Section of Anæsthetics

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An Assessment of Flaxedil (Gallamine Triethiodide, B.P.)

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Dr. W. D. Wylie: Flaxedil, or Gallamine triethiodide, as it is now named by the British Pharmacopœial Commission, is a British production of a synthetic curarizing agent (called tri-(β-diethylaminoethoxy)-benzene triethiodide) which was first synthesized in France by Bovet, Depierre and de Lestrange (1947). The first report on Flaxedil from this country was by Mushin, Wien, Mason and Langston (1949). They showed that Flaxedil produced muscle paralysis by neuromuscular block, that it exhibited a sparing effect on respiration, that it was effectively counteracted by neostigmine and that its period of action was shorter than that of tubocurarine.

Flaxedil has several possible clinical advantages when compared with tubocurarine and it is convenient to discuss some of the evidence substantiating this view. There is also a somewhat problematical disadvantage, namely tachycardia, which is worthy of further comment.

EXPERIMENTAL FINDINGS

Rapid breakdown.—Fig. 1 illustrates that Flaxedil is eliminated from the body more quickly than tubocurarine. This experiment was carried out on cats. The procedure was to inject

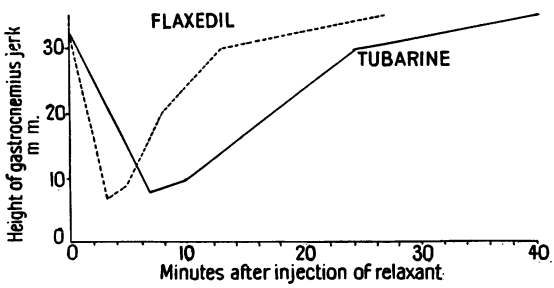

FIG. 1.

sufficient relaxant to produce a known depression of the normal gastrocnemius jerk of the cat. This ensured equipotent dosage and illustrated that the return to normal occurred about ten minutes sooner after Flaxedil than after tubocurarine.

Respiratory sparing effect.—Mushin *et al.* showed that in a comparison of the effect of these two relaxants on the gastrocnemius jerk in cats, a dose of Flaxedil which caused 100% depression left respiratory ventilation at 30% of normal, whereas with tubocurarine

respiratory ventilation was 25% of normal. They also showed that when decamethonium iodide was used the respiration was 45% of normal. On the conscious volunteer Mushin *et al.* showed that doses of about 40–70 mg. of Flaxedil could be tolerated without demonstrable decrease in pulmonary ventilation. The actual dosage given to any individual was estimated as that necessary to produce complete paralysis of the flexor muscles of the forearm as assessed by a dynamometer and of the muscles of the abdominal wall. Our experiments on conscious volunteers are in general agreement with this, though we have found that the paralysis is complete within one to one and a half minutes as against four minutes, and that even when neostigmine is given diplopia may persist for about one to two hours in some cases. Moreover, using a dose of ½ mg. per kilogram of body-weight, there is some diminution of maximum inspiration recorded on a spirometer, though not so great as with an equivalent dose of tubocurarine.

An assessment of the relative effect of the relaxants on respiration has been made on clinical cases under normal conditions of anæsthesia. This has appeared important and a recent paper by Paton and Zaimis (1950) has stressed the disadvantage of conscious volunteers who may have an abnormally high circulatory adrenaline, a fact which militates against a drug like decamethonium iodide. Clinically two series of cases serve to illustrate the respiratory sparing effect of Flaxedil. In a series of 70 upper abdominal operations anæsthesia was induced with a small dose of thiopentone and maintained at a light level with cyclopropane. A muscle relaxant was injected just before the surgeon incised the skin. The dose injected was either 20 mg. of tubocurarine or 100 to 110 mg. of Flaxedil, these being the rough equivalents suggested by Mushin *et al.* 45% of the cases given tubocurarine needed artificial respiration for some period of time as against 10% of the Flaxedil cases. The second series was of cases in which a muscle relaxant was used to facilitate intubation. Anæsthesia was with thiopentone, nitrous oxide and oxygen. Table I shows our results on 243 cases.

TABLE I

	Percentage of easy intubations				Percentage of easy intubations (Groups I and II) requiring artificial respiration
	Group I Very easy	Group II Easy	Group III Difficult	Group IV Failed	
Flaxedil 80 mg. 136 cases	27·9	52·2 (80·1)	16·2	3·7	8
Tubocurarine chloride 20 mg. 50 cases	26	50 (76)	18	6	26·3
Decamethonium iodide 4 mg. 57 cases	22·8	42·1 (64·9)	24·6	10·5	59

It was found before this series was started that the equivalent dosages of the three relaxants needed to produce an easy intubation were 80 mg. of Flaxedil, 20 mg. of tubocurarine and 4 mg. of decamethonium iodide. With these dosages it can be seen that the percentage of easy intubations is about equivalent for all relaxants. But the effect on respiration is considerably less with Flaxedil than with either of the others. Although we have included our experiences with decamethonium iodide we do not suggest that this is evidence of a marked respiratory depressant effect with this drug. The mode of action of decamethonium iodide at the neuromuscular junction is different from that of tubocurarine or Flaxedil, and its clinical effect on individual muscle groups varies also. The results show the limited effect of Flaxedil on respiration, and confirm its value as an aid to intubation. Incidentally they suggest that decamethonium iodide is not so satisfactory for facilitating intubation unless used in larger doses and then with consequent respiratory depression.

Counteraction by neostigmine.—The most interesting experimental results have been those which illustrate the very effective and immediate counteraction of the paralysis induced with Flaxedil by neostigmine. Fig. 2*a* shows a tracing of the depressant action of Flaxedil on the gastrocnemius jerk of the rabbit. The immediate, complete and sustained antidote effect of a dose of neostigmine is well illustrated. The procedure was to inject sufficient relaxant to produce depression of the gastrocnemius jerk to somewhere between 10 and 50 per cent of its initial height. A large dose of neostigmine was then injected and the return of the jerk to normal recorded. A large dose of neostigmine was used to ensure that its action was maximal. As will be seen when tubocurarine is injected (Fig. 2*b*) the effect of neostigmine, even when a considerably larger dose is used, is complete and sustained, but only completed over a period of ten minutes. Fig. 3 shows the direct comparison of these results on a graph.

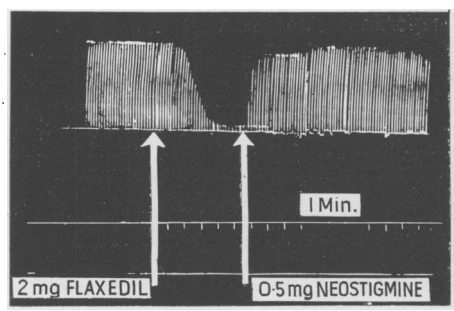

FIG. 2*a*.

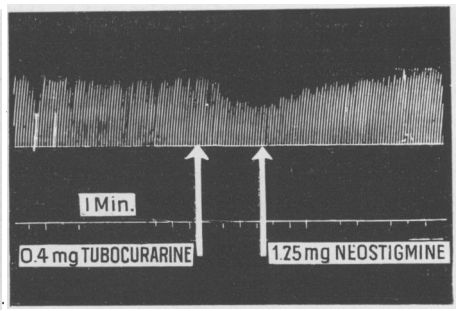

FIG. 2*b*.

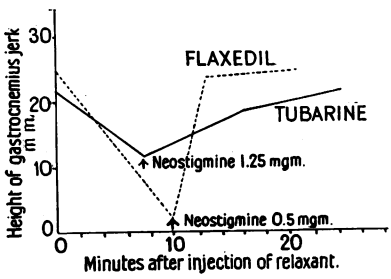

FIG. 3.

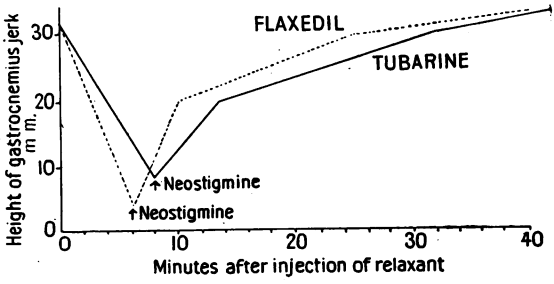

FIG. 4.

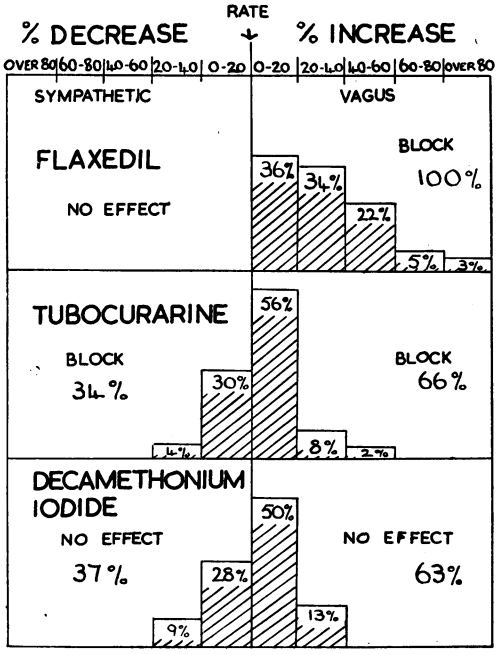

FIG. 5.—Pulse changes related to effect of relaxant on autonomic system.

Fig. 4 shows the results of a similar series of experiments carried out on the cat. Here the results are not so dramatic but nevertheless in keeping, and serve to illustrate the clinical impression that Flaxedil is completely and rapidly counteracted by a small dose of neostigmine—a point which is worth considering when it is appreciated that, apart from the remote possibility of neostigmine affecting the heart, there may be other systemic effects such as salivation and colicky abdominal pain, despite the buffering effect of atropine, when a dose of over 2·5 mg. is used. This point was confirmed on the conscious volunteer.

Tachycardia.—Occurrence: It is our opinion that tachycardia occurs frequently when Flaxedil is used. Indeed we believe that under certain conditions it is universal. Fig. 5 illustrates the results of 243 cases intubated under thiopentone anæsthesia coupled with a relaxant. Anæsthesia was maintained by nitrous oxide-oxygen sequence. For the conditions of the experiment the normal pulse-rate was taken as that found at rest in the ward before the operation. The dosages of Flaxedil, tubocurarine and decamethonium iodide were 80 mg., 20 mg. and 4 mg. respectively. The dosage of thiopentone was assessed as twice the sleep dose in every case and the pulse was taken at regular intervals over the ensuing period of the operation. The percentage increase over normal was recorded as the average of these readings. It will be seen that an increase in pulse-rate occurred in every case after the use of Flaxedil. There was a 20% increase in 56% of cases after the use of tubocurarine and a 20% increase in 50% of cases after decamethonium iodide. The significant factors are the absence of a decrease in pulse-rate in any case in which Flaxedil was used and the increases in pulse-rate of from 20% to 40% and 40% to 60% after Flaxedil as compared with the two other relaxants. It might be considered that the conditions of this experiment were too variable to offer a true comparison, but comparable results were obtained by stabilizing anæsthesia with thiopentone and nitrous oxide-oxygen sequence over a few minutes, estimating the pulse-rate and then injecting the dose of relaxant intravenously.

General considerations: Several interesting points emerge. The onset of tachycardia is practically immediate and coincident with the expected onset of curarizing effect. It occurs within one to one and a half minutes after the injection of Flaxedil and remains for a longer period of time than is apparent from the curarization of the patient. Moreover it appears to occur in some degree whatever the dose of Flaxedil. If 20 mg. of Flaxedil are injected during the course of a simple operation under light anæsthesia, though no apparent curarizing effect appears yet there is invariably an increase in pulse-rate. Moreover, additional injections of Flaxedil during the course of a long operation tend to reproduce a tachycardia or to sustain a pre-existing one, though there is little to suggest a summation effect in this respect.

The tachycardia is simple and uncomplicated. Continuous and frequent electrocardiographic recordings have shown no irregularity of rhythm. Indeed the absence of irregularities under light anæsthesia despite surgical stimulus has been a striking factor—always provided that the relaxation induced has been adequate. This factor, though, is common to the use of all relaxants in adequate doses.

Relationship of tachycardia to other factors: The direct cause of the tachycardia is the injection of Flaxedil into the body, but though the onset is almost immediate, its occurrence at all is dependent to some extent on one other factor, and that is the general anæsthetic agent. If cyclopropane is used for anæsthesia then the tachycardia may or may not occur, depending on the level at which anæsthesia is maintained. But with all other anæsthetics it varies very little. The type of premedication and the type of surgical stimulus, apart from direct operative procedures on the heart and its vicinity, exert very little influence. Though the level of adrenaline in the conscious patient may exert a considerable effect, nevertheless in the majority of such people there is a definite increase in pulse-rate associated with the injection of Flaxedil. This was assessed not only on volunteers, but on patients to whom a test dose was given prior to anæsthesia. The effect of a dose of neostigmine, even though buffered with atropine, was to produce an immediate decrease in pulse-rate. Furthermore it has been possible to produce some degree of tachycardia in patients with such differing pre-existing pulse-rates as a bradycardia of 50 beats a minute and a tachycardia of 120 beats a minute.

Causation of tachycardia: In an attempt to find the causation, animal experiments were carried out on both cats and rabbits, but it proved impossible to produce tachycardia either reflexly or by direct action on the heart in either of these animals. Table II gives a typical series of results when Flaxedil was injected into the left femoral vein of a cat. Recordings of the heart beat were taken on a moderately fast-running kymograph to distinguish individual beats, and connected via a mercury manometer to a cannula in the carotid artery. The direct action of Flaxedil on the heart was assessed by a perfusion experiment on the isolated heart.

TABLE II

Experiment	Dose of Flaxedil mg./kilo	Heart-rate Beats per 15 secs. Before injection Flaxedil	15/20 secs. after injection	At height of depression of jerk	% depression of gastrocnemius
1	0·4 mg.	48	50	—	—
2	0·4 mg.	50	52	48	30
3	0·65 mg.	55	56	49	90
4	0·8 mg.	58	56	57	95

(Normal heart-rate for cats is 50 per 15 secs. approximately.)

The control of the heart-rate is the balanced result of vagal and sympathetic action on that organ, either of which may be indirectly or directly affected by anæsthesia. A glance at Fig. 5, which further illustrates our results on intubated cases under nitrous oxide and oxygen anæsthesia, would suggest that Flaxedil is the only one of these three relaxants to have an unbalanced action. In fact we know that decamethonium iodide has little effect on either sympathetic or vagal ganglia and that tubocurarine affects both. Flaxedil blocks vagal ganglia only, and has little effect on the sympathetic. It is interesting to note the relative effect of tubocurarine and Flaxedil on the autonomic ganglia. Table III is taken from

TABLE III

	Ratio of curarizing action to autonomic block action Sympathetic	Vagus
Flaxedil	40	4–6
Tubarine	4	1–2·5

(After Jacob and Depierre, 1950.)

a recent paper by Jacob and Depierre (1950) and shows the ratio of the curarizing activity to the autonomic block activity. These figures imply that 40 times as much Flaxedil is needed to block the sympathetic completely as is needed to produce muscle paralysis, whereas only 4 to 6 times as much is needed in the case of the vagus. With tubocurarine 4 times the curarizing dose is needed to block the sympathetic as against 1 to 2·5 times for the vagus. The ratio of sympathetic blocking dose to vagal blocking dose of Flaxedil would therefore be 8 : 1 as compared with 2 : 1 for tubocurarine. Without doubt the effect of Flaxedil on the vagus predominates over its effect on the sympathetic, while with tubocurarine by comparison the effect is not so unbalanced. Nitrous oxide exerts no effect on the vital organs of itself, but cyclopropane exerts a direct effect on the sino-auricular node and conducting mechanism of the heart. Thus it circumvents vagal block, and of its own accord may depress the cardiac rate. This accounts for the fact that tachycardia is not universally found when Flaxedil is used with cyclopropane anæsthesia. Ether has little or no effect on the increased heart-rate induced by Flaxedil. It is interesting, too, to compare the effects of an injection of a known vagal inhibitor such as atropine on the human. If a dose of 1/50 gr. (1·3 mg.) is given intravenously there is an immediate increase in pulse-rate of from 10 to 40 beats per minute. The failure to produce tachycardia in cats and rabbits may be explained by their considerable lack of vagal tone as compared with the human. Any alteration in that tone might therefore be expected to produce a less marked effect in these animals than in the human. However, Wien (1950) has recently produced tachycardia in dogs when using Flaxedil, and when their vagal tone has been increased by morphine.

From these results we would suggest that tachycardia occurring clinically when Flaxedil is used is due to vagal block unaccompanied by sympathetic block.

Implications of tachycardia: A rapid action of the heart affects that organ in two ways. First it causes the ventricles to expend more energy and second it shortens the time for recovery between beats. The actual heart-rate and the duration of the increased rate are factors to be noted when assessing the clinical implications of a tachycardia, but most important are the reserves of the heart. If the heart is relatively normal then it is extremely unlikely that a tachycardia such as that produced by Flaxedil could produce any serious disturbance. However, if the reserves are already diminished then a tachycardia might conceivably exhaust them and lead to the possibility of acute cardiac failure. Clinically we have had no cases in which a tachycardia produced by Flaxedil could be said to have caused trouble in this way, but we feel that in prolonged major surgery on patients with pre-existing cardiac disease Flaxedil may not be the relaxant of choice.

Other vagal block effects.—A knowledge of the effect of Flaxedil on the autonomic system has led us to look for other associated phenomena. We have already shown the advantage

of Flaxedil for intubation, and how a dose of 80 mg. is equivalent for this purpose to 20 mg. of tubocurarine. This may be due to the specific effect on the vagi which depresses the glottic and associated reflexes. This effect also would be expected to dilate rather than constrict the bronchial tree, and though there is no clinical or experimental proof to show that this is the case, experience with Flaxedil during bronchography has suggested that it occurs.

An interesting effect of the unilateral action is frequently seen when hypertensive patients are anæsthetized and when Flaxedil is used for relaxation. It is a peculiarity of patients with arteriosclerotic disease that they react more actively to drugs which affect the sympathetic ganglia than otherwise normal individuals. This is noticeable for example when pentamethonium bromide is used for controlled hypotension, since only a small dose is needed in such cases. Similarly with Flaxedil it is not uncommon to see a rise of blood pressure and usually a maintenance of the normal. Wilson and Gordon (1949) in their paper on Flaxedil noted the rise in blood pressure and attributed it to light anæsthesia. However when tubocurarine is used on similar patients one expects some slight fall.

Histamine release.—Both Flaxedil and tubocurarine liberate histamine, but the amount is considerably less with Flaxedil. In animal experiments Mushin *et al.* showed that with Flaxedil the amount of histamine was 1/5 to ½ less than with tubocurarine, and an injection of Flaxedil into the arterial supply of the hindleg of a dog had no effect. When tubocurarine was injected there was a slight fall of pressure and dilatation of the vessels. Dos Santos and Soares (1950) have injected tubocurarine intra-arterially in the human and produced swelling and œdema of the limb, whereas with an equivalent dose of Flaxedil there has been no effect. We have noted no effects which we could reasonably put down to histamine other than some flushing of the skin and possibly a slightly increased bleeding at the site of operation. However the use of antihistaminics has not diminished these effects. Interestingly enough on some conscious volunteers there was a marked flushing of the skin and a great sense of warmth associated with the onset of paralysis. We have had no cases of bronchospasm nor gross hypotension associated with the use of Flaxedil.

Fate of Flaxedil in the body.—Flaxedil is not broken down in the body. It is excreted unchanged by the kidneys and thus an adequate renal function is a prerequisite for its use. It has been estimated that the greater proportion of a given dose is eliminated within two hours and to this extent any further doses given within this period are bound to be cumulative. From our experience we do not believe that people show a sensitivity to Flaxedil nor that a previous dose renders that person sensitive to a further dose. We feel that a second dose given before complete elimination of the original dose, even though no apparent curarization persists, may lead to an enhanced effect simply due to cumulation. As with tubocurarine, the addition of a central respiratory depressant or of a small quantity of ether may produce an effect which is easily mistaken for excessive neuromuscular paralysis by the relaxant.

Dr. A. G. Doughty:

CLINICAL FINDINGS

From the point of view of the clinical anæsthetist there are four important differences between Flaxedil and tubocurarine. These are:

I. With Flaxedil there is a greater margin between muscular relaxation and diaphragmatic paralysis.

II. Flaxedil has an equally effective but shorter period of action.

III. Flaxedil's action is more readily and rapidly reversed by neostigmine.

IV. Flaxedil does not lower the blood pressure.

We will now describe the use of Flaxedil in clinical anæsthesia under these four headings and will attempt to show how the experimental findings may be applied in practice.

I

Abdominal relaxation.—The most important role of the relaxants in anæsthesia is undoubtedly the production of relaxation of the abdominal wall without resort to deep general anæsthesia. Anæsthetists are now very familiar with the scope of action of tubocurarine in anæsthesia for abdominal surgery, so by this yardstick the properties of Flaxedil may conveniently be judged.

Mushin has estimated that a dose of 15 mg. of tubocurarine is approximately equivalent in curarizing potency to 80 mg. of Flaxedil. Clinical use of the two drugs for abdominal surgery has confirmed the accuracy of this estimate.

There is a very wide variation in the techniques used in administration of relaxants for this purpose, so it is difficult to compare and contrast tubocurarine and Flaxedil with any degree of accuracy. We propose to mention two commonly used techniques, because we believe that they best serve to illustrate the differences between the drugs under discussion. These are, firstly—induction with thiopentone, injection of relaxant, and maintenance of anæsthesia with cyclopropane without controlling the respiration; and secondly—induction with thiopentone, injection of a paralysing dose of relaxant, followed by controlled respiration with nitrous oxide and oxygen, relaxation being maintained by subsequent small increments of relaxant as required.

With the first technique, namely thiopentone, single dose of relaxant and cyclopropane without controlled respiration, there seems to be little difference in the quality of the relaxation provided by the two drugs, or in the time for which relaxation lasts. It is possible, of course, that the anæsthetist instinctively compensates for the shorter period of action of Flaxedil by maintaining the patient at a slightly deeper level of anæsthesia. The difference between the two drugs is apparent on comparing the character of respiration. With Flaxedil, the characteristics of third-plane chloroform anæsthesia are simulated. Breathing is quiet, the respiration mainly diaphragmatic, but there is still sufficient tone left in the lower intercostals to fix the lower ribs so that the diaphragm can contract in a co-ordinated manner. With tubocurarine in equivalent doses, paralysis of the lower intercostals is more marked, and a pronounced chin-tug is an indication of the inco-ordination and the relative inadequacy of the diaphragmatic respiration. This advantage of Flaxedil over tubocurarine is particularly welcome in gynæcological laparotomies when respiration may be embarrassed by the Trendelenburg position and abdominal packs.

With the second technique, namely, thiopentone, paralysing dose of relaxant followed by controlled respiration with nitrous oxide and oxygen, Flaxedil is not so satisfactory. In order to keep control of the respiration a very large initial dose of the drug is necessary, and, owing to the readiness with which diaphragmatic respiration returns, very frequent maintenance doses of Flaxedil are needed. Once spontaneous respiration has returned, relaxation soon becomes unsatisfactory in the upper abdomen if the patient is having only nitrous oxide and oxygen as the supplementary general anæsthetic. For the type of controlled respiration required for this technique, we find that tubocurarine is more suitable owing to its prolonged action in depressing the activity of the diaphragm and the more gradual wearing off of its relaxant effect.

If, at the end of an operation, relaxation for sewing up the peritoneum is insufficient, we would use a small dose of Flaxedil rather than tubocurarine as its effect is more immediate and wears off more rapidly.

Thoracotomies.—At this point it is convenient to mention the use of Flaxedil in thoracotomies because the same difficulties in maintaining control of respiration arise. If nitrous oxide and oxygen alone are used for the accompanying general anæsthetic, it is necessary to give a large initial dose of Flaxedil and very frequently repeated maintenance doses of the drug. Incidentally, as the heart is so readily visible to the surgeon, he may find that the tachycardia induced by large and repeated doses of Flaxedil is very disquieting.

Although our experience with Flaxedil in chest anæsthesia is small, we prefer the better control of respiration afforded by the longer-acting tubocurarine.

Cæsarean section.—Obstetric surgeons vary in their demands for relaxation in this operation. Some will find the already well-stretched recti no obstacle to their progress, while others demand relaxation sufficient to allow large packs to be placed between the intestines and the uterus. Whatever the surgical requirements, it is well recognized that the patient must be given the minimum of anæsthetic agents until the baby has been extracted. The maintenance of this light anæsthesia has been made easier and safer by the reflex depressant effect of a muscle relaxant.

When tubocurarine is used, its marked depressant effect on the intercostal muscles and the restriction of diaphragmatic movement by the gravid uterus very often make assisted respiration essential if maternal anoxia is to be avoided. In equivalent doses, Flaxedil does not paralyse the intercostals so markedly and assisted respiration is rarely needed. We therefore prefer to use it in Cæsarean section rather than tubocurarine, and give a dose of 60–80 mg. immediately after induction of anæsthesia.

External versions.—Another application of the effective but short-lived abdominal relaxant effect of Flaxedil is in the anæsthesia for external versions. Of all obstetric operations this is considered to require the most profound depth of anæsthesia. Some obstetricians would still like their patients to be given deep chloroform, while the majority regard ether to

the third or fourth plane as absolutely essential. We believe that, by the use of Flaxedil, the mother can be spared a deep general anæsthetic with its unpleasant sequelæ (Doughty, Hindle, MacDonagh, Sturton and Wylie, 1950).

In the majority of cases failure by the obstetrician to turn the baby without an anæsthetic is due to the mother's inability voluntarily to keep her abdominal muscles relaxed during the procedure. This difficulty can be overcome by giving her a small dose of thiopentone together with 60–80 mg. of Flaxedil. Anæsthesia is continued with nitrous oxide and oxygen. In most cases the uterine muscle will remain passive and allow the operator to turn the fœtus without opposition. In a smaller number of cases the uterus is irritable, particularly if the attempt at version is made after the thirty-sixth week of pregnancy. This irritable state may sometimes be appreciated by feeling the hard uterus through the mother's abdominal wall even before the induction of anæsthesia. In these circumstances, Flaxedil cannot be expected to relax the smooth muscle of the uterus and ether will have to be given. However, if anæsthesia is induced with a small dose of thiopentone and relaxation of the abdominal wall established with Flaxedil, it is quite surprising what a small amount of ether is required to relax the uterus. The mother is thus spared the soaking in ether which she would have had if no Flaxedil had been given.

Flaxedil in intubation.—The rapid establishment of an endotracheal anæsthetic has long been the goal of anæsthetists. During the last three years the use of muscle relaxants to facilitate intubation has become increasingly popular, though there are some quarters in which the method has not found favour.

We have attempted to make a clinical assessment of the relative merits of Flaxedil, tubocurarine and decamethonium in facilitating intubation. The ideal we aimed at was, first and foremost, to provide conditions in which an easy atraumatic intubation could be carried out. At the same time it was desirable that the dose of relaxant should not be such that the patient would require artificial respiration following intubation. The dose of thiopentone given with the relaxant was twice that required to send each patient to sleep. We classified each intubation into one of four groups according to the ease or difficulty of the intubation (Table I).

These figures show that with a dose of Flaxedil of lower curarizing potency than the dose of decamethonium or tubocurarine, the highest percentage of easy intubations was achieved.

Table I also shows the number of cases requiring artificial respiration of those in whom an easy intubation was carried out.

These figures suggest that Flaxedil is the most suitable drug of the three in establishing endotracheal anæsthesia. Of course better results would be obtained with all three drugs by varying the amounts of thiopentone and relaxant used in the light of one's experience of the method. But in order to make a fair comparison, we had to adhere to a fixed standard of dosage (Doughty, 1950; Doughty, Hindle, MacDonagh, Sturton and Wylie, 1950).

Bronchoscopy.—The insertion of a bronchoscope is but a step away from laryngeal intubation, yet there are many difficulties in providing a satisfactory general anæsthetic for it. From the surgeon's point of view an efficient topical analgesia may be the most satisfactory contribution that the anæsthetist can make, as the conscious patient can, to a certain extent, control his coughing. From the patient's point of view both the application of the "local" and the bronchoscopy itself must be a very unpleasant experience, so, if adequate conditions for the surgeon can be provided, a general anæsthetic has obvious advantages.

Our experience with Flaxedil in facilitating intubation can be applied to anæsthesia for bronchoscopies. Here it is of particular importance that the passage of the bronchoscope should be easy and that artificial respiration during the bronchoscopy should not be necessary.

We have had very satisfactory results by inducing anæsthesia with thiopentone and Flaxedil, followed by a thorough application of cocaine or amethocaine to the larynx, trachea and carina by means of the Macintosh spray. Any tendency to cough during the bronchoscopy can be checked by further small injections of a Flaxedil-thiopentone mixture.

By this means we have been able to anæsthetize for bronchoscopies without the anxiety occasioned by inadequate respiration if tubocurarine is used as the relaxant. With Flaxedil the cough reflex is depressed without seriously interfering with respiratory efficiency.

Recently we have found that an intravenous injection of 25 mg. of pethidine given immediately before induction of anæsthesia seems to increase the tolerance of the bronchoscope by the patient and less thiopentone and Flaxedil seem to be required for maintenance.

II

The second main property of Flaxedil is its effective but short period of action. This brings us to a group of circumstances in which this property is utilized.

For instance, for œsophagoscopies the anæsthetic requirements are a clear airway and relaxation of the cricopharyngeus muscle. The clear airway is ensured by intubation under thiopentone and Flaxedil. The relaxation of the cricopharyngeus due to the Flaxedil is transitory, but it lasts long enough provided the surgeon is ready to pass the œsophagoscope as soon as the patient has been intubated.

Hæmorrhoidectomies and sigmoidoscopies are short but notoriously stimulating operations normally requiring quite deep anæsthesia. They may now be carried out quite safely under light anæsthesia using Flaxedil as a depressant of the reflexes and as a temporary relaxant of the anal sphincter.

The reflex depressant effect of Flaxedil can be used in the treatment of persistent or recurrent laryngeal spasm. Quite a small dose, say 20 to 40 mg., will relax the vocal cords and enable the anæsthetic to proceed smoothly. This spasmolytic effect of Flaxedil is particularly useful when one is teaching a student to give ether to a resistant patient. There comes a time when one's duty to the patient and the waiting surgeon overrides one's teaching obligations to the student. On such an occasion a syringe of Flaxedil is more elegant in use and less traumatic than a boxwood wedge, a Mason's gag and a tongue forceps.

Flaxedil may find a place in the production of relaxation for orthopædic manipulations and reductions of dislocations. The most commonly used anæsthetic for this purpose is intravenous thiopentone given rapidly. The surgeon insists on a rapid injection of the thiopentone as he knows that adequate relaxation does not last much longer than the period of apnœa. Anæsthetists who have had experience of sudden and unexpected circulatory collapses following the rapid injection of quite moderate doses of thiopentone will find that a thiopentone-Flaxedil mixture injected slowly is safer and provides less transient relaxation. The mixture used is 0·5 gramme of thiopentone with 40 mg. of Flaxedil. This is injected slowly until a little more than the sleep dose has been given. The operator must be restrained for about a minute and a half in order to allow the Flaxedil to work. In most cases sufficient relaxation will be obtained for a manipulation of the back or for reduction of a dislocated hip or shoulder without subjecting the patient to the risk of a large dose of barbiturate.

III

The third important characteristic of Flaxedil is that neostigmine appears to be a more effective antidote to its action than to tubocurarine. We will now indicate two different circumstances in which it is considered justifiable to paralyse a patient with Flaxedil and to hasten his recovery from the drug by means of neostigmine.

Electro-convulsive therapy.—In electro-convulsive therapy, a muscle relaxant is commonly used in small doses in order to soften the intensity of the induced convulsion. In the clinic in which we have worked it is not the practice to give an anæsthetic or a relaxant to every patient, as it is believed that a full unmodified convulsion has the best therapeutic effect. But we have been asked to render patients almost completely immobile when the current is passed if there is a danger that an existing disability would be aggravated by a convulsion. Examples of this type of patient include those with severe hypertension or coronary disease and those suffering from severe osteoarthritis or convalescent from recent fractures or orthopædic operations. The production of immobility in these cases involves the use of doses of Flaxedil considerably greater than in those in which it would be given merely to soften the effect of the convulsion.

Our patients are premedicated with atropine and are given a dose of thiopentone just sufficient to send them to sleep. Flaxedil is then injected in doses of about 160 mg. for a large man to 120 mg. for a woman. Oxygen is given for a minute and a half while the Flaxedil is exerting its effect. The current is passed and the only movement of the patient is a twitch of the facial muscles. The clonic phase follows and is manifested by regular movements of the facial muscles and sometimes by a shrugging motion of the shoulders. After the clonic phase the lungs are gently inflated with oxygen for about a minute, by which time the patient usually begins to make some respiratory effort. This period of apnœa normally follows a convulsion unmodified by a muscle relaxant. It is quite remarkable that respiration should start so promptly after such large doses of Flaxedil, but this is believed to be due to the large amount of acetylcholine which must be liberated at the neuromuscular junction at the time of the convulsion.

Neostigmine with atropine is injected intravenously—at first 2·5 mg. neostigmine and 1/100 gr. (0·65 mg.) atropine—and the effect observed. This is followed by a further smaller dose if the intercostal respiration appears to be inadequate after the first injection. During the procedure a Boyle's machine with oxygen, laryngoscope and endotracheal tubes is kept ready at hand but in our experience laryngeal intubation has never been necessary.

Angiocardiography.—Another occasion on which it is considered justifiable to paralyse a patient with Flaxedil and to abolish its effect by means of neostigmine is in angiocardiography. This is a radiological investigation of a patient with cyanotic congenital heart disease on whom an operation of the Pott's or Blalock type is contemplated. A radio-opaque solution—diodone—is injected into an antecubital vein and its course through the heart and great vessels followed by a series of twelve X-ray exposures taken in very rapid succession. The surgeon can then determine the operability of the congenital lesion and which particular operation is practicable.

For the accurate interpretation of the angiocardiogram it is essential that perfect X-ray pictures are taken and this is only possible if the patient is kept absolutely still during the exposures. The conscious patient cannot be relied upon to keep still and hold his breath, as the injected solution produces very unpleasant sensations. Under light anæsthesia the injected solution causes coughing and laryngeal spasm. The alternatives that remain are anæsthesia to respiratory arrest with cyclopropane or ether, or light anæsthesia with neuromuscular paralysis. On account of the explosion risk in an X-ray department, we prefer the latter method and accelerate recovery from the paralysing dose of Flaxedil by means of neostigmine and atropine.

At first it may seem rather drastic completely to paralyse a patient for an X-ray examination and to use what might be a dangerous drug as an antidote, but it is felt that the importance to the patient of accurate assessment of his operability outweighs the possible risk of the anæsthetic procedure.

Use of neostigmine.—The disadvantage of neostigmine is that in addition to reversing the muscle-paralysing action of the curarizing drugs, it causes salivary and bronchial secretion, intestinal spasm and other effects of parasympathetic stimulation. Among these is the dangerous depression of the heart due to vagal stimulation. Strong vagal stimulation need not necessarily cause death, for the heart may start beating again by virtue of the vagal escape phenomenon even in the presence of continued stimulation of the vagus. The impulses which re-start the heart are thought to arise from some level in the junctional tissue below the sino-auricular node. However, if the junctional tissues are depressed as by cyclopropane or if the heart muscle is in poor condition, it is reasonable to suppose that the heart may not be able to escape from the inhibitory influence of the vagus and will remain arrested.

Another factor which may play a part in the risk of death following neostigmine is that its effect in slowing the heart-rate may be enhanced by the direct action of cyclopropane in depressing the activity of the sino-auricular node.

The patient may be protected to a certain extent from the vagal effects of neostigmine by atropine or a similar drug given as premedication, and by atropine given with or before the injection of neostigmine. The customary dose is 1/100 (0·65 mg.) to 1/75 (0·9 mg.) grain with each 2·5 mg. of neostigmine, though one should remember that it is necessary to give 1/20 (3·2 mg.) to 1/15 (4·3 mg.) grain to produce complete vagal block in the average adult. It should not be forgotten that both tubocurarine and Flaxedil have some vagal blocking activity which may contribute to the protection afforded by the atropine.

In 1949 three deaths following neostigmine were reported in the *British Medical Journal* (Macintosh; Clutton-Brock; Hill). Two of these cases were associated with cyclopropane anæsthesia. In one case necropsy showed "a very poor myocardium". In the other the heart was said to be "dilated" and was associated with a very severe peritonitis due to a gangrenous appendix. This patient may well have had some degree of toxic myocarditis which rendered his heart unable to withstand the depressant effect of neostigmine combined with cyclopropane. The third death following neostigmine was a baby who was given a very large dose in circumstances in which it would appear from the report that its use was not indicated at all.

It follows, then, that neostigmine should be used with caution and only when genuinely needed, as for instance when the anæsthetist is faced with the problem of an apnœic patient at the end of an abdominal or thoracic operation. Here, there is usually an element of both medullary and neuromuscular depression, neither of which by itself would be sufficient to cause apnœa. Thiopentone, cyclopropane, acapnia due to hyperventilation with carbon dioxide absorption, and pethidine may all contribute to the medullary element of respiratory depression.

It is therefore logical and safer to eliminate the medullary depression before giving neostigmine. The carbon dioxide absorber should be disconnected and the patient ventilated with nitrous oxide and oxygen to expel cyclopropane, which we have already seen is an undesirable associate for neostigmine. If apnœa continues, an adequate dose of a safe respiratory stimulant such as 5 c.c. of nikethamide should be given intravenously.

When respiration starts one can judge from its character whether an injection of neostigmine is necessary. After the abolition of medullary respiratory depression, only a comparatively small dose may be needed to restore the activity of the intercostal muscles.

We use neostigmine without hesitation when respiratory depression is due mainly to curarization. We attempt to reduce to a minimum the occasions on which it must be used, by giving the patient the smallest effective dose of relaxant. We always give atropine with neostigmine, and always eliminate cyclopropane from the patient before the injection.

IV

The fourth main property of Flaxedil is that it does not cause a lowering of the blood pressure.

Tubocurarine, in common with other drugs which block the sympathetic ganglia, causes a fall in blood pressure which is usually negligible in normal subjects but is often very marked in the hypertensive. Flaxedil does not block the sympathetic ganglia so that a patient's blood pressure is maintained at a higher level under anæsthesia than after tubocurarine.

This difference between tubocurarine and Flaxedil is probably of little significance when dealing with normal patients, but with the elderly hypertensive arteriosclerotic patient undergoing a severe operation, it is desirable to preserve what little resilience is left in the peripheral arterioles by doing nothing to interrupt their sympathetic nervous control. An additional risk in this type of patient is that a period of undue hypotension may predispose to a cerebral or a coronary thrombosis.

In this connexion we have in mind 8 patients who were recently anæsthetized for retropubic prostatectomy. The youngest was 72, and 2 were 85. They were given a small dose of thiopentone as induction, 80–120 mg. of Flaxedil for relaxation and anæsthesia was maintained with nitrous oxide and oxygen. A blood transfusion was set up before the start of the operation so that blood could be replaced as soon as it was lost from the operation site.

Fig. 6 shows the chart of the last one and demonstrates the high blood pressure being maintained after the induction of anæsthesia and the excellent response made by the patient to blood transfusion following a brisk hæmorrhage.

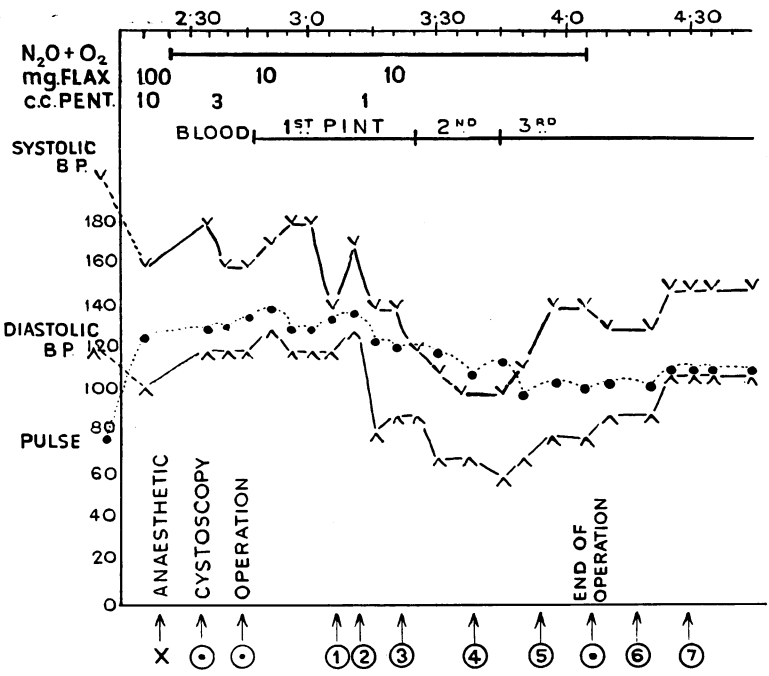

FIG. 6.—1.—Enucleating prostate. 2.—Hæmorrhage. Blood drip speeded up. 3.—Straining. More Flaxedil given. Hæmorrhage continues. 4.—Constant hæmorrhage. 5.—Hæmorrhage stopped. Sewing up. 6.—In the ward. 7.—Conscious.

These conclusions are drawn from only a few cases, but the operative and post-operative condition of the patients has been very gratifying; we therefore feel that it is worth recording this use of Flaxedil in helping to maintain an elderly hypertensive's blood pressure during an operation, especially at a time when so much interest is directed towards drugs having precisely the opposite effect.

Conclusions

This assessment of Flaxedil illustrates that it is a very versatile and safe muscle relaxant. The fact that it is a short-acting curarizing agent with an effective antidote has widened the field of application for this type of drug in clinical anæsthesia.

Its short period of action is not only one of its main advantages but it is at the same time its main limitation. Though it *can* be used for prolonged relaxation and for control of respiration if frequently repeated injections are given, the longer-acting tubocurarine seems to be more suited to these purposes.

Flaxedil's one main disadvantage—tachycardia—has been observed in many patients under thiopentone, nitrous oxide and oxygen anæsthesia, but not to the same extent under cyclopropane. Though the rapid pulse may be disquieting to the anæsthetist, and may, in theory, mask danger signals of the patient's general condition, we have been unable to attribute to tachycardia any undesirable effects on our patients.

We should like to express our thanks to those colleagues at St. Thomas's Hospital and at the Kingston Group of Hospitals who helped in much of the work, to W. Hindle, B.Sc., who carried out most of the experiments, and to Messrs. May and Baker Ltd. for generous supplies of Flaxedil.

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Dr. R. Wien: *Flaxedil tachycardia.*—Tachycardia with Flaxedil is not readily observed experimentally unless dogs, which have a high degree of vagal tone, are used. Under certain conditions, however, Flaxedil does cause an increase in the heart-rate in dogs, but not in cats or rabbits where the pulse is already high and the vagal tone comparatively low.

In dogs premedicated with morphine to stimulate the vagal centre and then anæsthetized with thiopentone, tachycardia was consistently observed following the intravenous injection of Flaxedil in a dose of 0·2–0·4 mg./kg., which is just below that required for a complete neuromuscular block. There was an increase in the heart-rate (120–176 per minute) of $20 \pm 3{\cdot}7\%$ (mean of 6 experiments), and the effect persisted for about ten to sixty minutes. Tubocurarine in an equipotent curarizing dose of 0·05–0·1 mg./kg. similarly caused tachycardia, but the effect was very transient, lasting only three to five minutes.

After vagal tone had been abolished with either atropine or hexamethonium (drugs which themselves caused an increase in the heart-rate) Flaxedil did not then cause any further increase in the rate, which suggests that there was no direct effect on the heart. This supposition was confirmed by observations in the spinal dog, where the vagal centre is destroyed; in this preparation Flaxedil did not cause a tachycardia. Moreover there was no rise in blood pressure, which would have occurred had there been any stimulant action on the sympathetic nervous system.

Tachycardia observed clinically can be accounted for by an action on the extrinsic nerves controlling the heart: this might consist of an effect on the parasympathetic and sympathetic systems. Though no evidence was found for a stimulant action on the sympathetic system, in equipotent doses causing neuromuscular block Flaxedil had a greater effect than *d*-tubocurarine in reducing the fall of blood pressure on vagal stimulation. In support of this evidence of an inhibitory action on the vagus nerves, it was found that Flaxedil had a weak anti-acetylcholine or atropine-like action, though only

about 1/500th of the potency of atropine itself. The partial removal of vagal control most probably accounts, therefore, for the tachycardia observed. This explanation is supported by other observations of Bovet *et al.* (1949), Unna *et al.* (1950) and Jacob and Depierre (1950).

Tubocurarine produces a much less marked and very much more transient tachycardia in dogs, and the absence of such an effect in patients might be explained by the comparatively greater inhibitory effect of this compound on the sympathetic and smaller effect on the parasympathetic system. In those circumstances where the vagal tone is sufficiently low or is abolished by the previous administration of atropine or scopolamine, the administration of Flaxedil should have no effect on the frequency of the heart-rate.

The practical implications of these findings are that some subjects may normally show a tachycardia with Flaxedil, which should not be confused with that due to other causes indicative of some upset of the anæsthesia or operation. The appearance of tachycardia will depend on the degree of vagal tone existing in the particular individual as well as on the type of anæsthetic, the depth of anæsthesia, and on the use of drugs such as morphine and atropine for premedication.

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Dr. L. Rendell-Baker (Department of Anæsthetics, Cardiff): The original experimental and clinical investigation of Flaxedil was carried out in the Department of Anæsthetics at Cardiff in 1949. Since then Flaxedil has been used instead of tubocurarine with equally satisfactory results.

Tachycardia has been noted, but has never given rise to any anxiety, though Flaxedil has been used in many cardiac operations and other poor risk cases. The difference between tubarine and Flaxedil can best be illustrated by some personal experiences during the experiments with Flaxedil. There were insufficient people in the Department to carry out a number of experiments on volunteers at one session, without also utilizing the volunteers as observers for subsequent experiments. Such was the speed of recovery from Flaxedil, however, and so few were the after-effects, following a suitable dose of prostigmine and atropine, that within five minutes of the termination of one experiment, the "experimental animal" was able to co-operate fully in the next. One afternoon after having Flaxedil, I drove home with another volunteer who had received tubocurarine. The contrast between us was most marked: I was able to drive with confidence, whereas my passenger was limp and unable to focus his vision clearly owing to diplopia. The effect of prostigmine on the bowel, in spite of the addition of atropine, was most marked, and this colic proved to be the most troublesome sequel to the experiment.

We feel it is most undesirable that a patient should be sent back to the ward before regaining full muscular power. It is almost a routine in our Department to give a suitable dose of prostigmine, preceded by atropine, to patients who have had Flaxedil. The degree of bradycardia which follows the administration of prostigmine, if the atropine has not had sufficient time to act, is most marked, and as a result we now inject the atropine intravenously fifteen to twenty minutes before the injection of prostigmine.

Flaxedil produces excellent operating conditions in thoracic surgery, provided the nitrous oxide anæsthesia is supplemented with small doses of pethidine, and I think that the inadequate depth of the accompanying anæsthesia was the reason for Dr. Doughty's having to use such large doses of Flaxedil.

Dr. J. G. Bourne: I disagree with my colleagues who prefer Flaxedil to C.10 (decamethonium iodide) to facilitate intubation. For two or three years I used "Tubarine" for this purpose in "steam hammer doses" and I had no trouble. However, when Flaxedil and C.10 became available it was clear that the shortness of their action was an advantage. Of these two relaxants I prefer C.10 since, unlike Flaxedil, its action is free from side-effects. It is also more transient.

In comparing the facility offered by these three relaxants for intubating, Dr. Doughty put C.10 lowest as making intubation "easy" in only 60% of cases. With this figure I disagree. Intubation is easy in 100% of cases if pentothal and C.10 are given in correct dosage. The dose can be computed as follows: The two drugs are mixed in solution so that 20 millilitres contains 1 gramme of pentothal and 5 mg. of C.10. The patient is weighed in pounds. 10% of this weight represents the number of millilitres to be injected intravenously. With this dosage intubation is easy in every case, and at worst all that is needed is manual compression of the bag for five minutes, a procedure which is nowadays a reflex with every anæsthetist.

Experience with this dosage in 200 consecutive cases of tonsillectomy in children aged 4 to 14 has illustrated both the usefulness of C.10 for intubating and its transient action. In this series the average time taken per case from the moment of injecting the drugs to the completion of the operation has been fifteen and a half minutes, anæsthesia being maintained with nitrous oxide-oxygen. In every case intubation has been easy, and in no case has it been necessary to use oxygen, artificial respiration or any restorative at the end of the operation. There have been no complications due to the anæsthetic.

Facilitation in intubation constitutes practically the sole indication for the use of C.10 in anæsthesia.

At least two or three minutes should be given for its full effect to develop, and during this interval the patient's lungs should be rhythmically inflated with oxygen.

Dr. William W. Mushin: Apart from the production of tachycardia there is very little obvious clinical difference between the effects of Flaxedil and those of *d*-tubocurarine. In fact I think it would be fairly safe to challenge anyone to walk into an operating theatre during an anæsthetic and to say which of the two relaxants was being used. My own reasons for continuing to use Flaxedil at Cardiff are based more on patriotism than on pharmacology. In Flaxedil we have a comparatively cheap and easily produced near-perfect substitute for *d*-tubocurarine and in any future emergency we would not have the previous difficulty of obtaining the natural substances from a distance of many thousand miles. Apart from the question of cost, availability and the tachycardia, I see little real clinical reason for using one rather than the other.

Dr. Doughty (in reply): I agree with Dr. Rendell-Baker that Flaxedil and nitrous oxide and oxygen will provide excellent conditions for control of respiration, if combined with small doses of pethidine, or for that matter any anæsthetic or analgesic more potent than nitrous oxide. I deliberately avoided mentioning the use of pethidine for this purpose since I was concerned with comparing Flaxedil and tubocurarine under comparable conditions. Owing to its more prolonged action and less diaphragm-sparing effect, tubocurarine provides better control of respiration than Flaxedil, when used with nitrous oxide and oxygen alone. I think this observation serves to underline one of the essential differences between the two drugs.

With regard to our contention that Flaxedil is the most suitable relaxant for facilitating intubation, I agree with Dr. Bourne and other speakers that other relaxants may be adequate for this purpose, if the dose of thiopentone given at the same time is varied according to one's experience of the method. We gave a fixed *small* amount of thiopentone, i.e. twice the sleep dose, in order to ensure that the conditions provided for intubation were due more to the relaxant than to the barbiturate. Larger doses of thiopentone would ensure an easier intubation, but, as Dr. Bourne admits, would result in a period of apnœa necessitating artificial respiration. If the ideal aimed at is an easy intubation followed by spontaneous respiration, the results we obtained with Flaxedil approached the ideal more closely than with tubocurarine or decamethonium.