The pharmacology of the toxiferines / by W.D.M. Paton and W.L.M. Perry.

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We owe to Boehm (1895) the classification of South American arrow poisons into tube, pot, and gourd (or calabash) curare—a classification based primarily on the type of container in which the curare was found. Since that time much botanical and chemical effort has been expended in attempts to distinguish and isolate the active principles of these different curares (see MacIntyre, 1947). The success of King (1935) in isolating and characterizing from tube-curare the crystalline alkaloid *d*-tubocurarine chloride has resulted in the widespread use of this particular alkaloid, or of preparations containing it, and the consequent amassing of detailed knowledge about its pharmacological actions. The pharmacological studies of other alkaloids have been directed largely to establishing no more than their potency, particularly because the most active alkaloids, those from calabash curare, have proved very difficult to isolate in quantities sufficient for pharmacological study. Thus Wieland, Bähr, and Witkop (1941) were only able to prepare a few micrograms of the materials which they named Toxiferines I and II.

Recently King (1949) has isolated, from the bark of *Strychnos toxifera*, which is known to be one of the principal ingredients of calabash curare, somewhat larger quantities to these two toxiferines, together with ten other substances, and we are indebted to him for supplying us with samples of eight of these alkaloids. The opportunity has thus arisen to study in some detail the properties of these substances and to compare them with *d*-tubocurarine. Toxiferines I and II were extracted as chlorides, the remaining ten as picrates, from 5 kg. bark. There were available for pharmacological test six of these picrates (Toxiferines IV, V, VI, IX, XI, and XII), about 3 mg. of each, and a somewhat more abundant supply of the two chlorides (Toxiferines I and II) amounting to 10 mg. of each salt.

Our experiments were intended to discover the main properties of the compounds and to analyse the type of block produced at the neuromuscular junction and at the ganglionic synapse, in view of the differences already described in the modes of action of other myoneural and ganglionic blocking agents (Burns and Paton, 1950; Paton and Perry, 1951).

METHODS

The methods used throughout were standard, and most of them were described briefly by Paton and Zaimis (1949); endplate potentials were recorded by the method of Brown and Burns (1949), and ganglion potentials as described by Paton and Perry (1951).

Results

Neuromuscular block

Effect on righting reaction of the frog.—The most rapid and economical method of assessing the potencies of the toxiferines was the classical one of determining their effect on the righting reaction of the frog. This has the additional advantage that it was the method used by Wieland, Bähr, and Witkop (1941) for toxiferines I and II. Our results with this method are summarized in Table I. Three sets of experiments

TABLE I

EFFECT OF TOXIFERINES ON THE RIGHTING REACTION OF FROGS

Toxiferine No.	March		August		October	
	ED50 μg./kg.	Potency × *d*.t.c.	ED50 μg./kg.	Potency × *d*.t.c.	ED50 μg./kg.	Potency × *d*.t.c.
I (chloride)	7.5	240			14	76
VI (picrate)			15	170	15	61
XI ,, ...			15	170	27	38
IV ,, ...			100	30		
V ,, ..			250	10		
IX ,, ...			400	6		
II (chloride)	4,600	0.4				
XII (picrate)			>1,160	<2		
d-tubocurarine chloride ..	1,800	—	2,500	—	900	—

were done, in spring, summer, and autumn; at each season the potency of *d*-tubocurarine was also determined. A sufficient number of animals was available during the spring and autumn assays to permit of a legitimate probit analysis of the results, and the figures for potency in terms of *d*-tubocurarine for these assays have been calculated from this analysis. In the summer assays, estimates of the ED50's were made by graphical interpolation, and the potency ratios with respect to *d*-tubocurarine were calculated directly.

The striking feature of these tests was the outstanding potency of three of the toxiferines, namely, Nos. I, VI, and XI, which were active at all seasons of the year in doses of less than 30 μg./kg. In the March estimate of the potency of toxiferine I, the ED50 was only 7.5 μg./kg., so that the dose to paralyse a 20 g. frog was then as low as 150 mμg. These figures for toxiferine I agree well with the rough figure of 300 mμg. for frogs of unspecified weight given by Wieland *et al.* (1941), and confirm that this compound and toxiferines VI and XI are the most potent known curarizing agents.

Of the remaining toxiferines, three are more active than *d*-tubocurarine (Nos. IV, V, IX), and the other two which we have tested are probably less potent.

Apart from differences in potency, the paralysis of a frog by toxiferines and by *d*-tubocurarine was much alike. With small doses, the animal was simply weakened, and the righting reaction was slowed but not abolished. Larger doses caused abolition of this reaction, but the animal was still capable of weak spontaneous movements and respiratory movements were still visible. A further increase in dose abolished all movements, respiratory or otherwise, although the heart could still be

seen beating through the thoracic wall. The whole gamut from the beginning of muscular weakness to complete paralysis was covered roughly by a 100 per cent increase in dose, both with the toxiferines and with *d*-tubocurarine. There was a definite difference in the duration of paralysis; the paralysis by *d*-tubocurarine was more rapid in onset and passed off more quickly than that due to the three most potent toxiferines.

We also found (Table I) that, whereas the potency of the toxiferines remains remarkably constant at different times of year, the absolute potency of *d*-tubocurarine varies considerably. It is this latter factor which is mainly responsible for the large swings in the relative potency of the toxiferines with respect to *d*-tubocurarine which were observed in the different assays.

It is known that there are many physiological differences between summer and winter frogs which, no doubt, account for the seasonal variations in the potency of *d*-tubocurarine. The relative constancy of the ED50's of the toxiferines for frogs at all seasons may be related to their remarkable constancy of potency in different species, described later.

Potency in other species.—In view of the very high potency of toxiferine I in the frog, together with the fact that our supply of this compound was relatively abundant, it was possible to extend our observations on its potency to other animal species. Table II summarizes the results of these experiments. The most striking

TABLE II

ACTIVITY OF TOXIFERINE I IN DIFFERENT SPECIES

Species	ED50 μg./kg.	Potency × *d*.t.c.
Frog (March)	7.5	240
Frog (October)	14	76
Mouse (righting reflex)	10	12
Rabbit (head-drop)	11	20
Cat (tibialis twitch)	15–20	15

fact about these observations is the similarity in the effective doses of toxiferine I, whether tested in frog, mouse, rabbit, or cat, the range of variation being no more than that among frogs at different seasons. The difference between the effective doses of *d*-tubocurarine for mammals and frogs presents a marked contrast.

In all species investigated, as in the frog, the onset of paralysis is slower and the duration of paralysis longer with the toxiferines than with *d*-tubocurarine. For instance, in the cat after an intravenous dose, the presence of toxiferine I is demonstrable two hours, or sometimes even three hours, later by the increased sensitivity of the animal to a further dose; and the period of actual paralysis is correspondingly longer than with *d*-tubocurarine.

Mechanism of muscular paralysis.—Although there could be little doubt that toxiferines, being the active principles of calabash curare, exerted their paralysing action by blocking transmission at the myoneural synapse, we thought it important to establish this for certain. To do this, it was necessary to show that the toxiferines affected neither muscle nor nerve directly. We found that there was no effect on

muscle, by observing that the response to direct stimulation of a cat's tibialis, fully paralysed to stimulation through its nerve, was completely unaffected. The usual way to demonstrate that a paralysis is not due to interference with conduction in the motor nerve is to record normal action potentials from the trunk of the nerve. The recording of an endplate potential, however, from a muscle paralysed with toxiferine, serves the same purpose. When the nerve impulse is blocked there is naturally no endplate potential; if, on the other hand, the nerve impulse is not blocked, a normal propagated response of the muscle fibre is elicited and the endplate potential is obscured by a spike potential. In neither case, therefore, can pure endplate potentials be recorded. Their occurrence, therefore, on nerve stimulation during motor paralysis is proof of block at the myoneural synapse. During paralysis after toxiferine I such pure endplate potentials can in fact be recorded, and Fig. 1 shows two endplate potentials recorded from the endplate region of a cat's gracilis after a dose of 200 μg. toxiferine I intravenously; the upper record is with complete paralysis, and the lower record was taken during partial recovery and shows the beginning of propagated spikes.

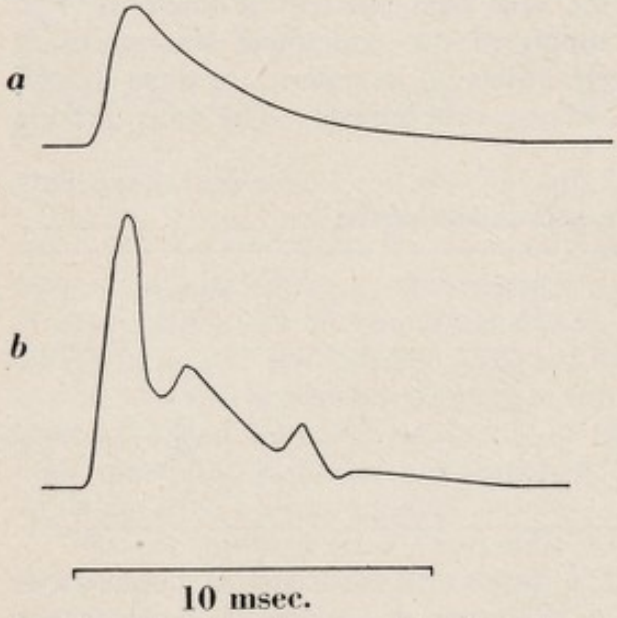

FIG. 1.—Cat, chloralose, gracilis. Records of endplate potentials. Electrodes on musculo-tendinous junction and endplate region. Intravenous injections. (*a*) After toxiferine I, 200 μg.; (*b*) later, during recovery from same dose of toxiferine I.

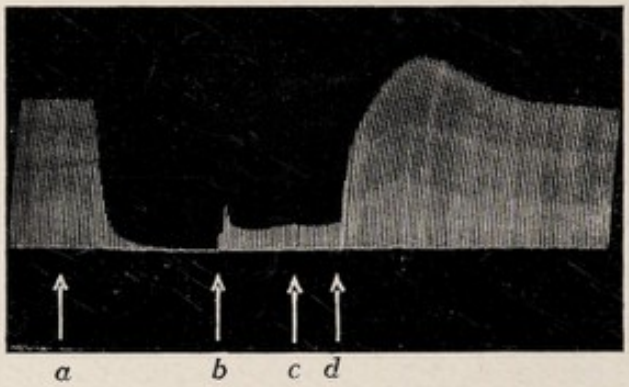

FIG. 2.—Cat, chloralose. Record of contractions of tibialis excited by supramaximal shocks to the sciatic nerve every 10 seconds. Intravenous injections. At (*a*) toxiferine VI, 20 μg./kg.; at (*b*) tetanus, 25 shocks per sec. for 10 sec.; at ( ) atropine sulphate, 0.3 mg./kg.; and at (*d*) prostigmine methylsulphate, 0.3 mg./kg.

Characteristics of neuromuscular block by toxiferines.—Several characteristic features of toxiferine-induced block of the cat's tibialis to nerve stimulation are shown in Fig. 2; 20 μg./kg. of toxiferine VI causes, after a latency of about one minute, a smooth and rapid onset of block. There is no preceding potentiation of the tension of the single twitch, nor any sign of muscular fasciculations; both these phenomena are typical of block by decamethonium and are absent with *d*-tubocurarine. Atropine causes a slight intensification of the effect of toxiferine VI. Prostigmine, given after the atropine, reverses the block very rapidly and even

produces a distinct potentiation of the maximal twitch tension. This antagonistic action of prostigmine was also shown for block due to toxiferine I and toxiferine XI.

When a brief tetanus of 25 shocks per second for 10 seconds is applied to the motor nerve at the height of the block (Fig. 2 (*b*)), the contraction of the muscle is well sustained, and the tetanus is followed by a definite reversal of the block to single shocks. The same decurarization after a tetanus was observed after toxiferine I and toxiferine XI. But the degree to which a tetanus was held, during block by the latter two toxiferines, was usually considerably less than with toxiferine VI. We also noted that there was considerable variation in the degree to which a tetanus was sustained, not only after doses of different toxiferines, but also after repeated doses of the same toxiferine.

It is only in this last respect that the toxiferines differ from *d*-tubocurarine or resemble decamethonium: for a nerve-excited tetanus is always poorly held with the former and well maintained with the latter. In the absence of an initial stimulant phase, the effectiveness of prostigmine, and the decurarization by a tetanus, the properties of the toxiferines are qualitatively identical with those of *d*-tubocurarine and dissimilar from those of decamethonium.

Antagonism to acetylcholine on frog's rectus.—One of the characteristic effects of *d*-tubocurarine is its antagonism to the action of acetylcholine on the frog's rectus

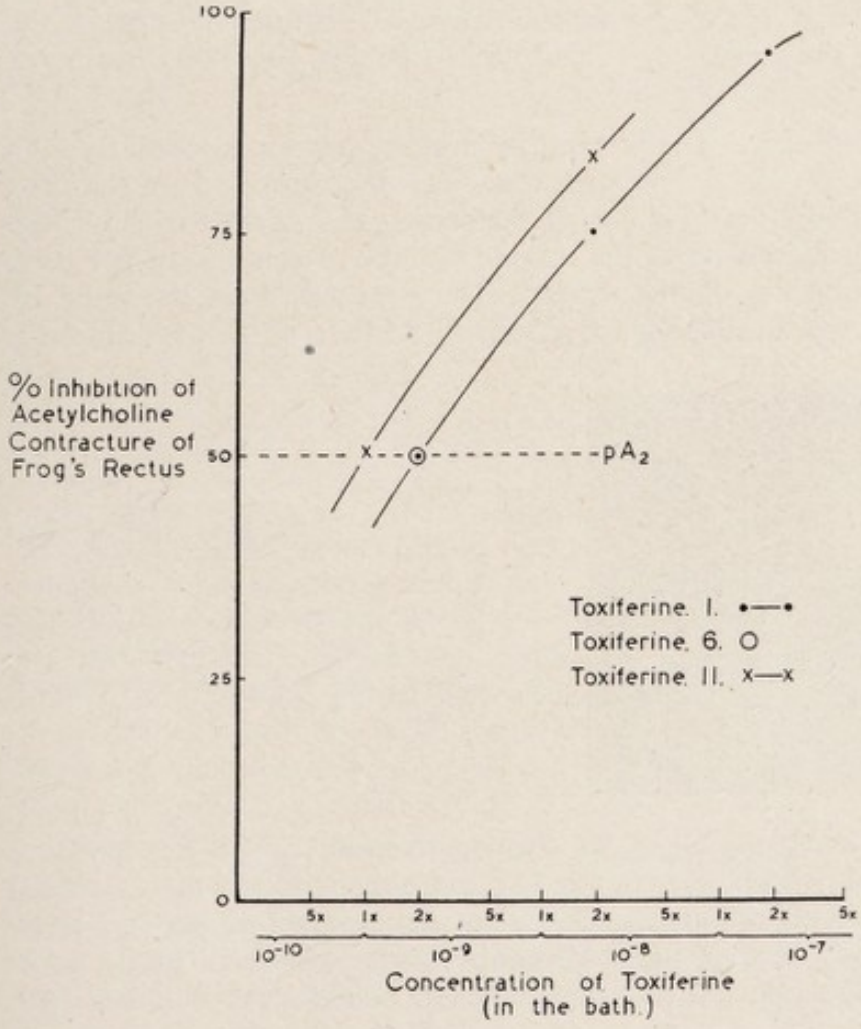

FIG. 3.—Frog's rectus abdominis. Graph of the antagonism by toxiferines to contracture produced by acetylcholine.

preparation: decamethonium, on the other hand, potentiates the effects of acetylcholine on this preparation, and itself produces a contracture. This experiment provides a simple and crucial test for analysing the nature of the neuromuscular block produced by toxiferines. The addition of a few micrograms of a toxiferine to the bath containing the frog rectus preparation produced a definite antagonism to acetylcholine, and there was no sign that the toxiferine itself could cause a contracture. The antagonism was measured quantitatively as follows: Several contractions to the same dose of acetylcholine were recorded; then toxiferine was added to the bath, and this reduced the acetylcholine response; the amount of acetylcholine necessary, in the presence of the toxiferine, to restore the response to the original size was then determined. Thus, if the original dose of acetylcholine must be trebled during toxiferine paralysis in order to produce the original effect, then two-thirds of this acetylcholine have been antagonized; i.e., there is 67 per cent inhibition. Fig. 3 gives the dosage-response lines relating the concentration of toxiferine in the bath with the percentage inhibition of acetylcholine calculated on this basis, and shows that toxiferine XI is more potent than toxiferines I and VI.

pA_2 (Schild, 1947) is the negative logarithm of the concentration of an antagonist which causes 50 per cent inhibition of some effect, and we have indicated it by a dotted line in Fig. 3. The single point determined for toxiferine VI corresponds exactly with a similar point for toxiferine I. The pA_2 for all three compounds thus lies between 8 and 9. This value is comparable with that of atropine against the action of acetylcholine on the guinea-pig's ileum (8.27; Schild, 1947) and illustrates quantitatively their extremely high activity.

Effect on respiratory muscles.—The respiratory muscles have a particularly high sensitivity to the toxiferines. Fig. 4 compares the effect of toxiferine I on the cat's tibialis with its effect on the minute volume of the same cat. A dose of 9 μg./kg. of toxiferine I produced a depression of the minute volume of some 5–10 per cent, without in any way affecting the tibialis twitch. The dose was then increased by the injection of 14 μg./kg., which, allowing for partial elimination of the previous dose,

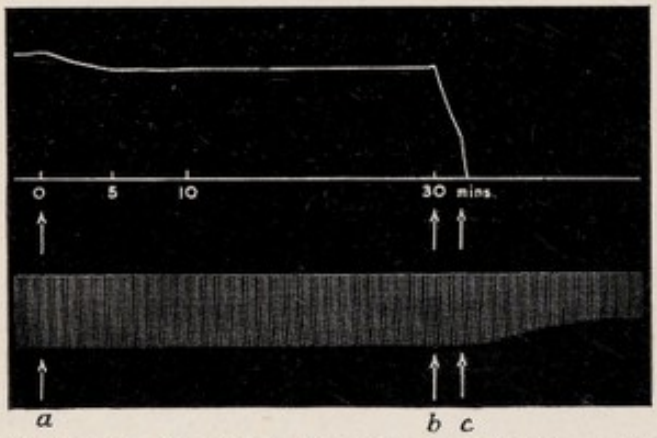

FIG. 4.—Cat, chloralose. Lower record, tibialis; nerve shocks' every 10 sec. Upper record, graph of respiration. Intravenous injections. At (*a*) toxiferine I, 9 μg./kg.; at (*b*) toxiferine I, 14 μg./kg.; and at (*c*) artificial respiration started.

increased the total dose to about 20 μg./kg., with the result that the respiratory movements were depressed to such an extent as to require the application of artificial respiration; the blocking of the tibialis muscle was of the order of 40 per cent only. The original 5–10 per cent effect on the respiration was accompanied by a rise in blood-pressure, presumably asphyxial in origin. Similar results were obtained with

toxiferine VI, but not with toxiferine XI, which had no selective action on the respiratory muscles.

Endplate potentials in the muscle blocked by toxiferines.—The analysis of the neuromuscular block by toxiferines was taken a step further by means of experiments on the cat's gracilis muscle, in which the convenient localization of the endplates makes the recording of potentials from them a simple matter. Fig. 1 shows a record of such an endplate potential, after an intravenous dose of 200 μg. toxiferine I. Its time-course is similar to that of the endplate potential produced in a muscle treated with *d*-tubocurarine.

The size of the endplate potential depends on the rate of excitation of the motor nerve, in the same way as does the tension of the motor twitch. If paired shocks are applied with different intervals between them (Fig. 5), the second endplate potential is reduced in size by slightly less than 10 per cent for intervals between 20 and 150 msec. With a shorter interval, summation of the two endplate

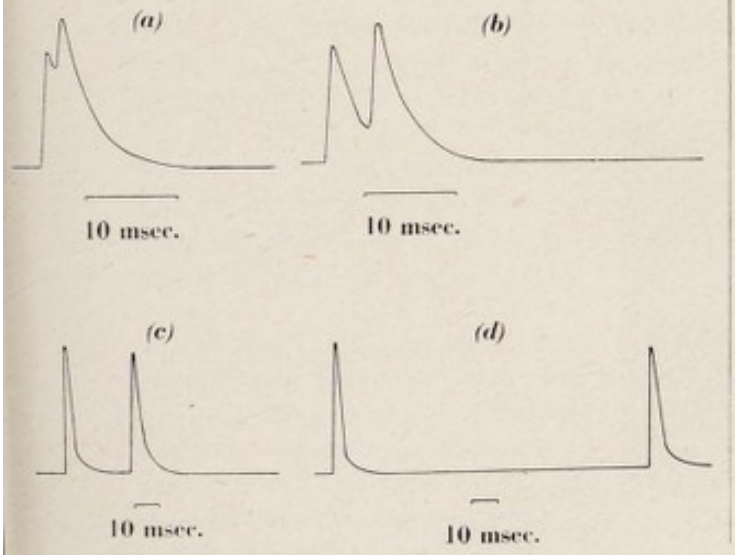

FIG. 5.—Cat, chloralose, gracilis. Records of endplate potentials after 75 μg. toxiferine I per kg. intravenously. Effect of paired shocks with different stimulus intervals: (*a*) 1.3 msec.; (*b*) 4.73 msec.; (*c*) 23.2 msec.; (*d*) 110 msec.

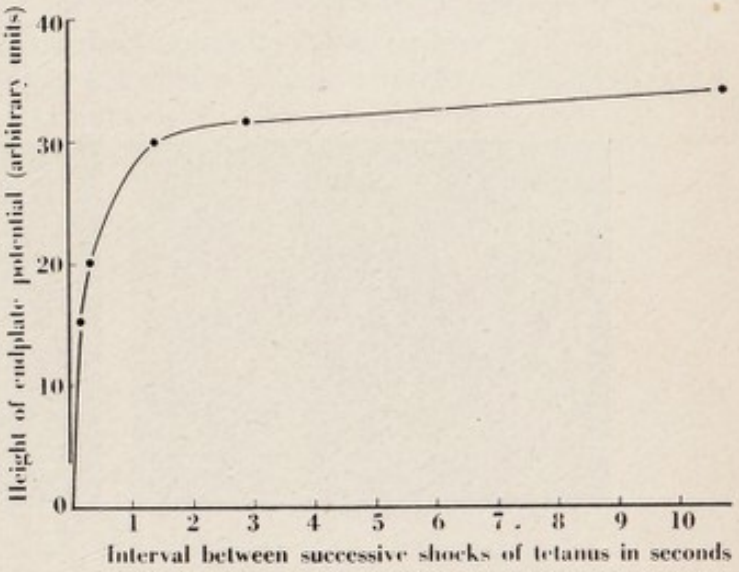

FIG. 6.—Cat, chloralose, gracilis. Graph relating the final height of the endplate potential during tetanic stimulation to the frequency of stimulation.

potentials occurs; but a correction can be made for the altered baseline of the second potential. It is then found that this depression in size of the second potential passes off gradually, as the interval is shortened, until the two potentials have the same height at an interval of about 5 msec. As the interval between the shocks is lessened still further, the second potential enters the refractory period of the first and begins to decay again.

When, instead of paired shocks, a tetanus is applied, the endplate potential falls continuously in magnitude until, in a second or two, it reaches a fairly constant level. This level varies with the rate of stimulation, and Fig. 6 is a graph of the relationship in one experiment between the final height of the endplate potential and the interval between the shocks of the tetanus. These results are obviously

relevant to the behaviour of the partially paralysed muscle during a tetanus, but we have not sufficient information to characterize the relationship further.

Immediately after such a tetanus, the endplate potential increases in size, often to such an extent that propagation of impulses is restored. During the succeeding few minutes, block slowly returns. This post-tetanic augmentation of the endplate potential is obviously the basis of the increase in twitch tension after a tetanus, described earlier in this paper. The magnitude of this post-tetanic effect appeared to be greater with the toxiferines than with *d*-tubocurarine.

Ganglionic block

Effect on the cat's superior cervical ganglion.—Doses of 100 μg. of toxiferine I, given by rapid injection into the lingual artery, cause no contraction of the nictitating membrane ; but when the nictitating membrane is in a state of contraction due to continued preganglionic stimulation of the cervical sympathetic, 50 μg. toxiferine I produce partial relaxation (Fig. 7). The degree of block is similar to that produced by 25 μg. *d*-tubocurarine, although the duration is much longer.

Fig. 8 is a record of action potentials obtained from the cat's superior cervical ganglion. The recording electrodes were placed on the ganglion and the cut post-

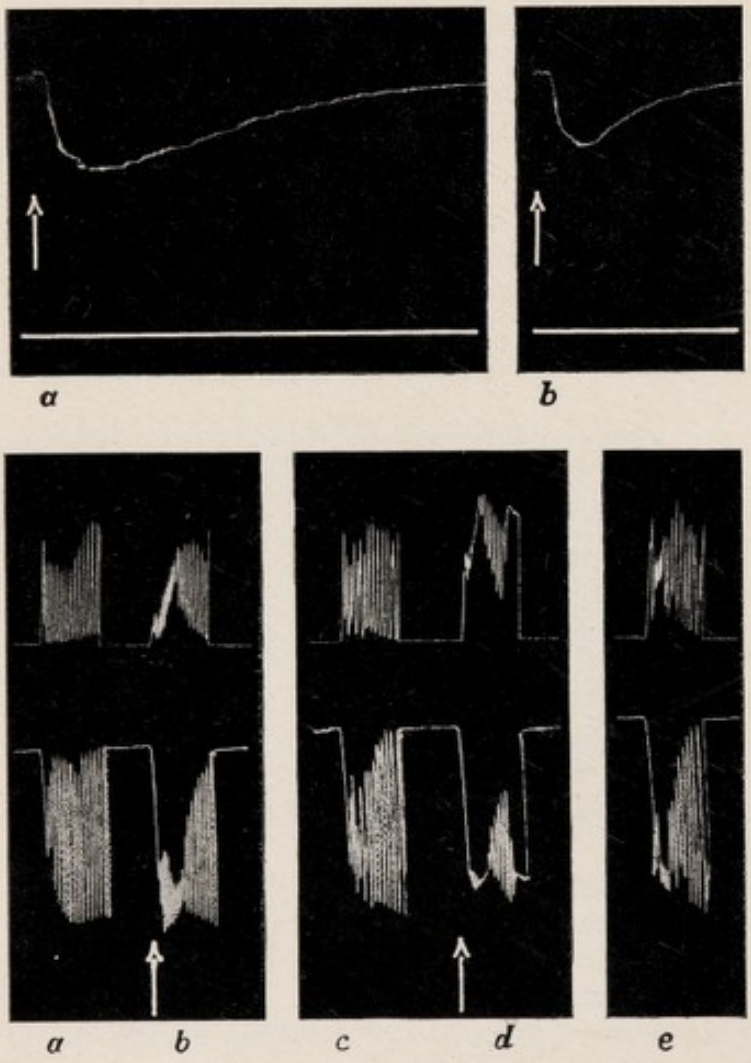

FIG. 7.—*Upper record :* Cat, chloralose, nictitating membrane stimulated preganglionically with supramaximal shocks at a rate of 10 per sec. Intra-arterial injections into lingual artery. At (*a*) 50 μg. toxiferine I; and at (*b*) 25 μg. *d*-tubocurarine. *Lower record:* Rabbit's ileum. Records of contraction of longitudinal muscle (top trace) and of volume change (bottom trace) in response to rise in pressure within lumen of gut. Normal controls (*a*), (*c*), and (*e*); before (*b*) 0.2 mg. *d*-tubocurarine and before (*d*) 0.1 mg. toxiferine I added to bath.

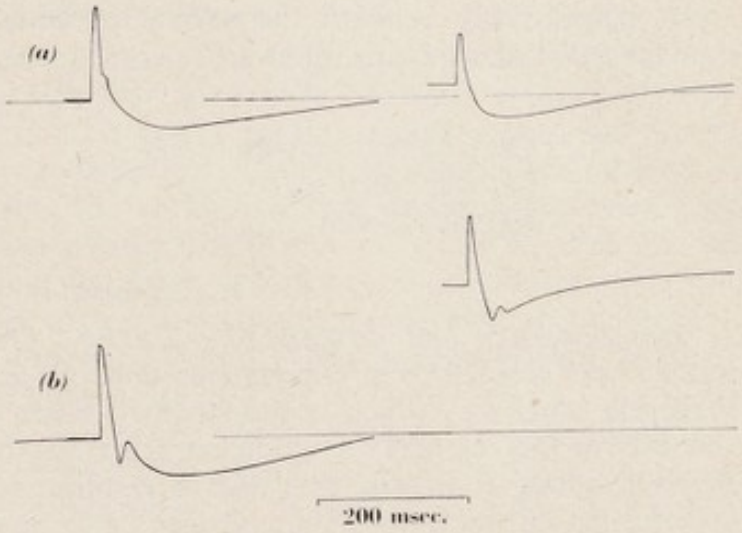

FIG. 8.—Cat, chloralose, superior cervical ganglion. Recording electrodes on ganglion and cut postganglionic trunk. Preganglionic stimulation. Intra-arterial injections into external carotid artery. (*a*) Before and after toxiferine I, 25 μg. (*b*) Before and after nicotine, 100 μg.

ganglionic trunk, the stimulating electrodes on the preganglionic trunk (Paton and Perry, 1951). The record (Fig. 8*a*) shows that the synaptic block by toxiferine is unaccompanied by a depolarization of the ganglion cells. This is to be compared with the records obtained with *d*-tubocurarine and with nicotine; *d*-tubocurarine block is also unaccompanied by depolarization, but after nicotine (Fig. 8*b*) there is a large depolarization of the ganglion cells accompanying the block. The mode of ganglionic blocking activity of the toxiferines appears, therefore, to be similar to that of *d*-tubocurarine.

Effect on the cat's parasympathetic submaxillary ganglion.—In one experiment a dose of 50 μg. toxiferine I was given intravenously to a cat, and records taken of the nictitating membrane stimulated preganglionically, and the salivary gland stimulated through the chorda tympani. In this experiment this dose produced a barely detectable effect on the nictitating membrane, together with a definite slowing of the rate of salivary secretion. A similar result was obtained with *d*-tubocurarine. This is in agreement with the general observation (Paton and Perry, unpublished) that the parasympathetic ganglion cells which supply the salivary gland are more sensitive to ganglion blocking agents than are the sympathetic ganglion cells supplying the nictitating membrane.

Effect on the myenteric plexus of the rabbit's ileum.—Fig. 7 (lower record) shows the effect of toxiferine I on the peristaltic reflex in the rabbit's ileum, the technique of Trendelenburg (1917) being used. The peristaltic waves of contraction of the circular muscle layer, in response to an increase in pressure in the lumen for one minute, are partially depressed by 0.2 mg. *d*-tubocurarine and by 0.1 mg. toxiferine I. It will be seen that 0.1 mg. toxiferine I is more potent than 0.2 mg. *d*-tubocurarine. *d*-Tubocurarine and toxiferine I affect only the waves of contraction of the circular muscle, which are dependent on the integrity of the myentric plexus, but not the contraction of the longitudinal muscle which is a myogenic response to the increased pressure.

Summary of ganglionic blocking actions.—The foregoing results show that the relative ganglionic blocking of toxiferine I compared with that of *d*-tubocurarine

varies considerably between the several autonomic ganglia investigated. Rough estimates of potency are as follows:

	Potency of toxiferine relative to *d*-tubocurarine
Cat's nictitating membrane	*c.* 0.5
Cat's salivary gland	3–4
Rabbit's ileum	*c.* 2.0

Other actions

Muscarine-like and atropine-like activity.—Our information about muscarinic activity was gleaned from experiments done for other purposes. A dose of 15 μg. toxiferine I per kg., which is too small to block sympathetic ganglia, given intravenously in the cat had no action on heart rate or blood-pressure, apart from the effects resulting from asphyxia due to respiratory paralysis. Furthermore, in the experiments on the rabbit ileum, a dose of 0.1 mg. toxiferine I did not itself cause any contraction of the gut. It follows from these observations that the muscarine-like activity of toxiferine I is certainly less than 1/1,000th that of acetylcholine, and must be negligible compared to its myoneural blocking action.

One test was made to determine whether toxiferine I had, like *d*-tubocurarine, any atropine-like activity on the guinea-pig's ileum. On this preparation the contraction to acetylcholine is either wholly or mainly an effect on the muscle fibres (Feldberg, 1950). The fact that toxiferine I produced an inhibition of the acetylcholine response of about 50 per cent (Fig. 9) indicates that the drug has an atropine-like activity. For this effect the approximate value for pA_2 is 4.2. Toxiferine I has, therefore, less than 1/5,000th the activity of atropine itself.

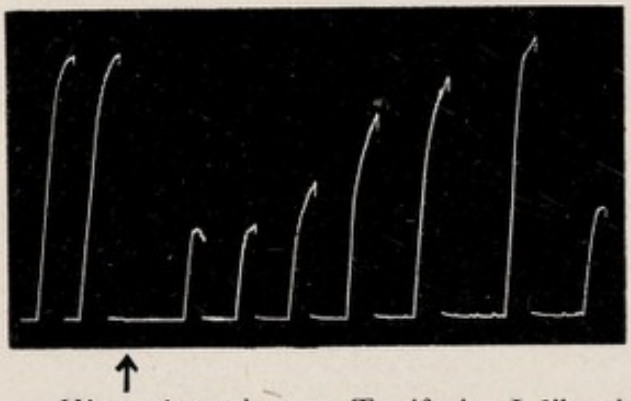

FIG. 9.—Guinea-pig's ileum. Records of contractions produced by 0.2 μg. acetylcholine, except for the final contraction which is the response to 0.1 μg. acetylcholine. At the arrow 0.1 mg. toxiferine I was added to the 15 c.c. bath, and remained in the bath only during the contraction immediately following.

Histamine release.—Toxiferine I, like *d*-tubocurarine, appears to cause the release of histamine, as shown by the following experiment. A solution of 1 mg./c.c. was injected in a volume of 0.02 c.c. intradermally into the skin of the forearm in two subjects, and a similar saline injection was made in an adjacent area. Five minutes after the injection there was a well-defined weal 5 mm. × 5 mm., with a flare 30 mm. × 25 mm. in each subject, with a sensation of itching at the sites of the toxiferine injection; at the control sites there was no more than the small lump formed by the injected fluid. It seems probable, therefore, that toxiferine I can liberate histamine from skin, although it is not a histamine-liberator of great potency; certainly its activity in this respect is small compared to its neuromuscular blocking power.

Discussion

In most respects the toxiferines share the pharmacological properties of *d*-tubocurarine. The paralysis is such that the muscle is always capable of a full contraction if excited directly, and such that a typical endplate potential can be recorded. The first observation is evidence that the muscle itself is not affected by the drugs. The second implies that the paralysis is not due to interference with nervous conduction ; for such a nerve-block could only progressively diminish the size of total propagated action potential at the endplate, and could not reveal the endplate potential itself. The two observations together constitute an unusual but valid way of demonstrating that toxiferine causes a true neuromuscular block.

Further common features to both drugs are the smooth onset of paralysis, antagonism by anticholinesterases, post-tetanic relief of block, and depression of the respiration. It follows from these findings that the paralysis must be due to a raising by the toxiferine of the threshold of the motor endplate to acetylcholine. We have not tested this directly, but the antagonism of toxiferine to acetylcholine on the frog's rectus abdominis verifies our conclusion on one type of skeletal muscle at least. It is clear, therefore, that the toxiferines must be classed with *d*-tubocurarine rather than with drugs such as decamethonium which cause neuromuscular block not by raising the endplate threshold to acetylcholine but by a prolonged depolarization of the endplate.

Nevertheless, there are certain important deviations from an over-all resemblance to *d*-tubocurarine which must be noted. In the first place, a muscle blocked with toxiferine often responds to a tetanus with a sustained contraction ; secondly, post-tetanic potentiation seems to be greater in the muscle exposed to toxiferine than in the muscle exposed to *d*-tubocurarine ; and thirdly, as Fig. 2 shows, prostigmine not only reverses block due to toxiferine, but also potentiates the normal twitch tension. This potentiation is not found in muscles blocked with *d*-tubocurarine.

In their actions on other organs, toxiferines show a qualitative resemblance to *d*-tubocurarine ; both produce a triple response in human skin, and have negligible muscarinic actions and a small but detectable atropine action. Representative members of the series can produce ganglion block ; and, on the superior cervical ganglion of the cat, at least, the block is of a similar type to that produced by *d*-tubocurarine, in that it occurs in the absence of any depolarization of the ganglion cells. The ganglionic activity of toxiferine is, however, of lower intensity than the neuromuscular action for, whereas it is 15 times as active as *d*-tubocurarine on muscle, it is less than 4 times as active as *d*-tubocurarine on all three ganglia tested in the cat and the rabbit. This provides yet another instance of the lack of correlation between the intensity of block at the myoneural and that at the ganglionic synapse. Since transmission at both synapses is mediated by acetylcholine, such discrepancies deserve closer examination.

The salient features of the pharmacology of the potent toxiferines are their high activity, and the uniformity with which that activity is displayed in different species. Weight for weight, they are more active than any other neuromuscular blocking drug, judged by any test. Since a substantial part of the molecule is anion, and since the toxiferine itself has certainly a high molecular weight, its molar potency is probably higher still, relative to other drugs. Certain other compounds,

indeed, have an activity of the same order in some species ; decamethonium iodide is active at 30 μg./kg. in the cat ; the dimethyl ether of *d*-tubocurarine at 10 μg./kg. in the rabbit. But no other compound displays so uniformly high an activity, not only in cat and rabbit, but in mouse and frog as well. Among the bewildering species differences found in the sensitivity to drugs of this type, importance must attach to a compound so exceptional in potency and uniformity of action. Given such a compound, stories frequent in the more adventurous traveller's tale of inexorable death after the merest scratch by a poisoned arrow take on some semblance of credibility.

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