropinic kind. In the laboratory a depressant action by *d*-tubocurarine on smooth muscle stimulated by acetylcholine can easily be demonstrated. The association of atropinic and curarizing action has an interesting corollary in the frog, in which atropine is a fairly powerful neuromuscular blocking agent; indeed, sometimes in the cat, a dose of atropine may be seen to deepen very slightly an incomplete block by *d*-tubocurarine. It is also interesting that with some other related alkaloids, such as the oxyacanthines, an atropine-like action is well developed.[9] For practical purposes, however, the atropinic effects of *d*-tubocurarine are probably negligible, especially since patients will most always have received medication with drugs such as scopolamine, and may well have received pethidine as well.

A more interesting case is the effect of gallamine on the heart rate. It has been shown by Riker and his colleages [10] that gallamine produces tachycardia by reducing activity of the vagus; and that this action is directed, not at vagal ganglia, but at post-ganglionic endings. Gallamine is equally effective in reducing the slowing of the heart produced by an injection of acetylcholine. Thus far gallamine's action can be characterised exactly as being analogous to that of atropine. The extraordinary feature is that gallamine seems to be devoid of other atropine-like effects. We have no clear idea as to how such a selective attack occurs. For practical purposes, the effect is important since it is exerted by gallamine in doses given clinically. The importance of this effect is simply that of any tachycardia produced by removing vagal inhibitory tone. For ordinary practice tachycardia is not of great importance; but any condition which exaggerates sympathetic activity renders gallamine less suitable for use, since the heart loses its possible reflex vagal protection.

Other relaxants do not appear to have any powerful, direct parasympathetic action. Sometimes a small atropine-sensitive fall in blood pressure can be produced by succinylcholine in animals; this has been disputed although the writer has seen it on occasion. It is clear that it is a minor phenomenon and is hardly likely to survive even the most trivial atropinic premedication. Decamethonium has no action of this kind, nor are atropinic or direct muscarinic effects significant for other relaxants.

Anticholinesterase Action. All the muscle relaxants, if exhibited in sufficient dose, can inhibit the cholinesterases of the body.[1] This however, is not necessarily of practical interest, and the question arises, how important is such inhibitory action. The case of decamethonium is interesting since it has a distinct anticholinesterase potency, with the interesting feature that it is somewhat more effective against so called "true" cholinesterase than against so called "pseudo" cholinesterase.[2] Careful study, especially by Zaimis,[11] has shown that none of the features of this neuromuscular blocking action can be attributed to anticholinesterase activity; and in the whole animal one cannot point to any physiological change which could be blamed on it. These are valuable results because decamethonium has been examined fairly intensively and its anticholinesterase activity has also been explored. This means that if we have any other agent with a similar or smaller anticholinesterase potency (in relation to neuromuscular potency), one can reasonably neglect that aspect of its action, for practical purposes.

A more important case is that of benzoquinonium. Its interesting molecule possesses oxygen as well as quaternary nitrogen atoms so disposed that one might even expect a distinct

anticholinesterase potency to be present. This is in fact the case and it is clear from clinical experience that this potency is sufficient to give rise to practical difficulties. Thus, to avoid excessive salivation or abdominal colic or bronchial secretion, a more thorough premedication with atropine or scopolamine than normal is recommended; it is interesting too that in the assessment of its neuromuscular blocking action, anticholinesterases are somewhat less effective as antagonists (although still exerting some action) than drugs such as *d*-tubocurarine. This last finding is perfectly intelligible if the cholinesterase is already partly inhibited (although the curare-like action is sufficiently intense to produce neuromuscular block). Under such circumstances the injection of a further dose of an anticholinesterase such as neostigmine will obviously have a limited field of effectiveness.

The Ganglionic Synapse. Ganglionic excitation by succinylcholine can be quite simply demonstrated. It is not a powerful action but large enough to reveal itself occasionally in clinical practice if a large or continued dosage of succinylcholine is employed. It is theoretically interesting since it illustrates the manner in which succinylcholine, consisting as it does of two acetylcholine molecules linked together, appears to display all the stimulant actions which acetylcholine can show. A decisive pressor response in man does not appear to have been described. But there is a tendency during the use of succinylcholine for the blood pressure to be maintained or to drift upwards in a way not usually experienced with other agents; such observations conform reasonably to pharmacological expectation. One cannot point to any special hazard attached to this, with one exception; if sympathetic vasomotor tone is being artificially increased in this way, an exaggerated sensitivity to a ganglion blocking agent, used for instance to induce hypotension, might appear so that a bigger fall of blood pressure would now be possible. The situation however would not differ from any other mild hypertension with which anaesthetists will already be familiar.

Ganglion block appears to be important only with *d*-tubocurarine. It is interesting that in a number of studies on the physiology and pharmacology of the ganglion, *d*-tubocurarine has been the standard drug to employ. Its potency is not far short of that of hexamethonium. It has been shown by Guyton and Reeder [12] to have a somewhat more intense action on parasympathetic functions than on sympathetic ones; thus salivary secretion and alimentary movement are blocked somewhat more effectively than contraction, say, of the nictitating membrane through excitation of the superior cervical ganglion. Interestingly enough, it was such a pattern of incidence of effect, together with contrasting patterns of effect seen with tetra-, penta- and hexamethonium, that encouraged the hope that ganglion blocking agents might possibly be produced to selectively block different sections of the autonomic nervous system. Despite determined investigations, however, a clinically useful selectivity has not been found.

The practical significance of ganglion block by *d*-tubocurarine does not seem to have emerged very clearly. Judging from its potency relative to other blocking agents, one would anticipate that it would be able to lower the blood pressure somewhat in a hypertensive, that it would produce postural hypotension, and that normally some modification of autonomic reflexes or a reduction of background autonomic activity such as secretions, sweating or intestinal movement, could be detected. One can find statements supporting some of these notions; but there has been no unambiguous proof that such actions are exerted. To establish and measure ganglion block by *d*-tubocurarine in the presence of premedicant and other drugs, and during the stress of a surgical procedure, is obviously a formidable undertaking, but it would be of value to attempt it.

The ganglion blocking agents, in general, have been shown to interfere with the excitation of chemoreceptors and other sensory endings by drugs such as acetylcholine or nicotine. This might be interpreted to mean that *d*-tubocurarine should be able to modify the normal sensory physiological responses. It must be emphasised, however, that it has not yet been shown that the response of chemoreceptors and sensory nerve endings to nicotinic drugs has any direct physiological significance.[13] If the response to nicotinic drugs is completely blocked, by hexamethonium or *d*-tubocurarine

or tetraethylammonium, the physiological responses (to CO_2 or anoxia, to rise in carotid pressure, or to touch) are still perfectly effective. There is no reason therefore to believe that *d*-tubocurarine will exert any effects in the body through being able to antagonize, as it undoubtedly can, nicotinic excitation of sensory endings. The significance of the possibility of such excitation may be no more than that acetylcholine can excite *any* sufficiently exposed afferent nerve ending; and this may be a fact, not so much about a physiological process at that particular site, but about the properties of exposed afferent terminations. Until there is proved to be a local release of acetylcholine at the sensory sites, together with apparatus for destroying it and synthesising it, there is no justification for assuming a cholinergic synapse of any kind to be present.

A final mention may be made of the interesting though somewhat puzzling results obtained by Lorente de No and later by Eccles [14, 15] on the action of *d*-tubocurarine on isolated ganglionic preparations (from turtle or rabbit). With deep curarization the ganglion might display, in response to an incoming train of volleys, and after the excitation was over, a striking after positivity; this is to be contrasted with the usual transient negativity with a modest after potential seen in the normal ganglion. The significance of this result is still obscure and it is worth noticing that it has only been obtained in well-developed form in isolated ganglia. The results suggest activity at inhibitory synapses in autonomic ganglia, interference by *d*-tubocurarine with the nerve terminals, as well as action by the drug at the surface of the post-synaptic membrane. These are, however, still speculative suggestions and no clinical inference can be drawn. The concept that *d*-tubocurarine can interfere with nerve endings was initially supported by claims that injection of *d*-tubocurarine within a nerve axone can paralyse conduction; but repetition of the latter experiment with refined technique has failed to show that this ion has any intra-axonal action.[16] It is probably best at present to think of *d*-tubocurarine action as being exclusively a process of competition with acetylcholine at synaptic receptor areas.

The Question of Central Actions

The discussion of the central action of curare-like substances dates back to the earliest experiments with these drugs. When impure preparations were used the possibility of important central actions was a serious one. With the pure compounds of known structure now employed the position is somewhat different, for all the muscle relaxants used in practice are salts of quaternary nitrogen. It is clear that there is little likelihood that these should be able to penetrate the central nervous system, when they are given by any route of administration other than directly into the cerebrospinal spaces. Thus, it is known that all the muscle relaxants are relatively inactive by mouth, indicating the extent to which epithelium forms a barrier to their penetration. The classical and courageous experiment by Smith and his colleagues,[17] in which several times a normal paralyzing dose of a *d*-tubocurarine preparation was given, shows decisively that in the presence of complete and long lasting neuromuscular block, cerebral function remains completely unimpaired and unmodified, as judged by the ability to think, remember and experience the usual sensations and emotions. More recent work by Eccles and his colleagues [18] on the Renshaw cell shows that only those curare-like substances which are not quaternary are able to interfere with this cholinergic synapse; thus the erythroidines can act but *d*-tubocurarine is ineffective. Similarly, only those anticholinesterases which do not contain quaternary groupings are able to potentiate transmission at the synapse. There are analogous observations with anticholinesterases as regards their central actions and their capability of inhibiting brain cholinesterase. Both among the amines and among the phosphorous-containing anticholinesterases, the extent of their central action is conditioned by the ratio of their fat to their water solubility, and any material which has a low fat solubility becomes inactive on central systems.[19] It is with considerable confidence, therefore, that one supposes that the relaxants discussed here will normally have no central action. If they are given centrally, then *d*-tubocurarine at least has dramatic effects, for it is a powerful convulsant, apparently exciting regions in the

basal part of the brain.[20] But no trace of evidence is yet available that this excitant action can be produced by intravenous administration.

It is necessary, however, to be cautious in making this generalization absolute for all clinical conditions. Although our understanding of the permeability of the blood brain barrier is distressingly sketchy there are a number of indications that conditions such as asphyxia, anaesthesia, dehydration, or haemorrhage may weaken the selectiveness of the entry from the blood to the brain. Under normal physiological experimental conditions all these measures are naturally avoided. In clinical practice, however, some of them may be unavoidably present. The problem therefore arises whether in special circumstances central actions, normally absent, may manifest themselves. Even now, one hesitates to assume that *d*-tubocurarine (which appears to be the most active centrally of the drugs under consideration) would exert any significant action. In animal experiments in which it was given centrally, directly into the cerebrospinal fluid, a dose of a few tenths of a milligram are needed to produce significant effects. In cats (the animal used in these researches) the total dose of *d*-tubocurarine needed to produce neuromuscular block is about 0.1 to 0.4 mg./kg. Thus the amount of *d*-tubocurarine required to produce significant action when administered directly into the brain is a large fraction of the amount required to produce neuromuscular block. If then the blood brain barrier was completely permeable, the dose of *d*-tubocurarine which the brain would receive in clinical practice might well be insignificant; for it would be, by a rough estimate, simply that fraction of the total dose of *d*-tubocurarine which would be brought to it by the fraction of cardiac output which goes to the brain. Since it is highly unlikely that the blood brain barrier ever breaks down completely (this indeed may be incompatible with life) it seems somewhat improbable that *d*-tubocurarine is ever likely to have significant central action in practice; and if not this drug, it seems less likely that the others in common use will have it.

There are of course reports in the literature of surgical operation made under muscle relaxants only.[21] These are countered by the somewhat distressing stories of patients in whom an anaesthetic has worn off while they are still paralysed, so that they experienced the pain of surgical operation as well as the muscular paralysis. Some care is needed in assessing either of these claims. Premedication may produce a satisfactory analgesia and the operation of suggestion might under the right circumstances produce a condition of light hypnosis, permitting occasionally an apparently normal surgical procedure to be carried out. It is conceivable that occasionally the peripheral actions of *d*-tubocurarine contribute to a sort of sedation; muscular relaxation (whether directly, or by a relaxation of contractile substance of the muscle spindles) is well known to be a means of inducing sleep. The reports by a patient of what happened at an operation, particularly if the patient had received premedicant drugs and an anaesthetic, must be regarded as untrustworthy since all these drugs are capable of interfering with memory and may produce flights of the imagination. It appears that for our best evidence as to central actions the data quoted earlier provide the surest guide.

Histamine Release

It is now known that a considerable range of organic bases can mobilize histamine from its bound state in the body.[22] Histamine appears to be bound in two ways. Part is contained in the mast cells, located especially in the skin, but widely distributed elsewhere, often in a perivascular position. The mast cells also contain heparin, and it has been tempting to think of the two as forming a complex of base and acid, although this is probably too simple a notion. When histamine is released, in anaphylaxis or by histamine-liberators, the mast cells lose their characteristic basophil granules and become distorted, although not destroyed. In the dog, at least, heparin is also released into the blood, rendering it less coagulable. The extent of mast-cell degranulation corresponds with the loss of histamine from a tissue. It seems probable, therefore, that the labile histamine in the body is largely mast-cell histamine. A large store of tissue histamine also exists, however, bound in some other way; for, especially in the intestine, high concentrations are present with no associated mast cells. This histamine cannot be released by liberators, and

indeed no way is known of mobilizing it without serious tissue damage. When, therefore, we discuss histamine release by muscle relaxants, it must be supposed that we are primarily considering the disruption of mast cells by these drugs.

Certain features of the release process are important. First, with the histamine-liberators, previous sensitization is not necessary. The release process, whether it is due to a sort of ion exchange in the mast cell of histamine for the basic liberator, or to an activation of mast cell lecithinase by interfering with a normal inhibitor, as Uvnäs and his colleagues suggest,[23] is a direct one requiring no previous formation of antibody or any similar material. This does not mean that all subjects will be equally sensitive to the effects of a histamine liberator. There are rather more sources of variation in responsiveness than usual, for the patient may be individual in the readiness with which his histamine is released, in the amount of labile histamine in his tissues, in the rate of disposal in his body, and in the reaction of his tissues to it.

A second important aspect of histamine release from mast cells probably arises from the fact that the mast cell contains about 1 per cent histamine,[24] although smooth muscle or blood vessels can respond to concentrations as low as 10^{-7} per cent. This means that tissues very close to a mast cell will be exposed to concentrations so high that it is doubtful if any tolerable dose of an antihistamine could ever succeed in antagonizing it. On the other hand, tissues more remote will be exposed to a lower concentration, depending on the diffusion gradient and on dispersal by the blood-stream, and hence may be sensitive to antihistamines. Therefore, the success or otherwise, of antihistamine therapy will depend on the anatomical relationship (still largely undefined) of the mast cells in which release occurs to the responsive tissues; and, in particular, failure of antihistamine therapy cannot be taken to exclude decisively the participation of histamine release in some pathological process. Of the responses to known histamine-liberators which are seen in animals, urticarial changes in skin can be considerably attenuated; hypotensive responses are reduced rather less; bronchospasm is rather resistant. Gastric secretion, of course, is not reduced, since even direct histamine-induced secretion resists antihistamines.

A third feature of significance is "refractoriness." After any substantial release, it becomes less easy to elicit a further release; and this refractory state persists for several days, depending on the intensity of the initial response. An obvious explanation is that once a mast cell has lost its histamine, it cannot release any more until it has made good its stores; this restoration appears to be a relatively slow process, taking in rats as long as a month after deep depletion. There are reasons for believing, however, that other factors may be involved in the refractoriness of the first day or two.

Fourth, histamine release, as judged by the depressor response to an intravenous injection of a liberator, is the more readily produced the more rapid the injection. Thus a dose near threshold may be ineffective if slowly given. This probably reflects the rather steep dose-response relation of the drugs; for a slow injection will, on its first circulation round the body, be at a lower concentration than a rapid injection. Since the release process appears to be initiated with great rapidity, the circumstances of this first exposure may be decisive. It must be remembered that even if a dose has been below threshold, it may reveal its presence if a second, normally subthreshold dose is given, by causing this second dose to become effective.

Lastly, there is evidence that anaesthetics can reduce the effectiveness of histamine-liberators. It is not clear how this is brought about; nor has the extent of the antagonism been explored in man, or investigated for different anaesthetics. This may constitute, however, a reason why histaminic effects are apparently rather uncommon at surgical operation, despite the known histamine liberating action of many of the drugs used (including *d*-tubocurarine, morphine, and pethidine).

The Activity of Muscle Relaxants in Releasing Histamine. All the muscle relaxants which have been tested exhibit histamine releasing action. The mere possession of such an action is of little significance, for it is displayed by a very large range of bases, if sufficiently high concentrations are administered. The crucial point lies in the comparison of doses required

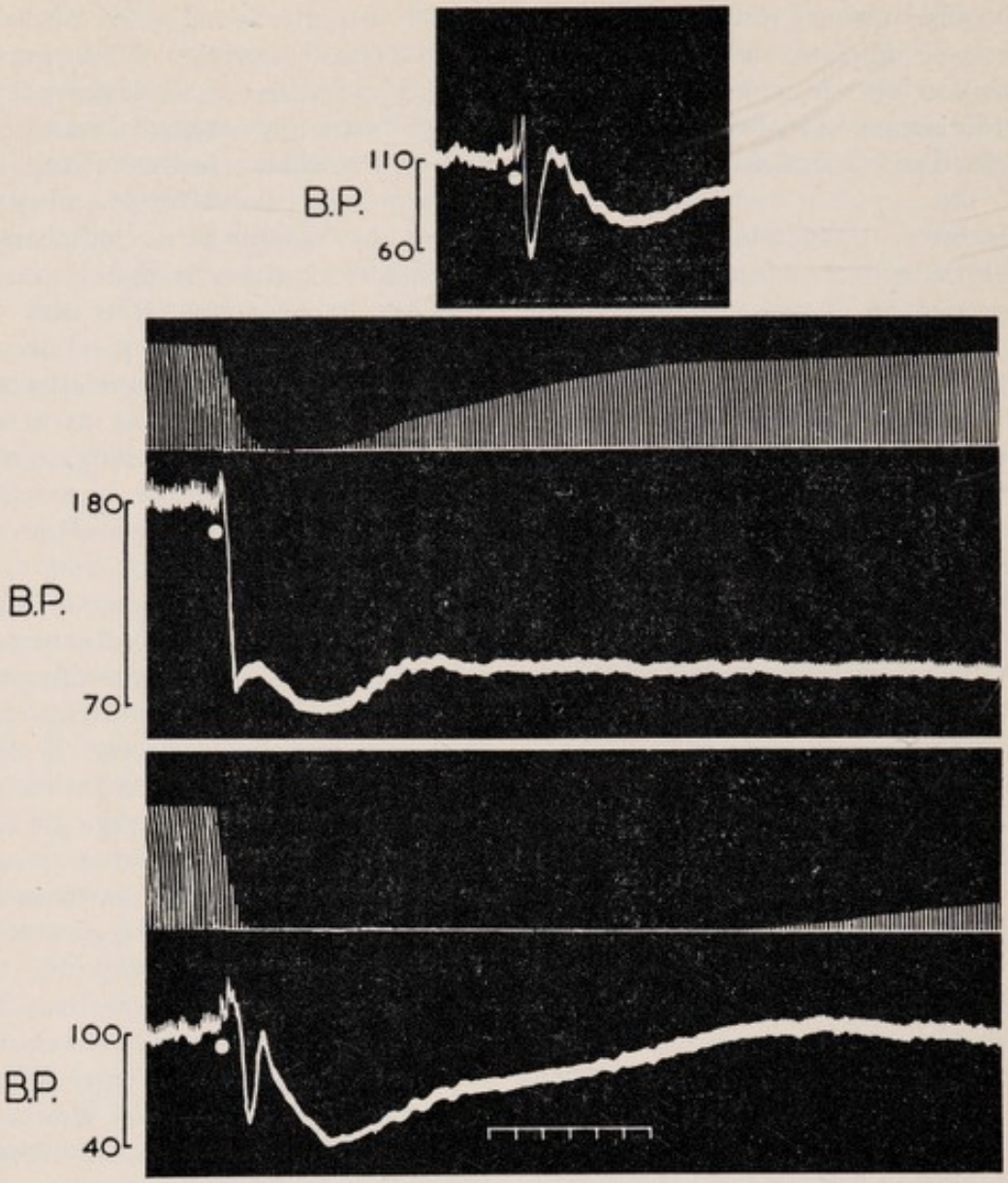

FIG. 1. *Upper tracing:* cat, 3.1 kg., chloralose. Blood pressure record. Injection of *d*-tubocurarine chloride 0.3 mg./kg. at white dot. *Middle and lower tracing:* cat, 2.7 kg., chloralose. Contractions of tibialis to excitation of sciatic nerve every 10 sec.; and blood pressure. Injections of *d*-tubocurarine chloride, 0.6 mg./kg. at white dots; second injection 95 min. after first. Time in minutes. The records show the delayed depressor response to a histamine-liberator; the temporary recovery of blood pressure after the first fall, followed by renewed hypotension; and the prolongation of the neuromuscular block by the hypotension.

to release histamine with those required to produce neuromuscular block.

By far the most important relaxant in this connection is *d*-tubocurarine. Some of the first important facts about histamine release were established with curare alkaloids, and *d*-tubocurarine is still a standard drug with which this reaction is studied. A problem arises as to how, in experimental work, an estimate of probable activity in clinical use can best be made. The writer believes that two tests are of special value which require mention. The first is on the blood-pressure of the cat anaesthetized with chloralose. When a specific histamine-liberator is injected, a highly characteristic response occurs. There is, first, a latency of 20–30 seconds, during which the only fluctuations of blood-pressure are those in response to the volume of the injection. Then an abrupt fall of blood-pressure occurs, of a speed similar

to that seen with histamine or acetylcholine; the difference lies in its occurrence 15–20 seconds later than with the latter drugs (fig. 1). Thereafter, as with histamine, a recovery of the blood pressure often occurs accompanied by tachycardia. If the dose is large this may wane, and a further, more or less prolonged hypotension resembling histamine-shock may ensue. If doses of a liberator only slightly above threshold are used, quantitative comparisons of potency can be made. The test has the advantage of being done in a whole animal whose sensitivity to histamine corresponds to that of man, and of exploiting a response directly comparable with one of the possible hazards in man, *viz.*, hypotension.

A second valuable test is that of intradermal injection in human skin. With due precaution this can be made quantitative, and offers the advantage that a human tissue is used. The obvious difficulty of interpretation arises, of course, as to how far local cutaneous responses mirror general responses to an intravenous injection. This difficulty, though always present, must not be overestimated; for it seems probable that in man, as in other species, the bulk of the histamine released comes from the skin, with muscle as the main subsidiary source.

Applying these tests to *d*-tubocurarine, a typical delayed depressor response in the cat can be obtained with doses of 0.3–0.5 mg./kg., and a significant wheal and flare can be produced in human skin with concentrations of around 0.1 mg./ml. The first result implies that a dose of 21 mg. in a 70-kg. man will be on the verge of histamine release; the second result that if the same dose is diluted in less than 210 ml. of plasma on its first passage round the circulation, histamine release may occur. Both tests show that there is a significant chance that in ordinary practice, *d*-tubocurarine may mobilise tissue histamine. The dimethyl ether has about the same absolute potency, but its higher neuromuscular activity renders histamine release less likely. The remaining muscle relaxants are rather inactive.

A problem arises, however, with succinylcholine. It is doubtful whether it would ever be active at doses less than 5 mg./kg.; and a dose as large as this would never be given as a single injection. A difference between succinylcholine and other relaxants, however, is that the first may be administered continuously or repeatedly, so that a large total dose may be received by the patient, and this total dose, given as a single injection, could well cause histamine release. What reason for confidence have we that succinylcholine infusions do not have a cumulative effect of this sort? The principal reason is our knowledge that succinylcholine is broken down in the blood, initially to the monocholine, then to choline. However, although the monocholine is much less active than its parent on the neuromuscular junction, it is (judged by intradermal injection) roughly equiactive in histamine release. If conditions existed, therefore, such that the monocholine accumulated significantly (and it is known that its hydrolysis is slower than that of the dicholine), it is difficult to exclude the possibility of histaminic actions.

There appears, then, to be some chance of histamine release with *d*-tubocurarine, and with large doses of succinylcholine. It is obvious from clinical experience that it must be a small chance, for otherwise these drugs would not be so successful. It may be that surgical anaesthesia is itself protective; or that the effect is too small to be significant under surgical conditions. The fact, however, that morphine, normally devoid of histaminic effects, and often used beneficially in cardiac asthma, may be lethal in bronchial asthma, leaves the suspicion that perhaps there is still something to be learned about histamine release by muscle relaxants in susceptible subjects.

Clinical Assessment of Side Actions

When one compares the known pharmacology of these drugs with clinical reports on their use, doubt arises as to how many of the actions apart from neuromuscular block have practical importance. But an important difference between laboratory work and clinical practice deserves emphasis. Most pharmacological analyses rest on experiments performed on a few tens of animals at most; but the drugs may be used clinically in thousands of patients. How is it possible, by necessarily limited animal work, to predict or assess for the clinician the possible abnormal responses which may occur, during his use of a drug both in healthy and

diseased men? Ultimately, of course, this assessment must be a clinical one. But in the preliminary stages, at least, it is useful to pay attention to two points. First, *any* action displayed by a drug, even if only in a particular species, may turn up in human practice. Thus the toxicity of oxygen at pressures below one atmosphere, especially marked in rats, has proved to have a human correlate; the excitant action of morphine in the cat likewise foreshadows a similar action in a few humans, contrasted with its normal "sedative" action. Secondly, it is sometimes possible, when a side-action by a drug is the therapeutic action of some other recognized drug, to assess the likelihood of the side-action by considering the known variations in response to the latter drug: thus the ganglion-blocking action of *d*-tubocurarine can be interpreted in the light of our experience with hexamethonium. Since as low a dose of hexamethonium as 1 mg. has been known to be effective in a hypertensive patient, clearly *d*-tubocurarine in normal dosage (equivalent perhaps to 5 mg. of hexamethonium) must sometimes be expected to do the same.

If this argument is admitted, then it would be reasonable for the clinician to seek from the pharmacologist both an accurate identification of all the significant side-actions of a new drug and also, where possible, an estimate of the intensity of those side-actions in terms of familiar drugs. A subsequent quantitative assessment of the side-actions in clinical practice then becomes of interest to the pharmacologist for the light it throws on human responses as compared with those of animals. Although the close study of side-actions is a less attractive and usually a less important side of therapeutics than, say, the attempt to discover new drugs or to explain the actions of familiar but mysterious ones, there can be little doubt that further attention to them would bring about a valuable refinement in anaesthetic technique.

REFERENCES

1. Foldes, F. F.: Muscle Relaxants in Anaesthesiology. Charles C Thomas, Publisher, Springfield, Illinois, 1957.
2. Paton, W. D. M., and Zaimis, E. J.: Methonium compounds, Pharmacol. Rev. **4**: 219, 1952.
3. Churchill-Davidson, H. C., and Richardson, A. T.: Decamethonium iodide (C10); some observations on its action using electromyography, Proc. Roy. Soc. Med. **45**: 179, 1952.
4. Masland, R. L., and Wigton, R. S.: Nerve activity accompanying fasciculations produced by prostigmine, J. Neurophysiol. **3**: 269, 1940.
5. Granit, R., Skogland, S., and Thesleff, S.: Activation of muscle spindles by succinylcholine and decamethonium. Effects of curare, Acta physiol. scandinav. **28**: 134, 1953.
6. Morris, D. D. B., and Dunn, C. H.: Suxamethonium chloride administration and postoperative muscle pain, Brit. M. J. **1**: 383, 1957.
7. Churchill-Davidson, H. C.: Suxamethonium (succinylcholine) chloride and muscle pains, Brit. M. J. **1**: 74, 1954.
8. Lincoff, H. A., and others: Effect of succinylcholine on intraocular pressure, Am. J. Opthal. **40**: 501, 1955.
9. Marsh, D. F., Herring, D. A., and Sleeth, C. K.: Curariform activity of N-methyloxyacanthine, J. Pharmacol. & Exper. Therap. **95**: 100, 1949.
10. Riker, W. F., and Wescoe, W. C.: Pharmacology of Flaxedil with observations on certain analogues, Ann. New York Acad. Sc. **54**: 373, 1951.
11. Zaimis, E. J.: Action of decamethonium on normal and denervated mammalian muscle, J. Physiol. **112**: 176, 1951.
12. Guyton, A. C., and Reeder, R. C.: Quantitative studies on autonomic actions of curare, J. Pharmacol. **98**: 188, 1950.
13. Douglas, W. W.: Is there chemical transmission at chemoreceptors? Pharmacol. Rev. **6**: 81, 1954.
14. Lorente de No, R., and Laporte, Y.: Synaptic transmission in sympathetic ganglion, J. Cell. & Comp. Physiol. **35**: suppl. 2, 9, 1950.
15. Eccles, R. M.: Responses of isolated curarized sympathetic ganglia, J. Physiol. **117**: 196, 1952.
16. Hodgkin, H. L., and Keynes, R. D.: Experiments on injection of substances into squid giant axons by means of microsyringe, J. Physiol. **131**: 592, 1956.
17. Smith, S. M., Brown, H. O., Toman, J. E. P., and Goodman, L.: Lack of cerebral effects of *d*-tubocurarine, ANESTHESIOLOGY **8**: 1, 1947.
18. Eccles, J. C., Eccles, R. M., and Fatt, P.: Pharmacological investigations on central synapse operated by acetylcholine, J. Physiol. **131**: 154, 1956.
19. Burgen, A. S. V., and Chipman, L. M.: Location of cholinesterase in central nervous system, Quart. J. Exper. Physiol., **37**: 61, 1952.
20. Feldberg, W., Malcolm, J. L., and Sherwood, S. L.: Some effects of tubocurarine on electrical activity of cat's brain, J. Physiol. **132**: 130, 1956.

21. Whitacre, R. J., and Fisher, A. J.: Clinical observations on use of curare in anaesthesia, ANESTHESIOLOGY 6: 124, 1945.
22. Paton, W. D. M.: Histamine release by compounds of simple chemical structure, Pharmacol. Rev. 9: 269, 1957.
23. Uvnäs, B.: Mechanism of histamine liberation, J. Pharm. & Pharmacol. 10: 1, 1958.
24. Graham, H. T., Lowry, O. H., Wahl, N., and Priebat, M. K.: Localization of Tissue Histamine in Mast Cells, Abstr. Comm. XIX Int. Physiol. Congress 404, Montreal, 1953.