

STUDIES ON MUSCLE-TONE WITH SPECIAL REFERENCE TO ANAESTHESIA

AND SPECIFIC RELAXANT DRUGS.

BY

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PART I.

TONOMETRY.

Statement of Objects.

Muscle-tone is of great interest to anaesthetists, because they are frequently required to "abolish" it to facilitate the work of the surgeon. A continuing state of "diminished muscle-tone" has also been cited as a factor in the causation of post-operative pulmonary complications. (Henderson 1938).

The interest of anaesthetists in this subject has not, however, led to much basic research, or even to criticism of the statements, apparently repeated from text-book to text-book, that muscle-tone decreases in the stage of surgical anaesthesia, and is abolished at the end of the second plane of this stage.

Since the introduction into anaesthetic practice of the specific relaxant drugs by Griffiths and Johnson (1944), and by Gray and Halton (1946), it has seemed to the author that the necessity for basic research into the changes in muscle-tone during anaesthesia has become even more clamant.

Accordingly, it was decided:

- (1) to re-assess the changes in muscle-tone produced by general anaesthesia.
- (2) to assess the effect of specific relaxant drugs on muscle-tone in the anaesthetised subject.
- (3) to express changes, where possible, in a quantitative fashion.

Definition of Muscle-Tone.

The word 'tone' has been used in the past with varied meanings, and many definitions have been proposed for it. Galen spoke of 'tone', but meant by this a voluntary and sustained contraction of muscle. The contraction of muscle without voluntary effort he attributes, rather vaguely, to an inherent property. This idea of "a characteristic vital force" appears again in the work of Haller (1762). Johannes Müller (1833) used the word 'tone' to denote a characteristic slight tension of skeletal muscle at rest. Müller introduced the idea that in addition to purely physical forces, a nervous influence was responsible for the resting tension of muscle. This was a controversial idea, but the general opinion developed that the resting tension of muscle was associated with an "automatic" activity of the nerve-centres.

Brondgeest (1860) succeeded in finding a preparation in which the influence of afferent impulses on the tension of muscle could be demonstrated. He sectioned the afferent spinal roots of one hind-limb of a frog, and showed that, when the frog was held in a vertical position, the untreated limb was flexed more than the treated limb. The relaxation of the treated limb on cessation of centripetal impulses showed the reflex nature of tonic flexion, and disproved the older ideas of tone controlled by automatic activity of the central nervous system. (Above authors cited by Spiegel, 1927).

The work of Brondgeest was repeated by Sherrington, who did a great deal of work on muscle-tone (1898, 1909, 1915), and on the myotatic reflex in association with Liddell (Liddell and Sherrington 1924, 1925). Following these authors, it has been customary to

define muscle-tone as the slight state of tension present in normal muscle at rest, and absent in denervated muscle. This slight state of tension is ascribed to a reflex contraction of muscle-fibres in response to a stretch induced by gravity.

The concept of muscle-tone used by Sherrington was not wholly accepted by Bayer and Ihrenfeldt (1949). They studied relaxed and tensed muscle clinically and electromyographically in various positions over the range of movement. They concluded that there was no relationship between tone as determined by the electromyograph and that found by palpation. They distinguish between specific and non-specific skeletal muscle-tone. Specific tone is a function of muscle-fibre activity and is shown by the electromyograph. Non-specific tone is what is usually termed "consistency" and depends on many factors such as fluid-content, blood-flow, temperature, and the different degrees of hardness produced by the contraction of the muscle fibres.

A similar view seems to be held by Clemmesen (1951) who speaks of a passive elastic tension present in all striated muscle, and independent of voluntary or reflex stimulation through the motor nerves. He claims that there is no evidence to support the view that tone is due only to reflex activity. A universal muscle-tone, not localised to anti-gravity muscles, is postulated.

It is proposed to adopt a definition of muscle-tone which covers passive elastic tension as well as the effects of activity in muscle-fibres. The tone of a muscle is defined as the capacity of that muscle to resist extension (Roberts 1951).

Roberts

PART 1.Measurement of Tone.

The principal methods which have been adopted for measuring muscle-tone in Man fall into two main groups. The first group of methods depends essentially on measurement of the hardness of muscles, as in palpation with the fingers. The second group of methods depends on a measure of the resistance of a muscle to imposed extension.

(1) Under the heading of 'hardness' or 'palpation' methods we may consider the work of Noyons and von Uexkull (1911) and Mangold (1922). These workers, using a method of static elastometry, applied weights to the surface of a muscle, and related the amount of deformation of the muscle to the magnitude of the deforming force.

Ballistic methods have also been employed, based on the technique used in industry for determining hardness, using the principle of 'rebound' described by London (1943). The muscle is struck by a hammer operated by a pendulum. Note may be taken of the indentation of the muscle, contact-time, rebound speed, and amount of rebound. This method was used by Gildemeister (1914) and by Springer (1914). The technique was improved by Simonson et al (1949).

Another measure of the hardness of muscle may be obtained by determining the pressure necessary to inject saline through a hollow needle introduced into the muscle. This method was used by Kerr and Scott (1936) and by Henderson (1936). Henderson et al. suggested that tonus creates a pressure within a muscle in essentially the same way as a rope pulled taut produces a pressure between its strands, and that this pressure might be measured by the pressure necessary to inject a

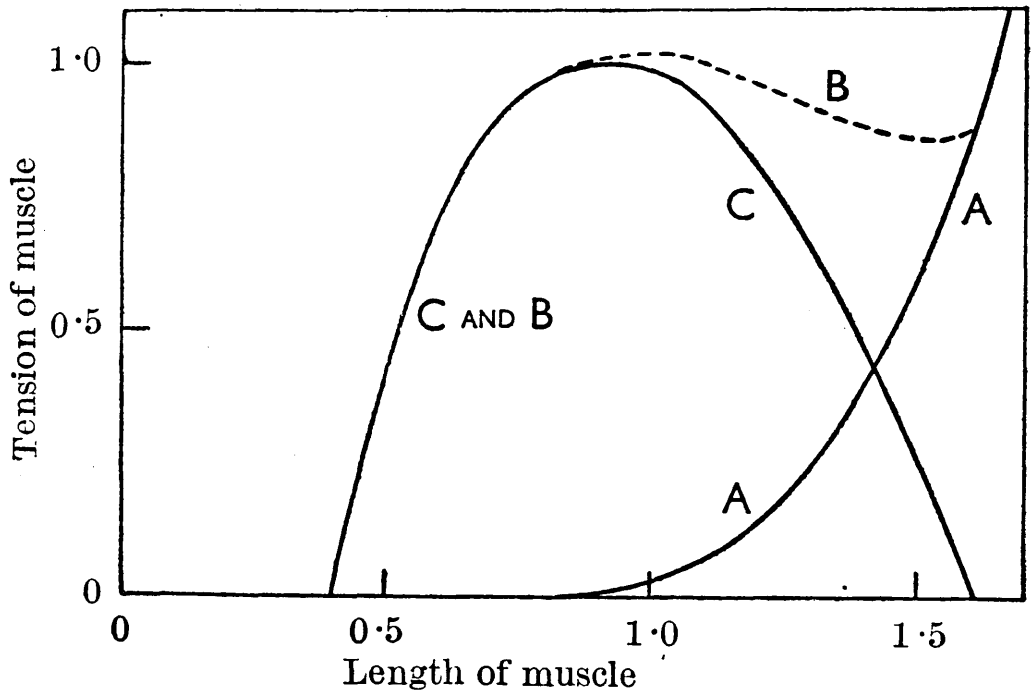
small quantity of saline into the body of the muscle through a hypodermic needle. For the measurement of pressure a manometer was used. All measurements were made on the left biceps muscle, flexed at an angle of "about 135^o," with the subject lying on his back. Experiments were made, inter alia, on patients before and after surgical operations. The authors reported a decrease in intramuscular tension in the post-operative period.

(2) 'Resistance to extension' methods include the usual method of clinical assessment of muscle-tone. This is commonly performed by estimating the limits and ease of passive movement in the subject's limb when manipulated by the observer.

An ingenious application of this method by McKinley and Berkwitz (1928) consists of passive displacement of a limb by a mechanical device, with measurement of the forces developed in opposition to the movement.

Electromyography: It is relevant also to note that electromyography may be used as a measure of changes in muscle-tone. If we are measuring such changes in a muscle whose length is reasonably standardised, thus eliminating any effect of developed elastic forces, then any alteration in the resistance to extension of the muscle must be due to muscle-activity. Hill (1950) has shown that, at normal lengths of muscle, change in elastic tension plays little part in the tension developed during muscular activity; (fig. 1) under such conditions we can assess tone in terms of muscle-activity. As muscle-activity can be expressed in terms of electromyography, some measure of electrical activity should be related to changes in tone.

FIG. 1. THE STATIC RELATION BETWEEN FORCE DEVELOPED IN MUSCLE, AND LENGTH. (HILL)



(A) Tension at rest; (B) total tension during contraction; (C) 'tension developed' = $(A - B)$. Length normally in body = 1.0

It has been shown that in normal muscle, fully at rest, no electrical activity can be detected in muscle, either by surface electrodes or by needle electrodes. (Adrian and Bronk 1929, Denny-Brown 1929, Smith 1934, Lindsley 1935, Hoefffer 1939, and Buchthal 1941).

Electrical activity during muscular contraction has been quantitatively estimated in various ways. Loofbourrow (1948) compared the mechanical and electromyographic responses of the tibialis anticus of the anaesthetised cat to electrical stimulation of the motor cortex. He used two measures of electrical activity, a measure of the amplitude of the electromyographic record, and the results given by an electrical potential integrator. When cortical stimulation was applied to the cat, he found that both of the electrical measures recorded changes in the tibialis anticus in parallel with the results given by a torsion spring myograph.

Lippold (1952) investigated the relation between the isometric tension developed in a voluntarily contracting human muscle and the integrated electromyogram. To integrate the electromyogram, he chose at random three lengths of the record, and measured with a planimeter the area enclosed by the spikes. He found a direct relation between the isometric tension of a voluntarily contracting human muscle and the integrated electromyogram.

It was decided that the method to be adopted for the assessment of tone must satisfy the following criteria:

- (1) it must not depend on the subject's active co-operation or movement.
- (2) it must allow the measurement of small differences in tone.
- (3) the apparatus must be easily portable.
- (4) the method must not be time-consuming, as this would interfere with the smooth running of routine operating-theatres.

For convenience, it was decided to use a "hardness" method, though a "resistance to extension" method would follow more easily from the definition adopted.

The use of a "hardness" or "palpation" method can be justified on lines similar to those propounded above in the case of electromyography. This method cannot be employed for comparing one patient with another, because of differences in the amount of subcutaneous tissue, fibrous tissue, etc. Under standardised conditions, the length of the muscle being constant, changes noted will, however, afford a satisfactory comparison of the tone present in the same muscle at different times.

It will be shown later that in certain conditions, the two measures can be regarded as equivalent, so far as changes in the tone of a particular muscle are concerned.

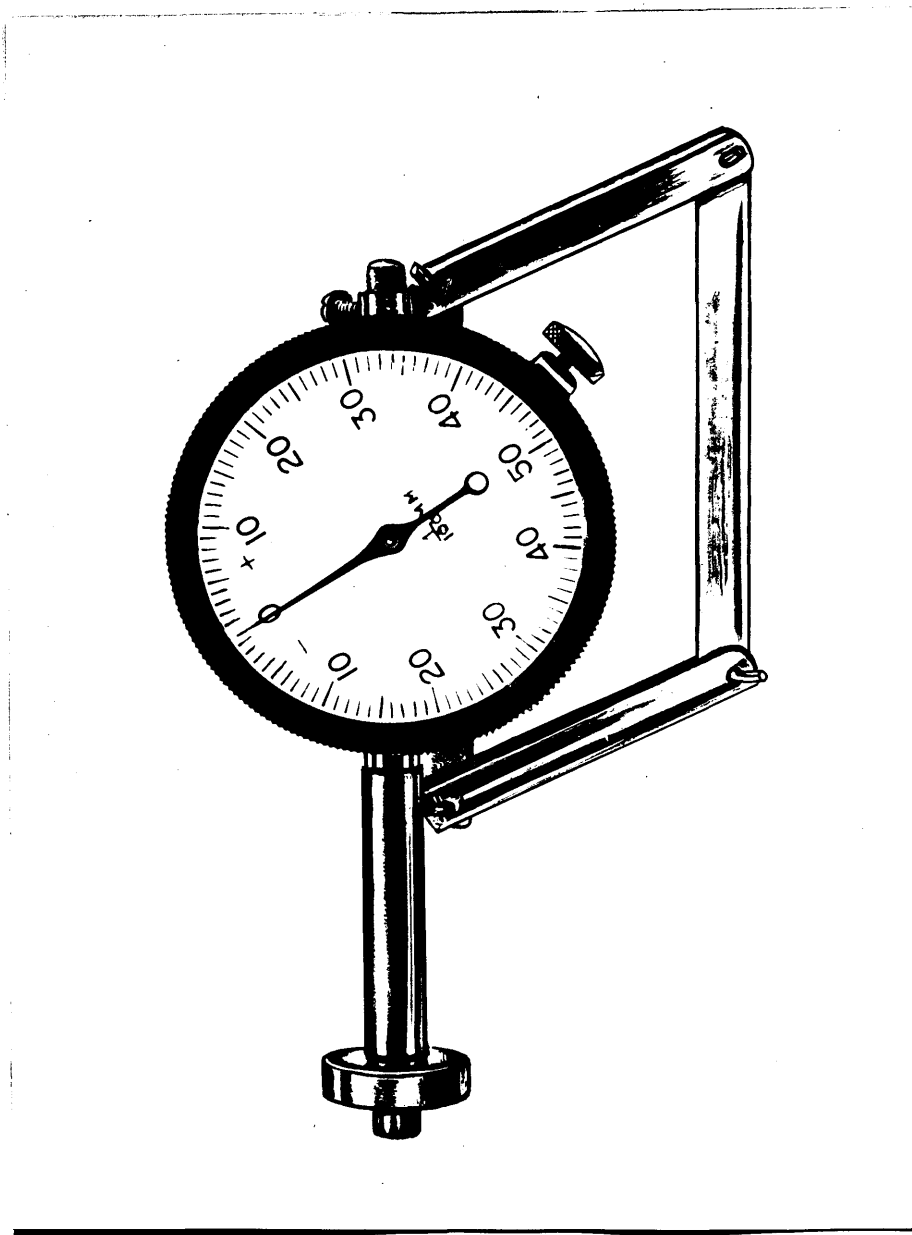
Tonometer: An instrument has been designed (fig.2) to satisfy the criteria outlined above. It will be referred to as a "tonometer." Its operation depends on the principle of static elastometry. The instrument is allowed to rest with its flat, circular base-plate on the skin overlying a suitable muscle. The weight of the instrument (250 grammes) is distributed between the base-plate (1.9 cm. in diameter) and a spring-loaded plunger (6 mm. in diameter) in its centre. The degree of protrusion of the plunger is determined by the hardness of the supporting surface and is indicated on the dial of an engineer's "clock-gauge" reading in hundredths of a millimetre.

To obtain consistent readings, the instrument must be allowed to rest by its own weight on the skin, with the axis of the plunger vertical. The instrument is fitted with a hinged handle, in the form of an articulated parallelogram, so that no vertical forces are transmitted to the instrument by the operator.

As the instrument is lowered gently into place the movement of the plunger from its limiting position of maximum extrusion (about 7 mm.) is read from the gauge. In comparing the various states of tone of a particular muscle, the ^{least} reading obtained with this muscle was deducted from all other readings, and the differences were taken as a measure of changes of tone.

Pilot experiments were performed with the instrument: on relaxed and tensed muscle, with the subject conscious; and on subjects before and during anaesthesia. The biceps brachii, rectus femoris, and rectus abdominis muscles were used.

FIG. 2. THE TONOMETER.



These brief preliminaries demonstrated that:

- (1) the instrument showed clearly gross alterations in the tone of underlying muscle.
- (2) minor changes were demonstrable in the tone of muscle during anaesthesia.
- (3) difficulty might be expected in recording changes of tone in abdominal muscles because of alterations in tension with respiration.

In one anaesthetised patient there was a considerable rise in abdominal tension during hiccups.

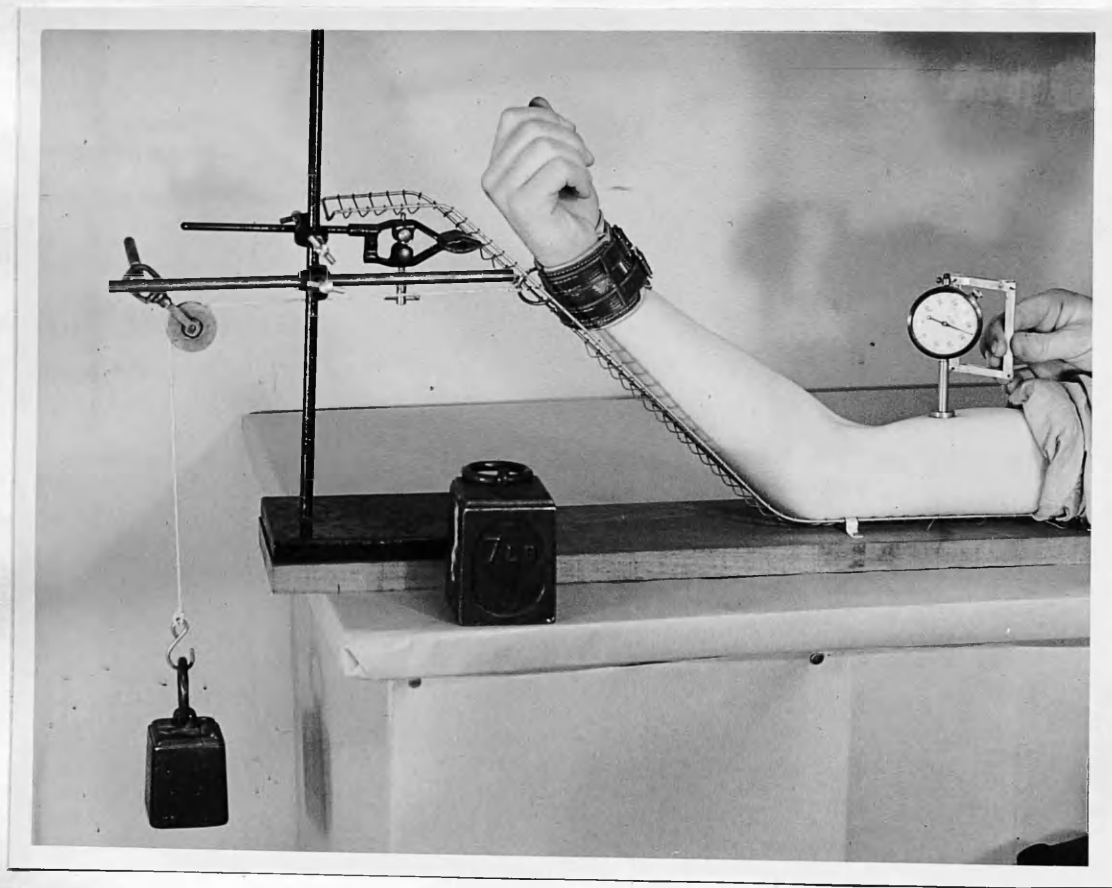
The instrument was now tested under laboratory conditions. It was applied to the biceps brachii, which was subjected to graduated loads. Six subjects, five male and one female were used. To check these results, the output of action-potentials muscle was determined under identical conditions of load.

Assessment of Performance of the Tonometer.

Technique: The subject's arm was placed on a stand as shown in figure 3. On this support, the upper arm rested in a horizontal position at shoulder-level. The forearm was supported in a position of partial flexion at an angle of 135° . A soft leather cuff was strapped on the wrist. A cord led from a small metal ring on the cuff, over a pulley. From the far end of this cord weights could be suspended. A mark was made on the skin-surface overlying the biceps brachii, and a series of ten tonometer readings was recorded.

Action-potentials from the muscle were picked up from two drawing-pins, fixed head-down on the skin, approximately four centimetres

FIG. 3. TESTING TONOMETER IN LABORATORY.



apart, and led to an amplifier and oscilloscope. The output of amplified action-potentials was rectified, smoothed, and indicated on a moving-coil meter. The needle of the meter was closely observed during the experiment. It displayed a constant flicker, but its usual position for any condition was comparatively easy to determine. The modal deflection of the needle was recorded.

The forearm was then raised just clear of the supporting stand, and the mechanical and electrical observations were repeated. The observations were also repeated when a series of weights was suspended by a cord from the wrist-cuff. Various weights were used, in random order, in the range 1 - 12 pounds. In each case, readings were taken during a "steady state."

Results: With a little practice in the use of the tonometer, remarkably consistent results could be obtained, as is indicated by the following results obtained from the thigh muscles.

Sixty-two successive determinations at a point overlying the relaxed anterior thigh muscles of a supine subject gave a range of observations of 205 - 209, a mean value of 206.1 and a standard deviation of 0.88.

Twenty-two successive determinations at a point overlying the relaxed posterior thigh muscles of the same subject in a prone position gave a range of observations of 234-237, a mean value of 235.7, and a standard deviation of 0.69.

The relation between tonometer-reading and load imposed are shown in Table 1, and Figures 4 - 9. The tonometer-reading shown for each load represents the mean of ten observations made in rapid succession. In the case of subjects 2, 3, and 6, results are shown for experiments separated by some weeks.

It is shown that the increased tension in the biceps brachii in voluntary activity to support a load is reflected by the tonometer reading. The increase in tonometer-reading is closely related to the increase in load. The relation can be regarded as approximately linear.

The importance of the position of the arm was realised more acutely during clinical testing. Accordingly, the effect of alteration in flexion-extension position was determined experimentally in two subjects. With the upper arm resting in a horizontal plane, the forearm was supported in various positions relative to it, in a vertical

TABLE 1. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND
MEANS OF TONOMETER READINGS.

Case	R.	N.R.	1	2	3	4	5	6	7	8	10	12 pounds.
1	209	263	236	270		290		301		326		
2	146	238	151	210		216			272			
	165	185	187	205		227			286			
3	206	281	277	302		320			354			
	203	264	270	306		331		350		364		
4	190	254	267	278	286	287	303	312	324			
5	165	175		205		232		240		275	295	315
6	215	225		250		270		265		295	305	315
	207	256		260		266		282		284		320

The figures represent the mean of ten determinations on one day.

Where two sets of figures are shown, the second set was obtained some weeks after the first set.

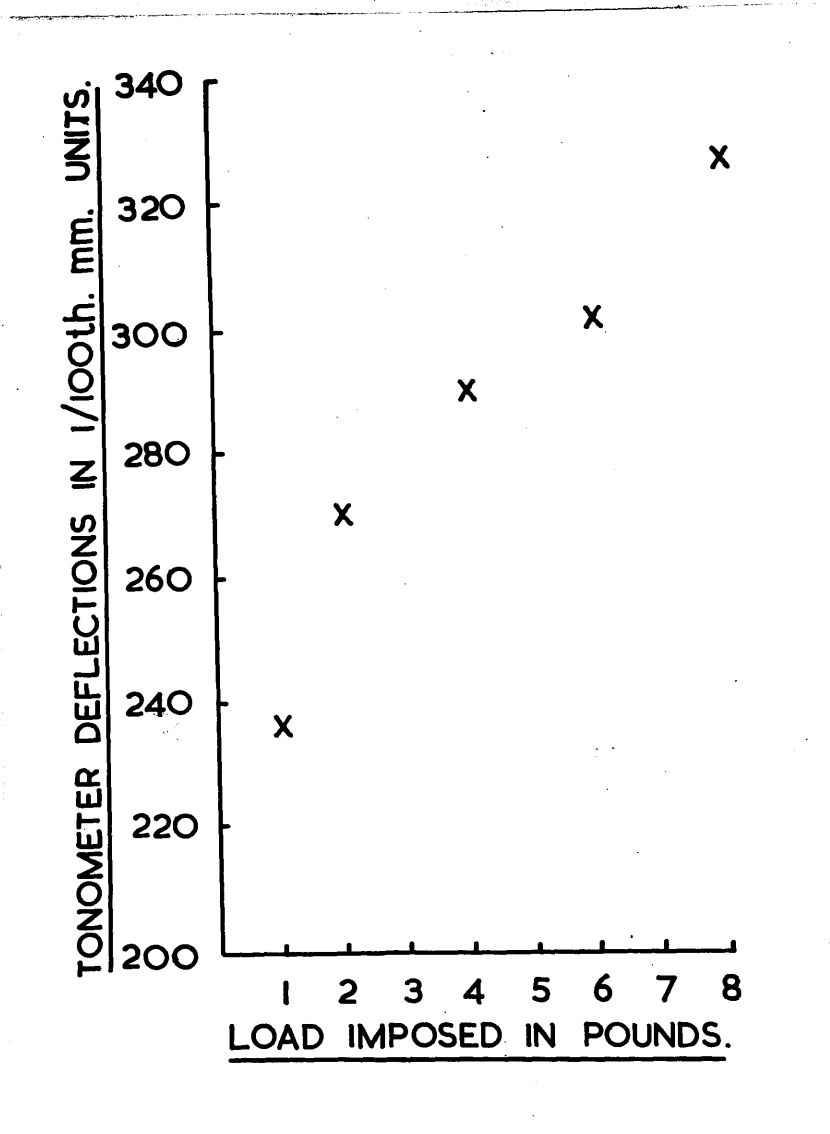
The weights mentioned represent the load in pounds imposed on the arm. The subject pulled against this weight until the forearm was just clear of the support.

R = Resting. i.e. Arm rests on the stand.

N.R. = Not Resting. i.e. Arm is held just clear of the stand.

The tests with different weights were performed in random order.

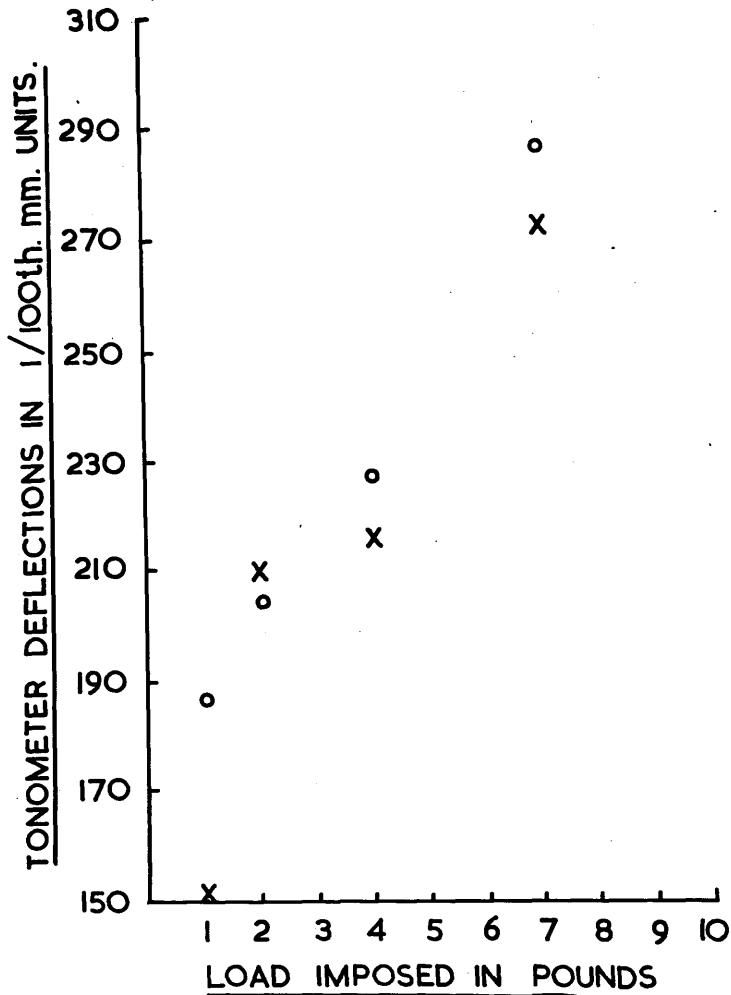
FIG. 4. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MEANS OF TONOMETER READINGS. (Subject 1).



Each recorded reading is the mean of ten successive determinations, made in rapid succession.

The weights were used in random order.

FIG. 5. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND THE MEANS OF TONOMETER READINGS. (Subject 2).

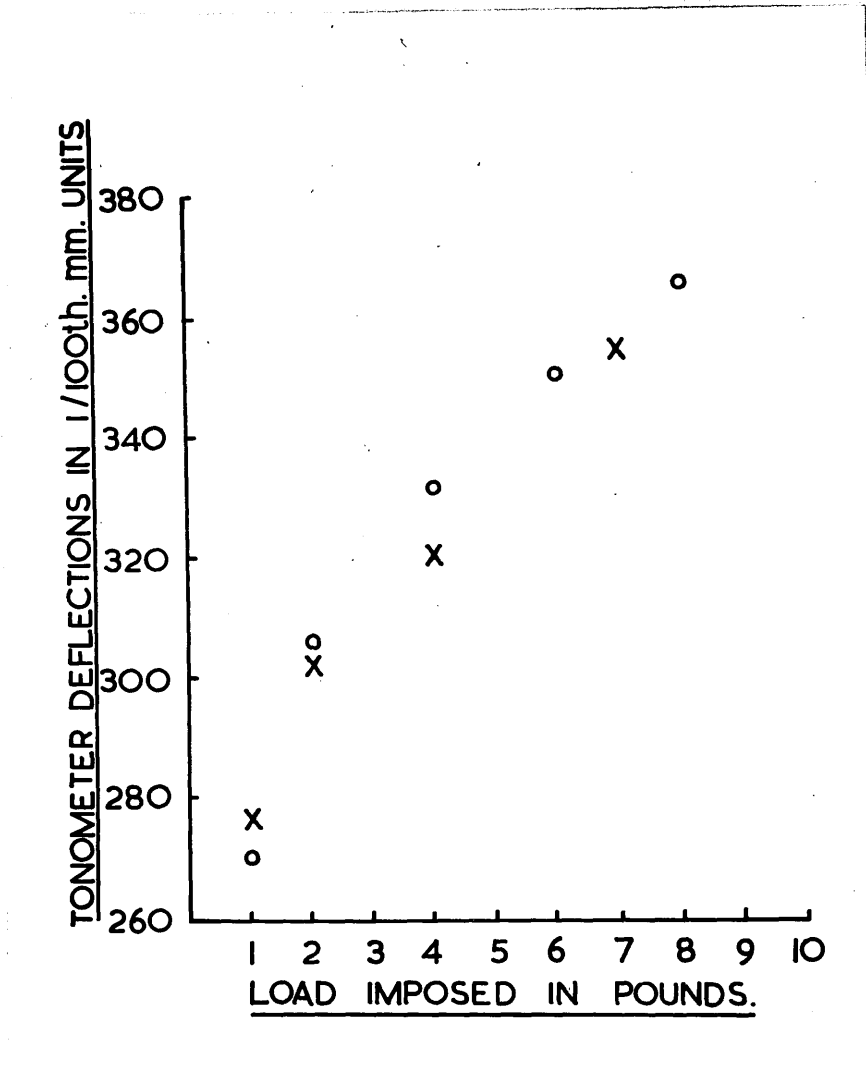


Each recorded reading is the mean of ten successive determinations, made in rapid succession.

The two symbols represent the results of experiments separated by an interval of several weeks.

The weights were used in random order.

FIG. 6. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND THE MEANS OF TONOMETER READINGS. (Subject 3).

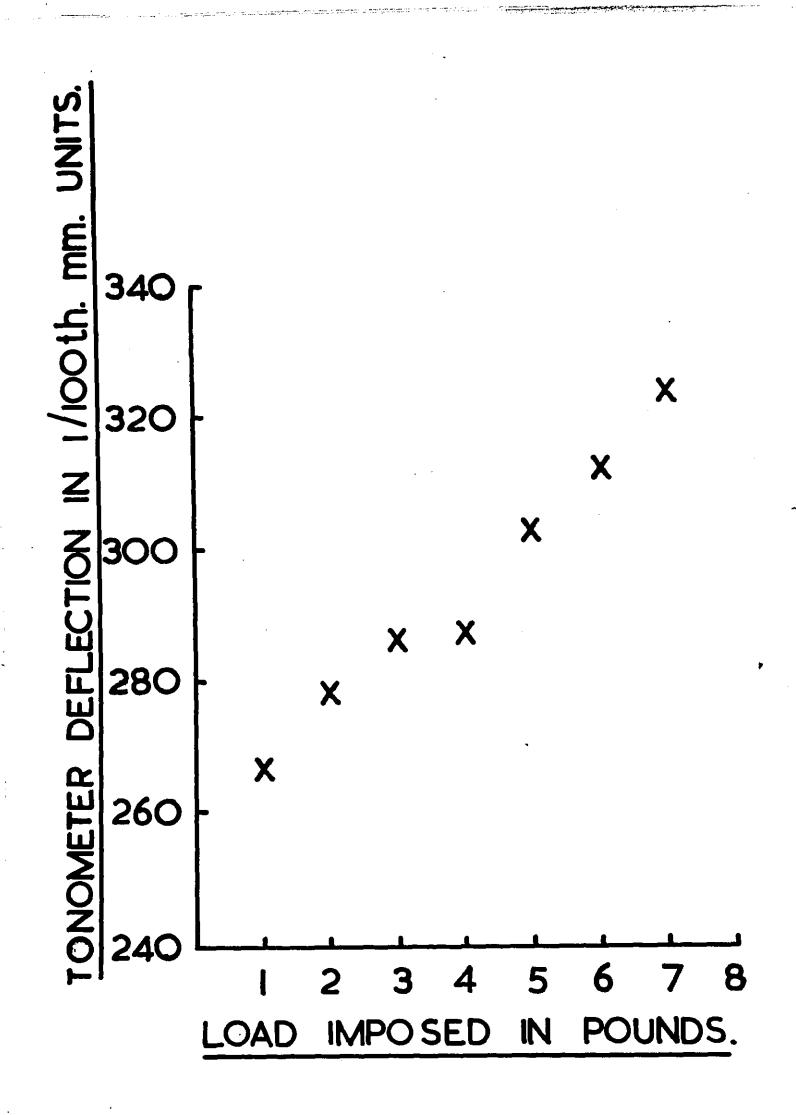


The two symbols represent the results of experiments separated by an interval of several weeks.

Each recorded reading is the mean of ten determinations, made in rapid succession.

The weights were used in random order.

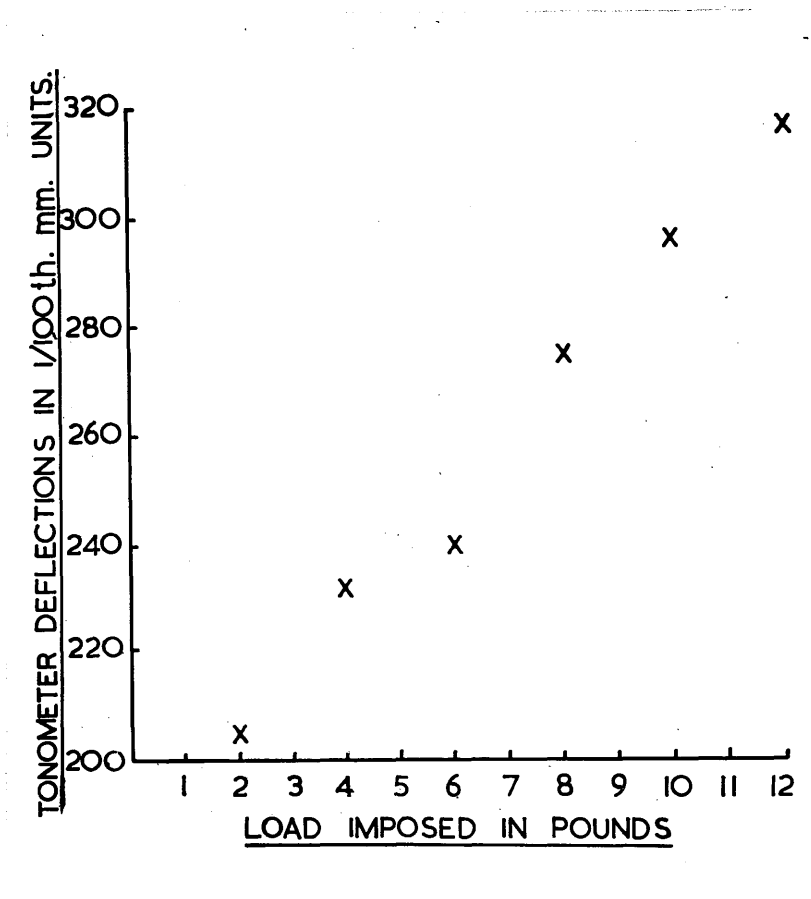
FIG. 7. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND THE MEANS OF TONOMETER READINGS. (Subject 4).



Each recorded reading is the mean of ten determinations, made in rapid succession.

The weights were used in random order.

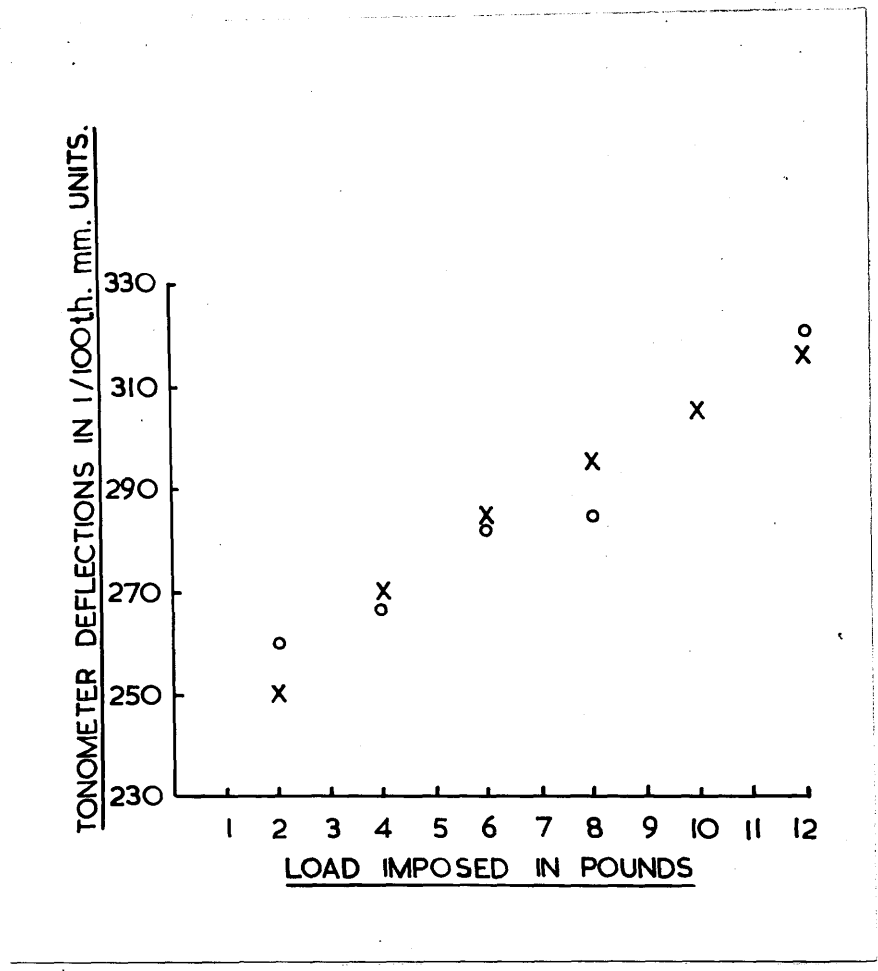
FIG. 8. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND THE MEANS OF TONOMETER READINGS. (Subject 5).



Each recorded reading is the mean of ten determinations, made in rapid succession.

The weights were used in random order.

FIG. 9. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND THE MEANS OF TONOMETER READINGS. (Subject 6).



The two symbols represent the results of experiments separated by an interval of several weeks.

Each recorded reading is the mean of ten determinations, made in rapid succession.

The weights were used in random order.

plane. The angle made by the upper arm and the forearm varied from 90° - 180° . Tonometer-readings were taken over the same segment of the biceps brachii at each of the angles examined. The mean of ten observations taken in rapid succession is recorded for each angle examined. The results are shown in Table 2 and Figure 10. They show that muscle-tension in the biceps brachii, as determined by the tonometer, is markedly less in the flexed, relaxed arm than in the extended, relaxed arm. In Figure 10 the similarity between the slopes of the observations in the two subjects is notable. These results are held not to invalidate the method used for testing the tonometer in the laboratory, because the alteration in the position of the forearm, to remove it from the support of the stand, was minimal and constant.

The results obtained by electromyography, in terms of the modal meter-reading, are shown in Table 3 and Figures 11 - 16. The results show that, over the range of effort examined, there is a linear relation between output of action-potentials and the load imposed on the muscle.

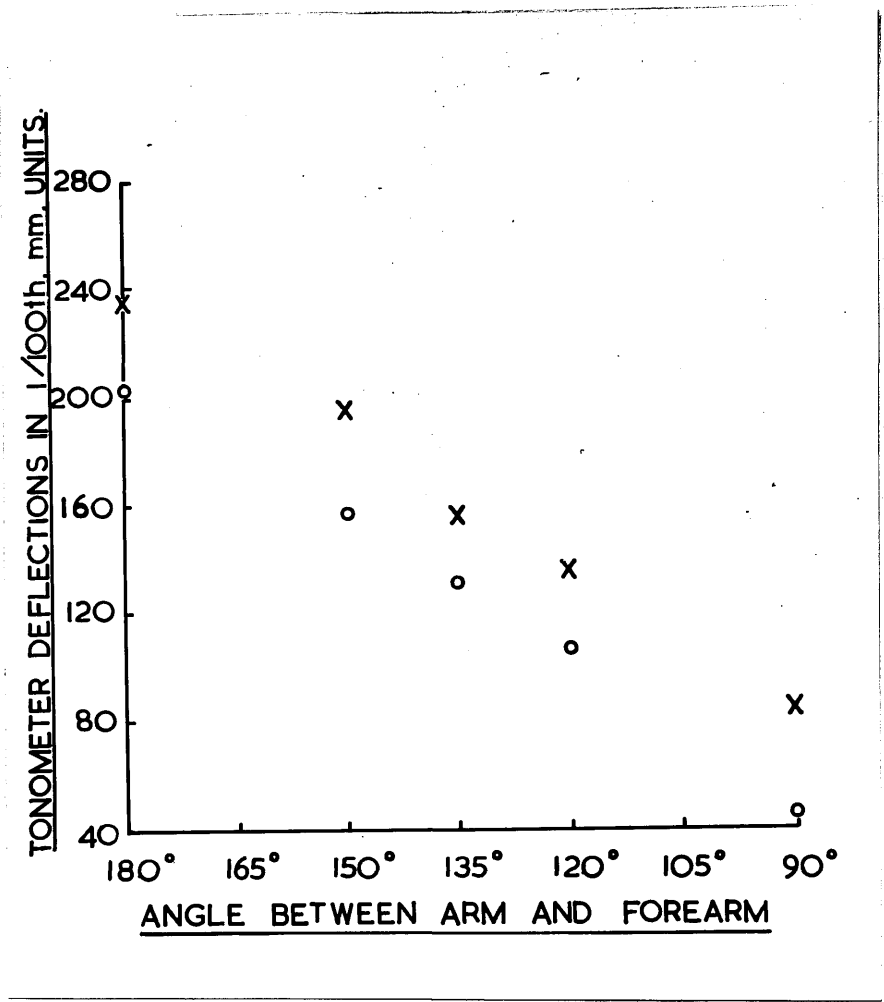
TABLE 2. RELATION OF ANGLE BETWEEN ARM AND FOREARM AND
MEAN TONOMETER READINGS.

<u>Angle.</u>	<u>First Subject.</u>	<u>Second Subject.</u>
180°	235	205
150°	195	155
135°	155	130
120°	135	105
90°	85	45

The recorded readings are each the mean of a set of ten determinations, made in rapid succession.

The upper arm was horizontal, and the forearm was supported in various positions, in a vertical plane through the shoulder.

FIG. 10. RELATION OF ANGLE BETWEEN ARM AND FOREARM AND MEAN TONOMETER READING. (2 subjects).



Each reading is the mean of a set of ten determinations, made in rapid succession.

The upper arm was horizontal, and the forearm was supported in various positions, in a vertical plane through the shoulder.

Note the similarity in the slope of the results, given by the two subjects.

TABLE 3. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL ELECTRICAL METER READINGS.

Case	R.	N.R.	2	4	6	8	10	12 pounds.
1	0	15	25	30	38	48		52
2	0	20	20	32	30	38	42	45
3	0	20	30	40	48	52		
4	0	20	30	38	50	62		
5	0	15	20	30	35	38	45	50
6	0	10	11	16	21	28	31	39

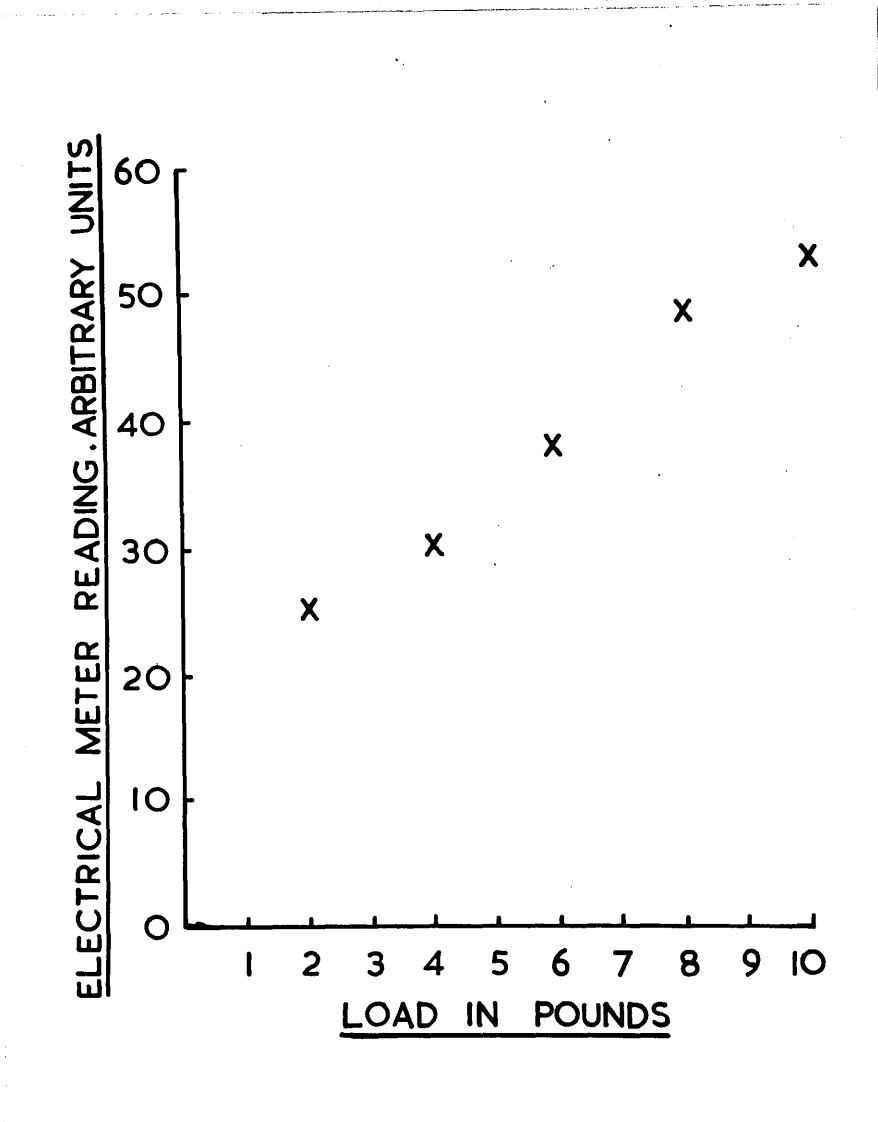
The figures indicate the modal dial reading on the meter indicating electrical output. The scale is arbitrary. Readings are not comparable from subject to subject.

The weights represent the load in pounds imposed on the arm. They were taken in random order.

R = Resting. i.e. Arm rests on the stand.

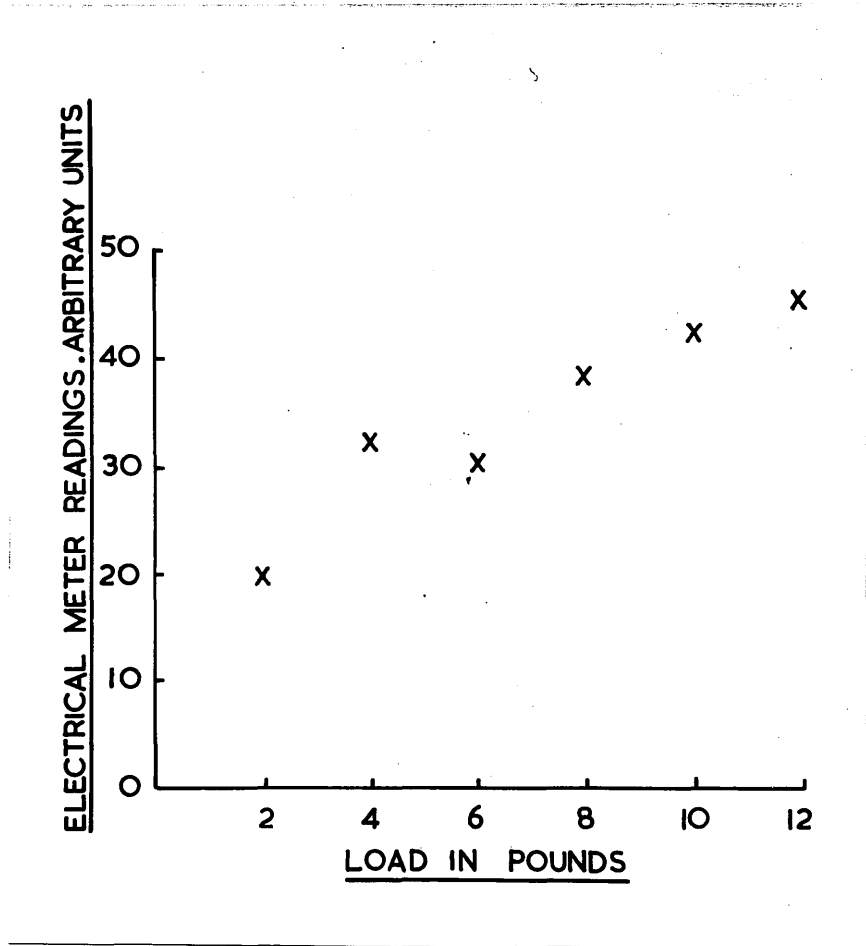
N.R. = Not Resting. i.e. Arm is held just clear of the stand.

FIG. 11. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 1).



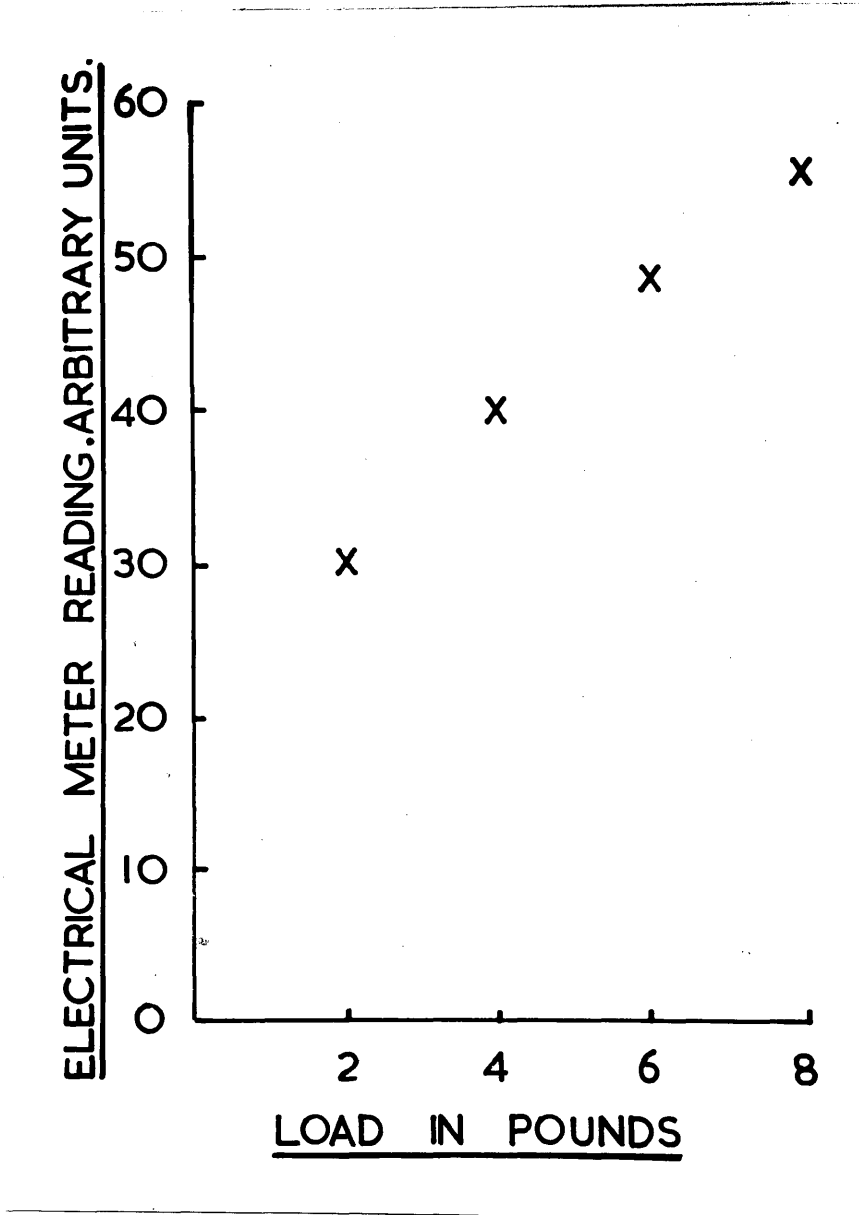
The weights were taken in random order.

FIG. 12. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 2).



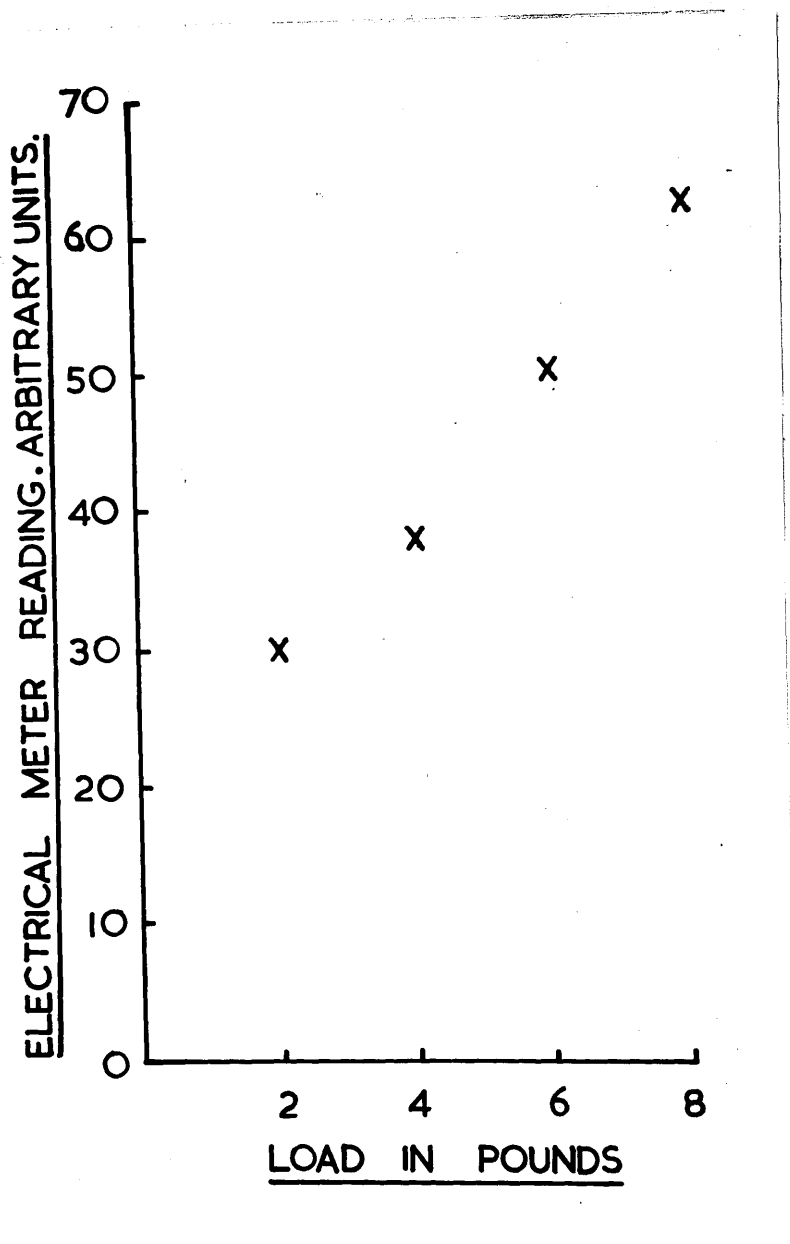
The weights were taken in random order.

FIG. 13. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 3).



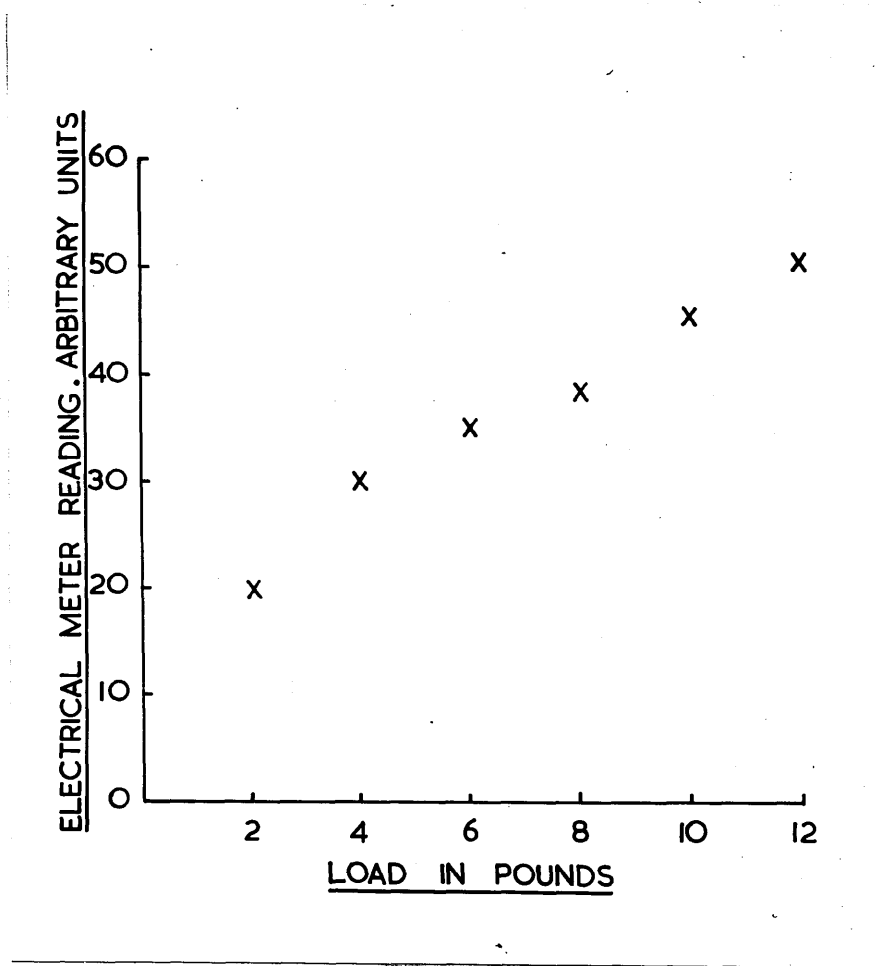
The weights were taken in random order.

FIG. 14. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 4).



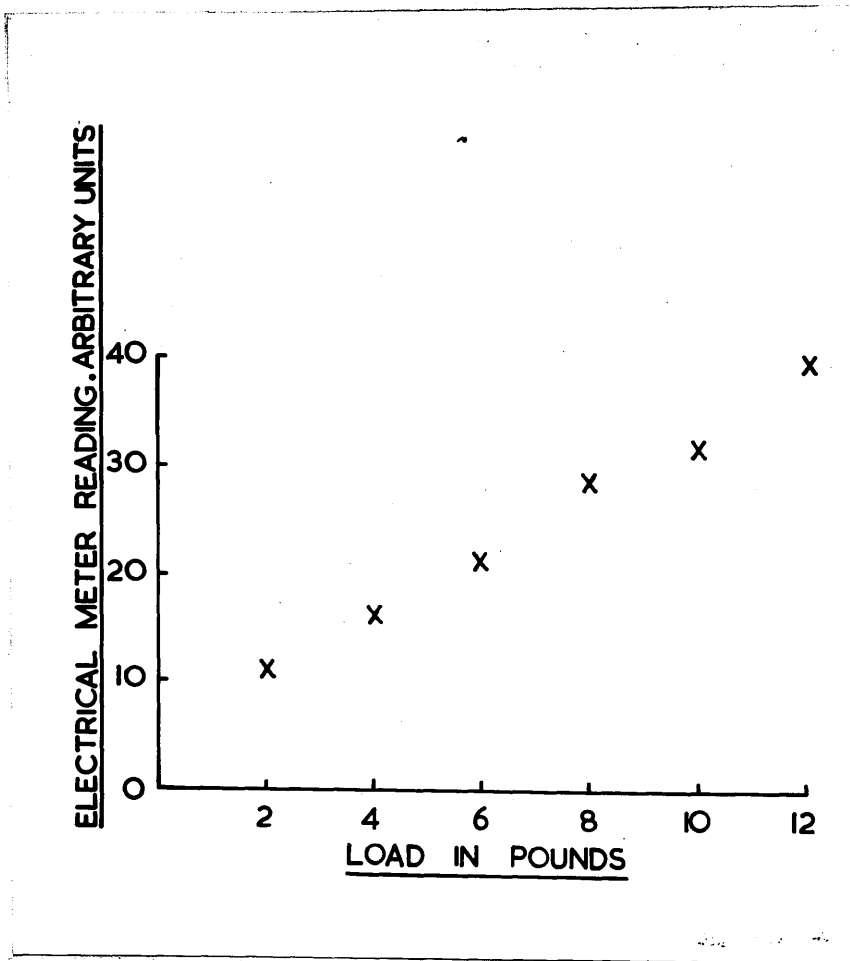
The weights were taken in random order.

FIG. 15. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 5)



The weights were taken in random order.

FIG. 16. RELATION BETWEEN LOAD IMPOSED ON MUSCLE AND MODAL DEFLECTION OF ELECTRICAL METER. (Subject 6).



The weights were taken in random order.

Assessment of the Performance of the Tonometer.

Table 1 and Figures 4 - 9 show the performance of the Tonometer as assessed by measuring the tone in the biceps brachii subjected to various imposed loads.

The difference between the tonometer readings obtained with the forearm supported and those obtained when the forearm was raised just clear of the stand, appears to show that an effort equivalent to several pounds of applied load is required to support the forearm alone. An additional load, however, may lead to a reduction in the reading of the tonometer. This is taken to indicate that, when the arm is supported just clear of the stand without imposed load, there is some activity in the extensor muscles antagonistic to the biceps brachii. The magnitude of this effect differed from subject to subject, as it was difficult to persuade some subjects to relax adequately during the tests. These subjects gave inconsistent results at first, but improved with practice.

Over a certain range, a linear relation is obtained between the tonometer reading and the imposed load.

The electrical measure provided by the integrated action-potentials of the contracting muscles gives an indication of the degree of activity of the muscle. If the "tone" or "capacity to resist extension" of a muscle in particular conditions is altered mainly by changes in the activity of the muscle (see page 5) we should expect this electrical measure to be related to the load imposed on the muscle. It has been shown, (page 13), that this relation is linear over a certain range of loads. Lippold (1952) has also found a linear

relation between isometric tension developed in voluntarily contracting human muscles and the integrated electromyogram. This provides independent confirmation of the findings reported above, which are based on experiments carried out in 1951.

The tonometer provides a measure of tone based on the "hardness" or "resistance to palpation" of the muscle. It has been shown, (page 11) that the tonometer readings also bear a linear relation to the imposed load over a certain range. It follows that "hardness" and "activity" can be regarded as equivalent measures of the "tone" of a particular muscle over a certain range of loads, and under limited conditions. The tonometer can therefore be regarded as providing a satisfactory measure of changes in the tone of a particular muscle.

Changes in Tone during Anaesthesia.

The tonometer was applied clinically in two series of patients to determine the changes in muscle-tone produced, firstly, under general anaesthesia, and, secondly, under general anaesthesia with the superimposed effects of specific relaxant drugs.

The anaesthetic agent usually employed was di-ethyl ether. It was given in the nitrous-oxide, oxygen, ether sequence using the semi-closed circuit of a continuous-flow apparatus. This was chosen for two reasons:

(1) The signs of anaesthesia given by this sequence are, in practice, those of ether anaesthesia, as described by Guedel (1937).

(2) It was considered safe, with this sequence, to obtain a wide range of depth of anaesthesia in selected healthy subjects.

The stages of anaesthesia were considered to be as follows:

Stage I. This stage, which was not examined, terminates in a state of analgesia.

Stage II. This stage, frequently called the stage of excitement, is that in which control by the higher centres is lost, and marked muscular activity may occur.

Stage III. This is the stage of surgical anaesthesia. It is divided into four planes:

Plane 1. This is indicated by the commencement of automatic respiration. The eyeballs are mobile, or fixed out of centre.

Plane 2. This is indicated by central fixation of the eyeballs, by a slight slowing in the rate of respiration, and a slight decrease in its depth.

Plane 3. This is indicated by commencing failure of intercostal activity. There is an expiratory pause.

Plane 4. The intercostal muscles are said to be paralysed. Jerky diaphragmatic movements are present.

The signs are present during both induction of anaesthesia and recovery from it. In the recovery phase, however, signs are not clear-cut and reliable. It was necessary in this investigation to judge levels of anaesthesia clinically, as an electroencephalograph was not available. It was considered justifiable to push anaesthesia to the upper level of plane 4 for a brief period, in a few healthy subjects.

Technique:

Muscles examined: The muscles examined were:

(a) Biceps brachii. The arm was abducted at approximately 90° , and the forearm was supported to prevent hyper-extension at the elbow.

(b) Erector spinae. In two patients of the second series it was convenient to examine this muscle.

(c) Rectus abdominis. The upper rectus abdominis was used.

(d) Rectus femoris. The muscle-mass at the middle of the anterior aspect of the thigh has been called, for convenience, the rectus femoris.

General Anaesthesia: Tonometer readings were taken at a point overlying the selected muscle, first with the patient conscious, then at various levels of ether anaesthesia.

General Anaesthesia with Superadded Specific Relaxant: Tonometer readings were taken at a point overlying the selected muscle, firstly with the patient conscious, secondly in a state of light general anaesthesia (first or second plane of the third stage), and thirdly, after the intravenous injection of a specific relaxant drug. In a number of patients, readings were also taken in the immediate post-operative period; after giving prostigmine to counter-act specific relaxant drugs; and sometimes on recovery of full consciousness.

Anaesthesia was usually obtained, as before, by the nitrous-oxide, oxygen, ether sequence. A few variations were introduced, however. Eighteen of the twenty-seven patients received a small dose of sodium thiopentone (0.2-0.5 gramme.) to induce anaesthesia. Small doses were necessary to avoid masking unduly the signs of anaesthesia. In a few patients "Trilene," a preparation of trichlorethylene, was used instead of ether.

The most frequently employed specific relaxant drug was d-tubocurarine chloride (T in tables). This was given intravenously in doses of 10-20 mg. The small dose was used in children and in association with ether, as Auer and Meltzer (1914) and Gross and Cullen (1943) have stated that ether potentiates curariform activity. Gallamine triethiodide (G. in tables), usually in doses of 80mg. intravenously, was sometimes used instead of d-tubocurarine chloride.

In a few cases larger doses of these agents were used in the course of major operations. For each state examined, five determinations with the tonometer were made in rapid succession at a point overlying the selected muscle. The mean of these readings was calculated. The figures in the tables reporting the results are the difference between this mean and the lowest such mean recorded for the same muscle, in the same patient, in the same experiment. The use of this method for reporting results is discussed later.

Results:

General Anaesthesia: The results are shown in Table 4.

(a) Biceps brachii: The tonometer readings seem to show that tone falls as anaesthesia deepens. A high reading in the conscious subject was frequently due to difficulty in persuading the subject to relax. Relatively high readings were also found in first plane anaesthesia. Low readings were found in planes 2, 3, 4. Subjects E2 and E7 unexpectedly show high readings in second plane anaesthesia. The biceps brachii was subsequently found to be an unsatisfactory muscle for clinical testing, as it was too easily affected by change of posture. (vide infra).

(b) Rectus abdominis: Results for the rectus abdominis do not seem to be consistent with respect to plane of anaesthesia. A high or low reading may be obtained in the anaesthetised subject. The governing factor would seem to be not the plane of anaesthesia but the depth of respiration.

TABLE 4. RELATION BETWEEN PLANE OF ANAESTHESIA AND VARIATION IN MEAN TONOMETER READING.

a. Biceps Brachii.

No.	Conscious.	Plane 1.	Plane 2.	Plane 3.	Plane 4.	Leaving Theatre.
E1.	15	8		0		
E2.	45		41		0	
E3.	5	5	5	0		
E4.	0	12	6			
E5.	21	26	0			
E6.	7		6	7	0	
E7.	28		27	0		
E8.	61	41			0	
E9.	28	44		0		
E10.	70		1			0
E11.	150		8	0		
E12.	70	10		0		40

b. Rectus Abdominis.

No.	Conscious.	Plane 1.	Plane 2.	Plane 3.	Plane 4.	Leaving Theatre.
E2.	7		45		0	
E3.	0	2	15	16		
E4.	35	8	0			
E5.	0		105			
E6.	0		26	0	24	
E7.	3		63	0		

See overleaf for explanations

TABLE 4.

c. Anterior Thigh Muscles.

No.	Conscious.	Plane 1.	Plane 2.	Plane 3.	Plane 4.	Leaving Theatre.
E9.	22			0		1
E10.	23		3	0		
E12.	0	10		0		10
E13.	15	5	0	0		
E14.	0	10	2	0	0	0
E15.	0	10	0	0		10
E16.	0	15	0	0		5
E17.	0	10	3	0	0	0
E18.	12	10	2	0	0	0

Column 1 gives reference number of patient.

Column 2 gives tonometer reading on muscle before start of anaesthesia.

Columns 3 - 6 give tonometer readings in successive planes of third stage anaesthesia.

Column 7 gives tonometer reading at conclusion of operation administration of anaesthetic had been discontinued.

In each state examined, five determinations were made in rapid succession, and the mean was calculated. The figures given here are the difference between this mean and the lowest such mean recorded for that patient.

In the pilot experiments it was found that there was a cyclic variation in reading, higher in the inspiratory phase of respiration. In one patient who chanced to have an attack of hiccups, a very high tonometer reading was observed during the attack.

Readings were taken whenever possible in the expiratory phase of respiration, to eliminate the cyclic variations as far as possible. The expiratory phase was chosen because it afforded more time for observations.

(c) Rectus femoris: Results obtained with this muscle are shown for nine subjects. The lowest reading was found in third plane anaesthesia.

General Anaesthesia with superadded Relaxant Drugs: The results are shown in Table 5.

(a) Biceps brachii: The lowest readings were obtained after the exhibition of relaxant drugs. There was an increased reading in the conscious state and in first plane anaesthesia. Great care was taken to avoid postural difficulties caused by alterations in flexion-extension, abduction-adduction, and pronation-supination position. A special support was devised and made in an attempt to ensure the maintenance of a standard position of the arm, but it was not completely satisfactory. It is therefore considered the results obtained with the biceps brachii are not reliable, and should be interpreted with caution. e.g. See result in case R11, Table 5a.

(b) Erector spinae: It was found convenient to test two subjects. The more interesting result is R7. Here the lowest value occurred in the conscious state. The subject was then turned

TABLE 5. THE EFFECT OF SPECIFIC RELAXANT DRUGS SUPERIMPOSED ON LIGHT ANAESTHESIA AS SHOWN BY DIFFERENCE IN MEAN TONOMETER READINGS.

a. Biceps Brachii.

No.	Relaxant.	Conscious.	Plane 1.	Plane 2.	With Relaxant.	Leaving Theatre.
R1.	10T	25	25		0	
R2.	10T	35	23		0	
R3.	8T	41	51		0	
R4.	10T	96	60		0	
R5.	10T	3	21		0	
R6.	10T	71	42	9	0	
R9.	10T	90	41		0	
R10.	15T	76	21		0	16
R11.	15T	0	13		56	26
R12.	15T	38	6		0	8
R14.	20T	8	8		0	18

b. Erector Spinae.

No.	Relaxant.	Conscious.	Plane 1.	Plane 2.	With Relaxant.	Leaving Theatre.
R7.	80G	0		50	100	
R24.	80G	40			0	10

c. Rectus Abdominis.

No.	Relaxant.	Conscious.	Plane 1.	Plane 2.	With Relaxant.	Leaving Theatre.
R1.	10T	47	45		0	
R2.	10T	70	82		0	
R3.	8T	0	100		20	
R4.	10T	3	13		0	
R5.	10T	0	12		24	
R6.	10T	40			0	

See end of Table for explanations

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d. Rectus Femoris.

No.	Relaxant.	Conscious before.	Plane 1.	Plane 2.	With Relaxant.	Leaving Theatre.	Conscious after.
R6.	10T.	24	12		0		
R8.	80G.	0	20		0		
R9.	10T	14	5		0		
R13.	20T	11	10		0	10	
R14.	20T	19	9		0	10	9
R15.	15T	11			0	11	10
R16.	10T	12		3	3		0
R17.	10T	1	27		10	9	0
R18.	10T	10		1	0		1
R19.	15T	1			0		2
R20.	7T	0		0	0	19	
R21.	80G	5		5	0	5	
R22.	60G	0	0	0	0	20	0
R23.	15T	0	10	0	0	10	0
R25.	20T	30			0	30	0
R26.	80G	0			0	30	0
R27.	80G	10			0	10	
R28.	80G	10		7	0	7	
R29.	20T	0	10		0	0	
R30.	10T	10		0	0	0	
R31.	80G	0	0		0		0
R32.	80G	0		0	0		0
R33.	15T	0	0	0	0	0	

See end of Table for explanations.

d. Rectus Femoris (contd).

No.	Relaxant.	Conscious before.	Plane 1.	Plane 2.	With Relaxant.	Leaving Theatre.	Conscious after.
R34.	15T	0	10	0	0	10	
R35.	35T	0	0	0	0	10	0
R36.	30T	0	10	0	0	0	
R37.	170G	0	0	0	0	10	0

Column 1 gives reference number of patient.

Column 2 gives dosage of relaxant drugs employed.

e.g. 15T = 15 mg. of d-tubocurarine chloride.

80G = 80 mg. of gallamine triethiodide.

Column 3 gives tonometer reading before anaesthesia started.

Columns 4 - 5 give tonometer reading in successive planes of anaesthesia.

Column 6 gives tonometer reading after injection of relaxant drug.

Column 7 gives tonometer reading at conclusion of operation and anaesthetic.

Column 8 (5d. only) gives tonometer reading when patient was fully

conscious on recovery from anaesthesia.

In each state examined, five determinations were made in rapid succession, and the mean was calculated. The figures given here are the difference between this mean, and the lowest such mean recorded for that patient.

back into the supine position, anaesthetised with 0.5 gramme of sodium thiopentone, nitrous-oxide, oxygen, and "Trilene." A nasal endotracheal tube was passed blindly in second plane anaesthesia. The patient was then rotated into the prone position and another series of readings was taken. They showed a considerable increase in mean readings. Gallamine triethiodide, 80 mg., was then injected intravenously, and five minutes later another series of readings was taken. Rather surprisingly a further increase in mean reading was found. It was then realised that, under the conditions of the experiment (a large man breathing through a rather narrow endotracheal tube), the erector spinae had become an active respiratory muscle. The reading has risen as his respiration (unaffected here by gallamine) had increased in depth. This recalled similar findings during the examination of the rectus abdominis.

(c) Rectus Abdominis: Six subjects were examined. Neither increased depth of anaesthesia nor curarisation necessarily produced a fall in tonometer-reading. A low reading was obtained when respiration was depressed, and vice versa.

(d) Rectus Femoris: Twenty-seven subjects were examined. It was found that muscle-tone rose in second stage anaesthesia (R23) and in first plane anaesthesia (particularly R17). Tone was minimal or near-minimal in second plane anaesthesia. Tone was minimal after the giving of relaxant drugs (not quite true in R17).

In the early stages of recovery, tone rose again. This corresponds with first plane anaesthesia, or with emergence into second stage anaesthesia. When the patient was conscious after anaesthesia, readings as low as those obtainable in the curarised subject were almost always

obtainable. The exceptions are R14 and 15. These subjects, however, found it difficult to relax when conscious, both before and after anaesthesia.

A special study of the tone of muscles in the immediate post-operative period was conducted in fifteen of the patients receiving relaxant drugs. Prostigmine was given to eight of these patients. The results are given briefly in Table 6. The following notes describe the experiments.

T = d-tubocurarine chloride.

G = gallamine triethiodide.

D = tone-difference. i.e. difference between mean tonometer readings and the lowest recorded mean.

R14. Given 20 mg. T.

2 minutes after operation, D = 10.

R15. Given 20 mg. T.

After prostigmine, D = 9.

1 minute after operation D = 11.

Fully conscious, D = 10.

R19. Given 15 mg. T.

1 minute after operation, D = 20.

R20. Given 7mg. T.

5 minutes after operation, D = 19.

R21. Given 80mg. G.

At end of operation, D = 0.

Given prostigmine, D = 5.

R22. Given 60 mg. G.

2 minutes after operation, D = 11.

(Patient still and quiet).

R25. Given 20 mg. T.

During skin-suturing, D = 0.

Five minutes after operation, D = 30.

(Patient still and quiet).

R26. Given 80 mg. G.

During skin-suturing, D = 30.

After prostigmine, D = 30.

(It is thought that the dose of relaxant was too small, as a considerable quantity of ether was needed to maintain relaxation).

R27. Given 80 mg. G.

During skin-suturing, D = 0.

Five minutes after operation, D = 10.

R29. Given 20 mg. T.

During skin-suturing, D = 0.

Unaltered by prostigmine or termination of anaesthesia.

R34. Given 15 mg. T.

During skin-suturing, D = 0.

Five minutes after operation, D = 10.

R35. Given 35 mg. T.

During skin-suturing, D = 0.

Unaltered by prostigmine.

Five minutes after operation, D = 10.

R36. Given 30mg. T.

During skin-suturing, D = 0.

Unaltered by prostigmine or termination of anaesthesia.

R37. Given 170 mg. G.

During skin-suturing, D = 0.

Unaltered by prostigmine.

Five minutes after operation, D = 10.

From this investigation it is clear that in most subjects there is an early post-operative rise in muscle-tone above the basal level. It appears when first plane or, more probably, second stage anaesthesia is reached. It will not appear early if general anaesthesia has not been sufficiently lightened towards the end of the operation.

Just as it has been shown that the injection of relaxant drugs does not produce any decrease in tone in a relaxed muscle, so it has been shown that prostigmine does not necessarily produce any increase in tone. Prostigmine must, of course, be given when there is an indication for it, but it will not, of itself, produce any increase in muscle-tone. An increase in tone will occur only when both anaesthesia and curarisation are sufficiently light.

TABLE 6. ALTERATIONS IN MUSCLE-TONE AS SHOWN BY DIFFERENCES IN MEAN TONOMETER READINGS AT END OF OPERATION.

Case.	Last Stitches.	After Prostigmine.	5 minutes after stopping anaesthetic.
R14.	0	-	10
R15.	0	9	11
R19.	0	-	20
R20.	0	-	19
R21.	0	5	
R22.	0	-	11
R25.	0	-	30
R26.	30	30	30
R27.	0	-	10
R29.	0	0	0
R33.	0	0	0
R34.	0	-	10
R35.	0	0	10
R36.	0	0	0
R37.	0	0	10

In each state examined, five determinations were made in rapid succession, and the mean was calculated. The figures given here are the difference between this mean and the lowest such mean recorded for that patient.

Discussion:

Definition of Muscle-Tone:

The usual definition of muscle-tone ascribes tone wholly to slight contraction of muscle-fibres. Yet in the relaxed state, as shown by Adrian and Bronk (1929), muscles have not been shown to give rise to action-potentials. Floyd and Silver (1950), recording patterns of activity in anterior abdominal wall muscles in Man, showed that no action-potentials could be recorded from the rectus abdominis while the subjects stood, or lay at ease.

Hoeffler (1941) demonstrated that no action-potentials could be recorded from limb muscles at rest even though they were under slight tension.

McKinley and Berkwitz (1933) suggest that in a stretched muscle in which no action-potentials can be recorded, the resistance or "tone" exhibited is due to the elasticity of the muscle.

If resting tone is due to contraction of muscle-fibres, some explanation must be found for the absence of action-potentials. If, on the other hand we ascribe resting tone principally to the elastic properties of the sarcolemma (Hill 1950), the difficulty is resolved. Muscle-activity still plays an important part in tone, particularly postural tone, which was the principal concern of Sherrington. The tone produced by muscle-activity is impressed on the basal tone due to the physical properties of the muscle, and increases the resistance of the muscle to extension. Resistance to extension includes the effects both of activity and of the elastic properties of the sarcolemma, and a definition of tone in terms of resistance to extension will cover the two concepts of tone which have hitherto been divergent.

Methods of Measuring Muscle-Tone:

Methods based on static elastometry have been attacked as unsatisfactory by Simonson et al. (1949), on the ground that a viscous-elastic system such as muscle has the property of being modified by the continued action of stress. They claim that deformation is progressive, and that because of this, it is difficult to define a true end-point.

In the experiments reported here, however, there has been no difficulty in defining an end-point, either in the laboratory tests, or in clinical tests on the thigh muscles. At least five observations have always been made before calculation of a mean, and the consistency of the observations has been high. This has been shown clearly on page 11.

The work of Henderson et al., since it was partly concerned with the effects of anaesthesia on muscle-tone, calls for a few comments. (These workers found a fall in intra-muscular pressure (which they equated with muscle-tone) after surgical operations)

(1) The work was done on the biceps muscle, which has been shown to be satisfactory under strictly controlled conditions in a laboratory, but unsatisfactory for clinical estimation of changes in tone when using a "hardness" method.

(2) It can readily be understood that a patient might be better able to relax after his operation than before it.

(3) No details of general anaesthesia are given, but it should be noted that similar changes were found after herniotomies conducted under local analgesia. The changes found would therefore appear not to be specifically associated with general anaesthesia.

(4) During an experiment conducted on cats under 'Nembutal'

anaesthesia, Henderson notes - "complete anaesthesia resulted, but with retention of nearly normal tonus, as indicated by very active knee jerks." If this can indeed be taken as an indication of "nearly normal tonus," it will be shown in the second part of this thesis that abdominal surgery can proceed very happily in curarised subjects under such conditions.

The tonometer has two disadvantages:

(1) Mean readings obtained from a muscle in a particular subject cannot be compared with mean readings obtained from the corresponding muscle in any other subject, or with mean readings obtained from any other muscle in the same subject.

This is because readings are modified by the thickness of subcutaneous tissue, and by variations in skin-tension (Dick 1951). This difficulty has, to some extent, been overcome by the adoption of a "difference" method for reporting results.

(2) The apparatus must be maintained in a vertical position, as it is dependent on gravity. This is a disadvantage in measuring the tone of many muscles.

The tonometer possesses the following advantages:

- (1) It is eminently portable.
- (2) Readings are rapidly obtainable.
- (3) It discloses fine alterations in the tone of muscles.

The tonometer thus satisfies the criteria set out on page 7, and it is considered that its disadvantages are largely counter-balanced by its advantages for this investigation.

Clinical Results:

The results obtained with the biceps brachii under clinical conditions were regrettably inconsistent. This is shown most clearly in Table 5a. Subject R11 gave a considerably higher tonometer reading after the administration of a relaxant drug than in the conscious state. Very high readings in the conscious state were obtained in subjects R4, 6, 9 and 10. In addition, in some patients it was found possible to produce considerable variations in reading from minor alterations in the position of the arm. From these peculiarities, it was concluded that, though the biceps brachii is a suitable muscle for testing with the tonometer in a laboratory with the subject conscious, it is unsuitable for use under clinical conditions in an operating-theatre, with the subject unconscious. Under such conditions the maintenance of precise control of the position of the arm is difficult. No other conclusions are drawn from these results.

Results obtained from examination of the rectus abdominis with the tonometer were likewise unsatisfactory. The difficulty here resulted from two associated factors:

- (1) Alteration in tone of the muscle with phases of respiration.
- (2) Alterations in intra-abdominal tension.

It is well-known that the abdominal muscles relax during inspiration and contract, if at all, during expiration. The tonometer, however, shows an inspiratory rise in reading. (pilot experiments). Mills (1950) has shown, using an intra-gastric balloon, an inspiratory rise in intra-abdominal tension. It is clear that the tonometer, when applied

to the abdominal muscles, was influenced principally by alterations in the intra-abdominal tension. This is confirmed by a study of Tables 4b and 5c, which show very large rises in reading in light anaesthesia (when this is associated with vigorous breathing) and a fall in reading in deep anaesthesia or after curarisation (only when these states are associated with depressed respiration). It follows that results obtained by tonometry on these muscles are of little value in determining alterations in muscle-tone. No other conclusion is drawn.

A method which has been used experimentally for showing changes of tone in abdominal muscles is that of Longo and Bovet (1949). The method entails determining the pressure necessary to inject a known volume of air into the sealed abdominal cavity of a rabbit. The method does not seem to be easily applicable under clinical conditions.

The results obtained by tonometry on the thigh-muscles are considered to be consistent and reliable.

The method used for recording results was dictated by the instrumental peculiarities mentioned on page 35. By taking as zero the minimum recorded mean, and expressing all the other results obtained with the same muscle as positive differences from this base-line, it became possible to compare results from patient to patient. The use of the zero for convenience did not imply that a minimal level of muscle-tone had necessarily been attained. A study of Table 5d, however, would suggest that the zero does represent a minimal level of tone in this table. R35, 36 and 37 were given much larger doses of a relaxant

drug than the other subjects in the Table. The readings obtained in the patients given large doses of a relaxant follow precisely the same pattern as the readings in patients given smaller doses. There is a slight rise in reading in first plane anaesthesia, a return to the basal level in second plane anaesthesia, unaltered by relaxant drugs; a possible rise in reading during recovery; and after recovery, a reading similar to that obtained in the conscious subject before the induction of anaesthesia. It seems reasonable therefore, to assume that when a zero is based on a reading taken in an adequately curarised muscle, it does in fact represent a minimal level of muscle-tone.

The results show that it is possible to obtain the same degree of relaxation of muscles in the conscious state as is obtainable in deep anaesthesia or after the administration of relaxant drugs. Some subjects found it difficult to relax in the conscious state both before and after anaesthesia, but this was not a general finding.

In four patients, tone was assessed during second stage anaesthesia. It was not convenient to show these few results in the tables. They merely confirmed the clinically apparent fact that there is a considerable rise in muscle-tone in this stage of induction of ether anaesthesia, even if muscular hyperactivity is not manifested in movement. There is also in many subjects a slightly increased muscle-tone in the first plane of third stage ether anaesthesia. It is suggested that this may be a continuation of the muscular activity of the second stage. It is shown that when second-plane anaesthesia is attained, muscle-tone is minimal or near-minimal, and that it is minimal thereafter.

As muscle-tone is not necessarily decreased by deep anaesthesia, it is difficult to incriminate "loss of tone" as the cause of post-operative pulmonary complications. After an improperly given anaesthetic, a patient may lie inert for several hours. This will certainly predispose to pulmonary complications, but the muscles will not be "tone-less." They will stay at their basal level, as there will be no motor activity. The tonometer will show a rise in the tone of such muscles only as the patient emerges into the second stage of anaesthesia.

The same features occur in curarised muscle. If a patient is still fully anaesthetised, muscle-tone will not be increased by giving an antidote to the relaxant drugs. Such an increase would result only in a patient who was adequately curarised but inadequately anaesthetised.

The purpose both of deep anaesthesia and of relaxant drugs would appear to be, not the obtaining of muscular relaxation, but its maintenance undisturbed by protective reflexes. This has been demonstrated only for the thigh muscles, but it is suggested that the findings are generally true for skeletal muscles. Even the abdominal muscles, which used to be the principal enemy of the anaesthetist, can almost be completely relaxed in the conscious state, as was shown by Floyd and Silver's failure to obtain action-potentials from them in the resting state.

Gentle palpation of the abdomen of a co-operative patient shows that the muscle is quite slack. Vigorous or painful manipulations, or apprehension of this on the part of the patient, will set up protective reflexes resulting in rigidity. The same sequence of

events occurs in the patient under light thiopentone narcosis. If a patient is anaesthetised so that he no longer responds to peripheral stimuli, he will still respond by a segmental reflex to severe peritoneal traction. If a lightly anaesthetised patient is given an adequate dose of a relaxant drug, the protective reflexes will be abolished, and muscle-tone will not be disturbed by the surgeon's manipulations.

The tonometer cannot give any information as to whether curarisation is adequate. If this is to be determined before surgical stimuli are applied, some other forms of stimulus must be applied to the patient before he is presented to the surgeon. Electrical stimulation of a peripheral nerve, with observations on alterations in the response obtained, suggests itself as a convenient method.

Conclusions.

- (1) The tonometer is an effective instrument, under the conditions described, for determining alterations in tone of skeletal muscles.
- (2) The increased muscle-tone characteristic of second stage anaesthesia may persist in the first plane of third stage anaesthesia.
- (3) Muscle-tone in the deeply anaesthetised subject is not necessarily less than in the conscious state.
- (4) Muscle-tone in the effectively curarised subject is not necessarily less than in the conscious state.
- (5) It is suggested that both deep anaesthesia and relaxant drugs have the same purpose; the maintenance of muscular relaxation by the abolition of protective segmental reflexes.
- (6) It is clear that the Tonometer can give little information as regards the effectiveness of relaxant drugs in maintaining the relaxation of muscle, as no further changes in muscle-tone are produced by the relaxant after adequate anaesthesia. The effectiveness of the relaxant must be judged by the absence of reflex increases in tone, rather than by any change in the basic level. An investigation of the alterations in reflex-response and the response to nerve-stimulation should provide this information. This is now reported in Part 2 of the thesis.

PART 2.

TENDON-REFLEXES AND NERVE-STIMULATION.

INTRODUCTION.

It is now proposed to examine further the effects on muscle of the administration of relaxant drugs. It has been shown in the first part of the thesis that the purpose of relaxant drugs is to abolish reflex response to operative stimuli. The effects of relaxant drugs on reflexes, and on the response to stimulation of peripheral nerves, will now be examined. It will be necessary to make a preliminary examination of the effects of anaesthesia on both phenonema.

The most easily available reflexes are the ordinary tendon-jerks. Those employed were, the biceps, triceps, supinator, knee, and ankle jerks. The effect of anaesthesia on these reflexes must be described first, so that the effects of superimposed relaxant drugs may become clear. The two nerves employed for electrical stimulation were, the ulnar nerve stimulated percutaneously at the elbow, and the tenth intercostal nerve stimulated by a needle electrode in the mid-axillary line.

It is difficult to gauge effective curarisation clinically before an operation starts. The amount of decrease in the depth of respiration is frequently employed as a sign of adequate curarisation. Apnoea, however, may occur from a combination of factors causing central respiratory depression, and may be prolonged by vigorous artificial respiration. In the absence of active respiration, it is necessary to judge the effectiveness of curarisation by the ease with which

the patient's chest may be inflated, or by the satisfaction of the surgeon. The ease of inflation of the patient's chest may, however, be influenced by factors other than the effectiveness of curarisation.

It is true that surgical satisfaction can be achieved very simply by excessive dosage of relaxant drugs. Although these drugs have no known toxic effects - provided efficient artificial respiration is maintained - such a practice is to be deprecated. Excessive curarisation may lead, without clinical indication, to inadequate anaesthesia. (Winterbottom 1950). If a patient is given so much of a relaxant drug that total neuro-muscular block results, it is conceivable that he might become conscious in the course of an operation, and be unable to protest. It is, however, possible to secure surgical satisfaction with only partial neuro-muscular block. If anaesthesia then becomes inadequate, reflex indications appear - in the form of a raised eyebrow, a wrinkling forehead, or a moving finger - long before the patient returns to consciousness. Anaesthesia may then be deepened rapidly. It is therefore clear that anaesthetists should present patients for operation at a level of curarisation sufficient to satisfy the surgeon, but insufficient to prevent signs of inadequate anaesthesia.

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Three stages of "curarisation" have been described.

("Curarisation" is employed merely as a convenient term to denote treatment with a relaxant drug).

(1) Stage of Bremer: This was described by Bremer et al. (1927). Bremer carried out animal experiments both on intact and on decerebrate mammifera. He describes the effect of injecting small doses of curare as follows - "La flaccidité de l'animal ainsi légèrement curarisé contraste avec la vivacité et la vigueur de ses réflexes et avec la régularité de sa respiration."

(2) Stage of Vulpian: Vulpian (1870) described a state of curarisation in which voluntary and reflex movements were absent, but electrical stimulation of a nerve produced contraction of the supplied muscle.

(3) Stage of Claude Bernard: Claude Bernard (1856) described a state of curarisation in which a muscle no longer responded to indirect stimulation through its nerve, but responded only to direct stimulation. (Bernard quoted by McIntyre, 1947).

It should be noted:

(a) That these observations were made with a crude preparation of curare, not with the refined product, d-tubocurarine chloride, used at the present time.

(b) Just as the stages of anaesthesia are described in relation to ether anaesthesia, and are not necessarily completely applicable in the case of other anaesthetics, so the stages of curarisation are described in relation to curare, and are not necessarily completely applicable in the case of other relaxants.

The Effect of Anaesthesia on Tendon-Reflexes and the Response to Nerve-Stimulation.

Technique:

Tendon-jerks were obtained by the standard clinical method, first in the conscious patient, then in the anaesthetised patient, in various planes of anaesthesia, induced by various agents. Any change in the tendon-jerks under these conditions was recorded.

The ulnar nerve was stimulated at the elbow by an instrument, hereafter called the stimulator, giving one-millisecond pulses of variable voltage (0-130 volts). The pulse-frequency used was either one or sixteen per second. (Output impedance varied according to voltage setting, with a maximum during pulses of 10,000 ohms).

The voltage setting of the stimulator was adjusted so as to give a minimal response - usually a slight movement of the little finger. The response was kept at a constant level by varying the voltage of the stimulus. Any voltage adjustment necessary to reproduce the minimal twitch was recorded.

Various anaesthetic techniques were used. Premedication consisted usually of papaveretum gr.1/3, and scopolamine gr.1/150. In small or feeble subjects, the papaveretum was replaced by morphine gr.1/6, and in elderly subjects the scopolamine was replaced by atropine gr.1/100. Closest consideration was given to techniques employing as the principal agent either diethyl ether or nitrous oxide.

Di-ethyl ether: Ether was employed in eleven patients, using the nitrous oxide, oxygen, ether sequence in a semi-closed circuit, as described in the first part of the thesis.

In another nine patients, the same technique was employed after a preliminary induction dose of sodium thiopentone by the intravenous route.

Nitrous oxide: Nitrous oxide was employed in two patients after induction of anaesthesia with sodium thiopentone. In another 44 patients, fifty mg. of pethidine hydrochloride was given intravenously in addition to the thiopentone. Anaesthesia was maintained with nitrous oxide/oxygen. This technique gave a stable level of anaesthesia with the signs expected in the first plane, or very early second plane of third stage anaesthesia.

Another technique tested was: thiopentone, nitrous oxide/oxygen, and "Trilene." (6 cases).

Results:

Ether techniques: With nitrous oxide, oxygen, and ether, the tendon-reflexes were present in first plane anaesthesia in all of the eight patients in whom they were tested. In second plane anaesthesia, reflexes were abolished in three patients, and ankle clonus developed in one patient. In third plane anaesthesia, all reflexes were abolished in all but two of the patients examined. In these two patients, the ankle jerk was retained until the onset of fourth plane anaesthesia.

The addition of thiopentone made the reflexes more variable in first plane anaesthesia in the eight patients in whom the reflexes

were tested, some reflexes being abolished at that level in three patients. In second plane anaesthesia, three patients retained the knee-jerk, and one patient retained the biceps-jerk. In third plane anaesthesia, one patient retained the knee-jerk, and one patient retained the biceps-jerk. All tendon-jerks were abolished in fourth plane anaesthesia.

Electrical stimulation of the ulnar nerve was performed in all eleven patients given nitrous oxide, oxygen, and ether without thiopentone, and in one patient given a thiopentone induction. No significant alteration in the threshold of stimulation was noted in any patient during the first and second planes of anaesthesia. Ten patients were examined in third plane anaesthesia, and in five of these a rise in threshold occurred, of about 15%. Five patients were examined in fourth plane anaesthesia. The threshold to stimulation in two of these showed a rise, not exceeding 10%, as compared with the threshold found in third plane anaesthesia.

Nitrous oxide techniques: A thiopentone induction, followed by nitrous oxide/oxygen maintenance, was used in two cases. No effect on the reflexes was noted. Reflexes were tested in another thirty-two patients, who received fifty milligrammes of pethidine in addition to thiopentone nitrous oxide/oxygen. No effect on the tendon-jerks was observed on thirty cases. In the other two cases, a few of the tendon-jerks were abolished, but most were retained.

The response to electrical stimulation was observed in a total of forty-four patients. No significant alteration was noted in thirty-nine patients. In the other five patients, marked alterations were observed in the voltage required to produce a response. In one of these, the difference was as much as 50%. It is thought that such large variations, only occasionally observed, are attributable to movement of the electrode relative to the nerve.

A thiopentone induction followed by nitrous oxide, oxygen, and "Trilene" was employed in six patients. In only one patient were all the reflexes retained in first plane anaesthesia, but usually only the supinator-jerk was lost. Second plane anaesthesia was attained in three patients. One of these patients had then lost all his tendon-jerks; the other two patients had lost some tendon-jerks, but not all.

It was then decided that the most satisfactory technique to adopt for further examination was the thiopentone, nitrous oxide/oxygen, pethidine technique. With this technique, a standard level of anaesthesia can easily be maintained. This technique also has the advantage of being, in combination with relaxant drugs, applicable to any patient, producing no significant alteration in the tendon-jerks, or in the response to stimulation of the ulnar nerve. It was realised that this choice inevitably encouraged early apnoea from central depression. This, though frequently welcomed by the anaesthetist as an advantage of the technique, was experimentally regrettable, as it excluded the possibility of relating apnoea to degree of curarisation.

The Effect of Relaxant Drugs on Tendon-Reflexes and on the Response to Nerve Stimulation.

Technique:

The patients selected for these investigations were all subjected to upper abdominal laparatomies. (There are a few exceptions to this in the cases in which the effects of ulnar and intercostal stimulation are compared).

The nerve chosen for stimulation was, in most cases, the ulnar nerve. This was stimulated by a surface electrode bandaged in position over the nerve at the elbow. It was considered of interest to compare the results obtained, with the results of indirect stimulation of the abdominal muscles. The tenth intercostal nerve was stimulated, in the mid-axillary line, by a needle electrode fixed in position by adhesive tape. By this technique, a reaction in the rectus abdominis must be due to indirect stimulation, but the oblique muscles may be stimulated directly. Any contraction of the oblique muscles was, therefore, disregarded. (By using an ultra-short stimulus, it is possible to produce indirect stimulation without direct stimulation. This was tried, but it introduced some technical difficulties, and was thought unnecessary).

The contraction of the rectus abdominis could be observed percutaneously in thin subjects, by observation of an umbilical twitch, or by palpation. After opening the abdomen, the muscle could be observed contracting, and could be palpated by the surgeon. It was thought that slight displacement of the needle might occur, as a

consequence of respiratory movements, and that this displacement, invoking the inverse square law, might produce considerable alterations in the minimal voltage at which a response occurred. Threshold measurements would then be invalid. For indirect stimulation of the rectus abdominis, therefore, a supramaximal stimulus was always employed.

The response to indirect stimulation by single shocks was recorded, in the case of ulnar stimulation, as alteration in nature of response, and alteration in the voltage at which a response first occurred. Three phases of response were distinguished. In phase 1, a series of stimuli at a frequency of one per second produced an equivalent series of twitches. In phase 2, a series of stimuli produced only an initial twitch or, at the most, a short series of twitches of diminishing intensity. Phase 2 corresponds to Wedensky inhibition (*Wedensky, 1886). In phase 3, a series of stimuli produced no twitch. In the case of intercostal stimulation, where a supramaximal stimulus was employed, only the alteration in phase of response was noted.

The relaxant drugs employed were d-tubocurarine chloride, gallamine triethiodide, and decamethonium iodide. The largest series of patients was treated with the first-named relaxant. It was felt justifiable in some patients to give very large doses of d-tubocurarine chloride or gallamine triethiodide. No such liberty was taken with decamethonium iodide, as no safe and efficient antidote is yet known.

Following this work, it was thought advisable, in the case of patients treated with d-tubocurarine or gallamine, to study the response to tetanising shocks applied to the ulnar and the intercostal nerves.

* Wedensky quoted by Rosenblueth, 1950

Tetanus was produced by supramaximal stimuli at the rate of sixteen per second. These stimuli were applied for periods of five seconds. Particular attention was paid to the ability of the muscle to maintain its tetanic contraction. Tetanus was assessed visually, and by palpation of the contracting muscles. Tetanus was said to be maintained, when it seemed to the observer that the initial strength of contraction was not reduced until the stimulus was withdrawn. Tetanus was said to be poorly maintained, when the initial strength of contraction was succeeded by maintenance at a lower level. Tetanus was said not to be maintained, when the initial contraction fell off rapidly to an undetectable level.

In studying the effects of relaxant drugs on tendon-jerks and on the response to nerve-stimulation, observations were made at the following stages.

- (1) In the conscious state.
- (2) After injection of pethidine hydrochloride.
- (3) After injection of sodium thiopentone, and commencement of inhalation of nitrous oxide and oxygen.
- (4) At intervals after the injection of varying doses of a relaxant drug.
- (5) Before and after the injection of prostigmine, if given.
- (6) On the termination of the operation and anaesthetic.

Other features observed were the level of curarisation associated

- (a) with surgical satisfaction.
- (b) with apnoea.

It is regretted that it was not possible to make observations of each event in each patient. Experimental conditions were not ideal, and

clinical considerations frequently forbade observations of purely experimental interest.

RESULTS.General Results:

The general results obtained with the three specific relaxants have been compressed, so far as possible, into Tables 7, 8 and 9. Table 7 shows the effect of the administration of d-tubocurarine on the tendon-jerks and on the response to stimulation of the ulnar nerve. This was the largest group, and it was thought useful to divide the patients into those who were or were not given unnecessarily large doses of d-tubocurarine chloride. In the case of those given very large doses, the relaxation was, of course, satisfactory but no dose-level is given for surgical satisfaction, as this was not tested until an unnecessarily large dose had been given.

The results in Table 7a, concerned with normal doses of d-tubocurarine, show that:

- (1) It is unnecessary to abolish tendon-jerks completely in order to obtain relaxation satisfactory for upper abdominal surgery.
- (2) Commencing failure of the tendon-jerks usually indicates a level of curarisation satisfactory for surgery.
- (3) A slight rise in the threshold to nerve stimulation is usually an indication of a level of curarisation satisfactory for surgery.

Table 7b, concerned with supra-normal doses of d-tubocurarine, shows that:

- (1) Flailing tendon-jerks are usually associated with a rise in threshold of stimulation.
- (2) A phase 2 response is obtained with a dose of 25-50 mg. of d-tubocurarine. The range as expressed is unnecessarily large because of large steps in the dosage scale.
- (3) A phase 3 response is obtained in a range of 40-60 mg. of d-tubocurarine. The range is unnecessarily large because of large steps in the dosage scale.

Table 8 shows the results obtained with gallamine triethiodide. This was a smaller series and was not divided up, but no value is shown for surgical satisfaction in patients given unnecessarily large doses of the relaxant drug.

It appears that gallamine triethiodide produces a series of effects similar at each stage to those produced by d-tubocurarine chloride and shown in Tables 7a and 7b.

Table 9 shows the results obtained with decamethonium iodide. With this agent it was not safe to use abnormally large doses, as there is no satisfactory antidote. The doses used here have been those generally adopted. (Organe, 1950). The results are:

- (1) It was more difficult to obtain surgical satisfaction.
- (2) Even when small doses were given, tendon-jerks were abolished. This was not necessarily associated with surgical satisfaction.
- (3) A rising threshold to nerve stimulation was not necessarily associated with surgical satisfaction.

It may also be noted that endotracheal intubation was found to be relatively difficult with this relaxant.

TABLE 7. THE EFFECT OF d-TUBOCURARINE ON TENDON - JERKS,
RESPONSE TO STIMULATION OF THE ULNAR NERVE,
and STATE OF MUSCULATURE.

a. Normal Dosage.

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery.
1.	65	F	100	Failing at 15 mg.	-	15 mg.
2.	51	F	-	Enhanced at 20 mg.	-	20 mg.
3.	37	M	115	Enhanced at 20 mg.	-	20 mg.
4.	32	M	117	Triceps jerk present, others absent, at 25 mg.	-	25 mg.
5.	60	M	153	Failing at 25 mg.	-	25 mg.
6.	51	M	127	Failing at 15 mg, still present at 20 mg.	Unchanged	20 mg.
7.	57	M	119	Unaltered at 20 mg.	Diminished at 20 mg.	20 mg.
8.	66	M	103	Failing at 15 mg.	Slight rise at 15 mg.	15 mg.
9.	50	M	140	Unaltered at 20 mg. Failing at 25 mg.	-	25 mg.
23.	23	M	134	Unaltered at 30 mg.	-	30 mg.
25.	44	M	137	Unaltered at 20 mg.	-	20 mg.

TABLE 7a (continued).

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery.
29.	67	M	158	Present at 15 mg. Failing at 20 mg.	Rising at 15 mg. Rising at 20 mg.	20 mg.
30.	40	M	125	Unaltered at 20 mg.	Rising at 20 mg.	20 mg.
31.	36	M	136	Failing at 20 mg.	-	20 mg.
32.	30	M	118	Failing at 20 mg.	Unaltered 20 mg.	20 mg.
33.	61	M	-	Unaltered at 15 mg. Failing at 20 mg. and 25 mg.	Rising at 15 mg.	25 mg.
34.	36	F	91	Absent at 20 mg.	Rising at 20 mg.	20 mg.
35.	49	M	146	Failing at 20 mg.	Rising at 20 mg.	25 mg.
37.	57	F	108	Absent at 15 mg.	Rising at 15 mg.	15 mg.
38.	46	F	119	Absent at 15 mg.	Rising at 15 mg.	15 mg.

TABLE 7 (continued)

b. Supra-normal dosage.

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve.
10	43	F	122	None elicited	Rising at 15 mg. Phase 2 at 25 mg.
11	30	M	130	Failing at 20 mg. Absent at 40 mg.	Rising at 20 mg. Phase 3 at 60 mg.
12	41	M	133	Failing at 10 mg. Absent at 20 mg.	Rising at 10 mg. Phase 3 at 45 mg.
13	43	M	114	Abolished by Anaesthetic.	Rising at 20 mg. Phase 2 at 40 mg. Phase 3 at 45 mg.
14	56	M	166	Absent at 30 mg.	Rising at 30 mg.
15	35	M	122	Absent at 30 mg.	Rising at 30 mg. Phase 2 at 50 mg. Phase 3 at 55 mg.
16	41	M	166	Present at 25 mg. Absent at 35 mg.	Rising at 25 mg. Phase 2 at 35 mg.
17	28	M	119	Failing at 20 mg. Absent at 30 mg.	Rising at 20 mg. Phase 2 at 30 mg.
18	26	M	158	Failing at 25 mg. Absent at 40 mg.	Rising at 25 mg. Phase 3 at 40 mg.
19	32	M	112	Absent at 30 mg.	Rising at 30 mg. Phase 2 at 45 mg.
20	31	M	160	Failing at 20 mg. Absent at 40 mg.	Rising at 20 mg. Phase 3 at 45 mg.
21	28	M	140	Present at 25 mg. Failing at 30 mg.	Rising at 25 mg.
22	34	M	103	Failing at 20 mg. Absent at 30 mg.	Rising at 20 mg.

TABLE 7 (continued)

b. (continued). Supra-normal dosage.

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve.
24	33	M	130	Present at 20 mg. Failing at 30 mg.	Rising at 20 mg.
26	44	M	126	Absent at 30 mg.	Phase 2 at 30 mg. Phase 3 at 40 mg.
27	31	M	150	Failing at 20 mg.	Rising at 20 mg.
36	24	M	130	Failing at 20 mg.	Rising at 20 mg.

A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or, at most, a short series of twitches of diminishing intensity. (Wedensky).

A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

TABLE 8. THE EFFECT OF GALLAMINE ON TENDON - JERKS, RESPONSE TO STIMULATION OF THE ULNAR NERVE, and STATE OF MUSCULATURE.

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery.
1.	55	F	96	Unaltered at 70 mg.	-	70 mg.
2.	50	M	106	Unaltered at 80 mg.	Rising at 60 mg.	80 mg.
3.	32	M	132	Failing at 80 mg. Knee-jerk present at 120 mg.	-	120 mg.
4.	40	M	120	Enhanced at 120 mg. Absent at 240 mg.	Rising at 120 mg. Phase 3 at 360 mg.	-
5.	52	F	108	Present at 120 mg. Absent at 160 mg.	Rising at 80 mg. Phase 2 at 240 mg.	-
6.	48	M	113	Present at 80 mg. Absent at 160 mg.	-	-
7.	40	F	125	Absent at 120 mg.	Rising at 120 mg. Phase 2 at 160 mg.	-
8.	44	M	122	Present at 120 mg.	Rising at 120 mg.	120 mg.

TABLE 8 (continued).

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery.
10	23	F	109	Failing at 80 mg.	Rising at 80 mg.	80 mg.
13	64	M	133	Present at 80 mg.	Rising at 80 mg.	80 mg.
14	56	F	173	Present at 100 mg.	Rising at 100 mg.	100 mg.

A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or, at most, a short series of twitches of diminishing intensity. (Wedensky).

A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

TABLE 9. THE EFFECT OF DECAMETHONIUM ON TENDON-JERKS, RESPONSE TO STIMULATION OF THE ULNAR NERVE, AND STATE OF MUSCULATURE.

Case	Age	Sex	Weight in pounds	Tendon-Jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery.
1	66	M	91	Absent at 3 mg.	-	Not satisfactory at 3 mg.
2	39	M	144	Present at 4 mg. Absent at 6 mg.	Rising at 4 mg.	Not quite satisfactory at 6 mg.
3	48	M	131	-	Rising at 3 mg.	Not satisfactory at 3 mg. but perhaps due to delay
4	39	F	-	Absent at 3 mg.	-	3 mg. (brief period)
5	67	F	-	Absent at 3 mg.	-	3 mg.
6	34	F	78	Absent at 3 mg.	Rising at 3 mg.	Not satisfactory at 3 mg. Fair at 5 mg.
7	36	M	117	Absent at 3 mg.	-	3 mg. (fair)
8	57	M	-	Absent at 3 mg.	Rising at 3 mg.	3 mg.
9	57	M	131	Absent at 5mg.	Rising at 5 mg.	5 mg.
10	41	M	103	Absent at 5 mg.	Rising at 5 mg.	5 mg.

The Tendon-jerks:

It was noted that, in some patients, one or other of the tendon-jerks might persist long after the others were abolished. This occurred once in the case of the biceps-jerk, and twice in the case of the knee-jerk and the ankle-jerk. In a few patients, it was impossible or difficult to elicit tendon-reflexes in the conscious state, but they frequently appeared or were enhanced following anaesthesia and curarisation. In this connection it is interesting to note that, in ten cases, ankle clonus was observed to develop in the curarised patient before the jerk was finally abolished.

The response to stimulation of the ulnar nerve:

The voltage at which a response to stimulation of the ulnar nerve first occurs, has been shown to rise on curarisation. In one case, however, to whom only 10 mg. of d-tubocurarine were given initially, it was possible to obtain a response at a lower voltage than before. This finding was followed up in later studies. (p. 78).

In many cases it was found that the time taken for the full effect of a dose of a relaxant on the threshold-voltage necessary for a minimal response took considerably longer than the time usually considered necessary for the development of a relaxant effect. Hewer (1948) states that the full effect of a dose of d-tubocurarine chloride injected intravenously should be apparent within $1\frac{1}{2}$ minutes. In the later cases of the general series, it was thought best to allow ten minutes for the full development of the effect of d-tubocurarine chloride, and six minutes for gallamine triethiodide. (After consideration of the results, it appeared of interest to investigate in more detail the initial effects

of relaxants on the response to stimulation of the ulnar nerve. (p. 78).)

A pattern of response to heavy curarisation was revealed.

Considerable difficulty was experienced in interpreting the results until the different phases of response were recognised. Five cases have been chosen to show this pattern of response, and are detailed in Table 10. They consist of cases 15, 16, 18, 26 and G 7.

Table 10 shows that more than five minutes may be required for the development of the full effect of the relaxant drug on the response to stimulation of the ulnar nerve. The Table also shows that once a phase 2 or phase 3 type of response is elicited, it may be very persistent. It may persist after the return of spontaneous respiration (Table 10b, c, d). Phase 2 response may persist until after the end of the operation (Table 10b, d, e). Prostigmine resolves this situation in the cases examined. It brings about a rapid alteration in a persistent phase 2 response. It also lowers the threshold when there is a phase 1 response with a high voltage-threshold.

TABLE 10a. THE PATTERN OF RESPONSE TO NERVE STIMULATION IN CURARISED SUBJECTS.

Age: 35 Sex: Male Weight: 122 pounds

Operation: Partial Gastrectomy.

Total Dose of Relaxant	Minimum Voltage at which Response Occurs	Phase of Response	Time in Minutes after Last Dose
(Anaesthetised)	18	1	-
20 mg.T*	22	1	5, 10
30 mg.T	35	1	5
	40 (1)	1	10
40 mg.T	50	1	5
	60	1	10
50 mg.T	75	1	5
	90	2	10
55mg.T	100	2	5
	-	3	10
	100	2	20, 35, 45, 50
(Prostigmine and Atropine given)	45 (2)	1	3
	40 (3)	1	8

*T = d-tubocurarine chloride.

- (1) Tendon-jerks and respiration abolished.
- (2) Spontaneous respiration returned.
- (3) Reflexes returned five minutes later.

See end of Tables for definition of phases.

TABLE 10b. THE PATTERN OF RESPONSE TO NERVE STIMULATION IN CURARISED SUBJECTS.

Age: 41

Sex: Male

Weight: 166 pounds

Operation: Laparotomy.

Total Dose of Relaxant	Minimum Voltage at which Response Occurs	Phase of Response	Time in Minutes after Last Dose
(Anaesthetised)	45	1	-
25 mg.T*	65	1	5
	75	1	10
35 mg.T	75 (1)	1	5
	80	2	10
40 mg.T	80	2	5, 10
	70 (2)	2	25
Prostigmine and Atropine given	60 (3)	2	5
	60	2	10
	70 (4)	1	15

*T = d-tubocurarine chloride.

- (1) Respiration and tendon jerks abolished.
- (2) Spontaneous respiration returned, relaxation good.
- (3) Operation and anaesthetic ended.
- (4) Tendon-jerks present.

See end of Tables for definition of phases.

TABLE 10c. THE PATTERN OF RESPONSE TO NERVE STIMULATION IN CURARISED SUBJECTS.

Age: 26 Sex: Male Weight: 158 pounds

Operation: Partial Gastrectomy.

Total Dose of Relaxant	Minimum Voltage at which Response Occurs	Phase of Response	Time in Minutes after Last Dose
(Anaesthetised)	25	1	-
25 mg.T*	30	1	5
	35	1	10
	35	1	15
40 mg.T	- (1)	3	5, 10
	100	2	13
50 mg.T	-	3	20
	50	2	30
(Prostigmine and Atropine given)	40 (2)	2	5
	50 (3)	1	10
	40 (4)	1	12

*T = d-tubocurarine chloride.

- (1) Tendon-jerks and respiration abolished.
- (2) Operation ended.
- (3) Knee and ankle clonus.
- (4) Patient coughed, opened eyes, raised head.

See end of Tables for definition of phases.

TABLE 10d. THE PATTERN OF RESPONSE TO NERVE STIMULATION IN CURARISED SUBJECTS.

Age: 44 Sex: Male Weight: 134 pounds

Operation: Partial Gastrectomy.

Total Dose of Relaxant	Minimum Voltage at which Response Occurs	Phase of Response	Time in Minutes after Last Dose
(Anaesthetised)	35	1	-
20 mg.T*	35	1	5, 10
30 mg.T	60	2	5, 10
40 mg.T	-	3	5, 10, 15, 35, 40, 75
	- (1)	3	90
(Prostigmine and Atropine given)	60 (2)	2	5
	50 (3)	1	10

*T = d-tubocurarine chloride

- (1) Spontaneous respiration returned, relaxation excellent.
- (2) Operation stopped.
- (3) Patient opened eyes.

See end of Tables for definition of phases.

TABLE 10e. THE PATTERN OF RESPONSE TO NERVE STIMULATION IN CURARISED SUBJECTS.

Age: 40 Sex: Female Weight: 124 pounds

Operation: Gastro-enterostomy.

Total Dose of Relaxant	Minimum Voltage at which Response Occurs	Phase of Response	Time in Minutes after Last Dose
(Anaesthetised)	20	1	-
120 mg.G*	30	1	5
	35	1	10
160 mg.G	45	1	5
	45 (1)	2	10
170 mg.G	45	2	5, 10
	45 (2)	2	30
	45 (3)	2	45
(Prostigmine and Atropine given)	45 (4)	2	2
	18	1	5

*G = Gallamine Triethiodide.

(1) Respiration abolished.

(2) Slight spontaneous respiration returned, very good relaxation.

(3) Operation ended. Prostigmine given.

(4) Tendon-jerks returned.

A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or, at most, a short series of twitches of diminishing intensity. (Wedensky).

A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

The response to stimulation of an intercostal nerve:

In fourteen patients, the tenth intercostal nerve was stimulated by a needle-electrode impinging on the nerve in the subcostal groove. The technique used, and the technical difficulties encountered, have been described on p. 50 . In most cases, it was possible to compare the response to intercostal stimulation with the response to ulnar stimulation in the same patient, under the same conditions. The latter half of the series is particularly concerned with the ability of the tested muscles to maintain an imposed tetanus after the injection of a relaxant.

Brief notes on the cases follow:

T 31. Age: 36. Sex: Male. Weight: 136 pounds.

Operation: Appendicectomy.

Intercostal stimulation only.

15 mg. d-tubocurarine given: Phase 1 response obtained.

20 mg. d-tubocurarine given: no clear response obtained.

(This may have been due to faulty technique).

T 35. Age: 49. Sex: Male. Weight: 146 pounds.

Operation: Partial gastrectomy.

Ulnar and intercostal stimulation used.

20 mg. d-tubocurarine chloride given:

Ulnar nerve: Phase 1 response at 42 volts, rising to 45 volts.

Intercostal nerve: Phase 1 response, seen through the skin.

25 mg. d-tubocurarine chloride given:

Ulnar nerve: Phase 1 response at 70 volts.

Intercostal nerve: Phase 1 response. Muscle seen contracting at operation. Relaxation very satisfactory.

T 37. Age: 57. Sex: Female. Weight: 108 pounds.

Operation: Laparotomy.

Ulnar and intercostal stimulation used.

15 mg. d-tubocurarine chloride given:

Ulnar nerve: Phase 1 response, 45 volts, rising to 65 volts.

Intercostal nerve: Phase 1 response. Muscle seen contracting at operation, and palpated by the surgeon. Relaxation good.

T 38. Age: 57. Sex: Female. Weight: 119 pounds.

Operation: Partial gastrectomy.

Ulnar and intercostal stimulation used.

20 mg. d-tubocurarine chloride given:

Ulnar nerve: Phase 1 response at 35 volts, rising to 43 volts.

Intercostal nerve: Phase 1 response, visible and palpable at operation. Relaxation good.

G 9. Age: 35. Sex: Male. Weight: 142 pounds.

Operation: Inguinal herniotomy.

Intercostal stimulation only.

80 mg. gallamine triethiodide given:

Phase 1 response obtained.

120 mg. gallamine triethiodide given:

Phase 1 response obtained. Relaxation good.

G 13. Age: 64. Sex: Male. Weight: 133 pounds.

Operation: Inguinal herniotomy.

Ulnar and intercostal stimulation used.

80 mg. gallamine triethiodide given.

Ulnar nerve: Phase 1 response at 95 volts.

Intercostal nerve: Phase 1 response. Relaxation good.

G 15. Age: 51. Sex: Male. Weight: 143 pounds.

Operation: Partial gastrectomy.

Ulnar and intercostal stimulation used.

100 mg. gallamine triethiodide given:

After five minutes: Ulnar nerve: Phase 1 response at 90 volts.

After ten minutes: Ulnar nerve: Phase 2 response at 100 volts.

Intercostal nerve: Phase 2 response.

After sixty minutes: Ulnar nerve: Phase 1 response at 90 volts.

After eighty minutes: Ulnar nerve: Phase 1 response at 85 volts.

Intercostal nerve: Phase 1 response.

120 mg. gallamine triethiodide given:

After five minutes: Ulnar nerve: Phase 1 response at 90 volts.

Intercostal nerve: Phase 1 response.

In this operation, no pathidine was used, but 1 fluid ounce of diethyl ether was consumed in 100 minutes.

T 50. Age: 39. Sex: Male. Weight: 152 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.8 gramme, nitrous-oxide/oxygen.

Given d-tubocurarine 20 mg:

15 minutes later:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained. Relaxation satisfactory.
(Mr. A. W. Kay).

Another 10 mg. of d-tubocurarine given:

15 minutes later:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus not maintained. (Mr. A. W. Kay).

T 51. Age: 38. Sex: Male. Weight: 150 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.8 gramme, nitrous-oxide/oxygen.

Given d-tubocurarine 25 mg.

15 minutes later:

Ulnar stimulation: Tetanus poorly maintained.

Intercostal stimulation: Tetanus not maintained. Relaxation satisfactory.
(Mr. D. Clark).

G 18. Age: 34. Sex: Female. Weight: 150 pounds.

Operation: Cholecystectomy.

Anaesthetic: Thiopentone 0.6 gramme, nitrous-oxide/oxygen.

Given gallamine 100 mg.

10 minutes later:

Ulnar stimulation: Tetanus poorly maintained. (Threshold-voltage for single shocks rose from 26 to 70 volts).

Intercostal stimulation: Tetanus poorly maintained. (Mr. D. Clark).

At end of operation, following prostigmine:

Ulnar stimulation: Tetanus maintained. (Threshold-voltage returned to 26 volts).

Intercostal stimulation: Tetanus maintained. Relaxation satisfactory throughout.

G 19. Age: 32. Sex: Female. Weight: 131 pounds.

Operation: Laparotomy.

Anaesthetic: Thiopentone 0.6 gramme, nitrous-oxide/oxygen.

Given gallamine 80 mg.

15 minutes later:

Ulnar stimulation: Tetanus maintained. (Threshold-voltage for single shocks increased from 18 volts to 28 volts).

Intercostal stimulation: Tetanus maintained. Relaxation satisfactory.
(Mr. A. W. Kay).

At end of operation, 40 minutes after the injection:

Ulnar stimulation: Tetanus maintained. (Threshold-voltage reduced to 17 volts).

Intercostal stimulation: Tetanus maintained. Relaxation satisfactory.
(Mr. A. W. Kay).

T 52. Age: 57. Sex: Male. Weight: 143 pounds.

Operation: Laparotomy.

Anaesthetic: Thiopentone 0.5 gramme, nitrous-oxide/oxygen.

Given d-tubocurarine 20 mg.

At 5 minutes:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained.

At 10 minutes:

Ulnar stimulation: Tetanus maintained.

At 15 minutes:

Ulnar stimulation: Tetanus maintained.

At 20 minutes:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained.

Operation ends. Relaxation satisfactory throughout.
(Professor C.F.W. Illingworth).

T 53. Age: 23. Sex: Male. Weight: 154 pounds.

Operation: Laparotomy.

Anaesthetic: Pethidine 50 mg., thiopentone 0.6 gramme, nitrous-oxide/oxygen.

Given d-tubocurarine 20 mg.

At 2 minutes:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained. (Felt through skin).

At 5 minutes:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained.

At 10, 15 minutes:

Ulnar stimulation: Tetanus poorly maintained.

Intercostal stimulation: Tetanus poorly maintained. Relaxation

satisfactory at five minutes and throughout.
(Professor C.F.W. Illingworth).

T 54. Age: 18. Sex: Male. Weight: 100 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.5 gramme, nitrous-oxide/oxygen.

Given d-tubocurarine 15 mg.

At 5 minutes:

Ulnar stimulation: Tetanus maintained.

Intercostal stimulation: Tetanus maintained.

At 10 minutes:

Ulnar stimulation: Tetanus poorly maintained.

Intercostal stimulation: Tetanus poorly maintained.

Given another 5 mg. of d-tubocurarine:

At 5 minutes: Ulnar stimulation: Tetanus not maintained.

Intercostal stimulation: Tetanus not maintained.

Relaxation satisfactory at 5 minutes, and throughout.

(Professor C.F.W. Illingworth).

The findings with intercostal stimulation are closely allied to the findings with ulnar stimulation, when single shocks are administered. A change of phase in the response to intercostal stimulation is associated with a change of phase in the response to ulnar stimulation. It is perfectly possible to have satisfactory abdominal relaxation in association with phase 1 response to single shocks.

It is also possible for the rectus abdominis to maintain tetanus when satisfactory abdominal relaxation is present after small doses of d-tubocurarine. It appears, however, that a tetanus which is well-maintained five minutes after the injection of the relaxant may be less well-maintained ten minutes after the injection of the relaxant. Therefore, if the power of maintaining an imposed tetanus is not tested until 10 - 15 minutes after injecting the relaxant, fewer patients will be found who are still capable of maintaining an imposed tetanus. This can be associated with the progressive rise in the voltage-threshold as the peripheral effect of the drug develops. (See p.92).

The initial effects of relaxant drugs on the response to stimulation of the ulnar nerve:

Earlier work has shown (p.63) that many minutes may elapse before the full effect is observed of a dose of a relaxant drug on the response to stimulation of the ulnar nerve. There often appeared to be a considerable discrepancy between this time and the time taken for the appearance of abdominal relaxation, or of respiratory paralysis. It was thought of interest to examine more closely the initial effects of relaxant drugs on the response to stimulation of the ulnar nerve. The relaxants used were d-tubocurarine and gallamine triethiodide.

The minimal voltage was noted at which single periodic shocks, applied percutaneously to the ulnar nerve at the rate of 1 per second, produced a minimal twitch, usually of the little finger. Any variation from this level produced by anaesthesia or relaxant drugs was also noted. When no twitch was visible or palpable, it was necessary gradually to increase the voltage of the stimulus. If the twitch became more than minimal, it was necessary to reduce the voltage of the stimulus. Fourteen patients were examined in this way. In eight of them the ability of the curarised muscle to maintain a tetanus was also examined. Tetanus was produced by supramaximal stimuli at a rate of 16 per second. The stimuli were applied for five seconds.

A co-operative surgeon was presented with an anaesthetised patient who had not received any relaxant drug. The surgeon was allowed to proceed until he was hindered by rigidity of the abdominal muscles. The relaxant drug was then given. It was thought unwise to subject the

patient to this procedure, under very light anaesthesia, without ensuring a clear airway by endotracheal intubation.

The anaesthetic technique used was modified as follows:

(1) Pethidine. This was omitted in subjects who did not look particularly 'resistant.'

(2) Thiopentone. It was sometimes necessary to increase the dose of thiopentone to maintain smooth anaesthesia.

(3) Succinylcholine chloride. In 'resistant' subjects, particularly those with a full set of teeth, it was usually necessary to use 50 mg. of succinylcholine chloride to obtain sufficient relaxation of the jaw for atraumatic endotracheal intubation. This was recognised to be an unfortunate complicating factor in judging the effect of a subsequent relaxant. The action of succinylcholine is, however, normally very short, and was so in all the cases in which it was used. The relaxant to be studied was not injected until full spontaneous respiration had been restored.

(4) Lignocaine hydrochloride. The vocal cords and trachea were sprayed with 4% lignocaine hydrochloride. This was done to prevent possible vagal reflex effects from intubation under light anaesthesia.

(5) Nitrous-oxide/oxygen. Anaesthesia was maintained with nitrous-oxide and oxygen, initially at a flow-rate of 6 litres and 2 litres respectively, using a semi-closed circuit. After the injection of the relaxant to be studied, the flow-rate was reduced to 3 litres of nitrous oxide and $1\frac{1}{2}$ litres of oxygen, using a closed circuit with an intentional leak, or an automatic respiratory pump which permitted a leakage of excess gases.

The cases examined are detailed below:

The nerve stimulated was in each case the ulnar nerve.

Times are recorded as from the most recent dose of relaxant.

G 15. Age: 58. Sex: Male. Weight: 150 pounds.

Operation: Gastro-enterostomy.

Anaesthetic: Thiopentone 0.6 gramme, N20 and O2.

Response to stimulation after anaesthesia:

Minimal response to stimulation at 25 volts.

Gallamine 80 mg. given.

At 30, 45 seconds, response at 22 volts.

At 60, 90, 120 seconds, response at 25 volts.

At 3, 4 minutes, response at 28 volts.

At 5, 6 minutes, response at 30 volts.

At 7, 8 minutes, response at 32 volts.

At 8, 9, 10 minutes, response at 35 volts.

Relaxation: Began at 45 seconds.

Satisfactory at 60 seconds.

At 15 minutes, response at 16 volts.

At 20 minutes, response at 15 volts.

Another 20 mg. gallamine given.

At 60 seconds, response at 14 volts.

At 2 minutes, response at 15 volts.

At 5 minutes, response at 17 volts.

Operation ends.

Respiration: Spontaneous throughout.

Relaxation: Satisfactory at 60 seconds. Poor at 20 minutes.

Satisfactory 60 seconds after second dose of relaxant.

G 17. Age: 59. Sex: Male. Weight: 120 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Pethidine 50 mg., thiopentone 0.5 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal at 18 volts.

80 mg. gallamine given.

At 30, 60, 90, 120 seconds, response at 16 volts.

At 3 minutes, response at 22 volts.

At 4, 5 minutes, response at 23 volts.

At 6, 7 minutes, response at 25 volts.

At 8, 9, 10 minutes. response at 28 volts.

Relaxation: Began at 40 seconds.

Satisfactory at 50 seconds.

T 40. Age: 52. Sex: Male. Weight: 123 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0,6 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal response at 34 volts.

20 mg. d-tubocurarine given.

At 30, 45, 60 seconds, response at 30 volts.

At 90 seconds, response at 32 volts.

At 2, 3, 4 minutes, response at 35 volts.

At 5, 6, 7, 8, 9, 10, 30 minutes, response at 38 volts.

At 45 minutes, response at 36 volts.

Another 5 mg. d-tubocurarine given. (For closing abdomen- precautionary).

At 30, 45, 60, 90, 120 seconds, response at 32 volts.

At 3 minutes, response at 32 volts.

At 45 minutes, response at 40 volts.

At 55 minutes, response at 37 volts.

Operation ends.

Relaxation: Began at 30 seconds.

Satisfactory at 45 seconds.

T441. Age: 49. Sex: Male. Weight: 130 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal response at 18 volts.

20 mg. d-tubocurarine given.

At 30, 45, 60, 90 seconds, response at 18 volts.

At 2, 3, 4, 5 minutes, response at 22 volts.

At 6, 7, 8, 9, 10 minutes, response at 22 volts.

Tetanus well maintained at 2, 5, and 10 minutes.

Relaxation: Began at 45 seconds.

Satisfactory at 60 seconds.

T 42. Age: 56. Sex: Male. Weight: 110 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Pethidine 50 mg., thiopentone 0.4 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal response at 17 volts.

15 mg. d-tubocurarine given.

At 30, 45, 60, 90 seconds, response at 13 volts.

At 2 minutes, response at 15 volts.

At 3, 4 minutes, response at 17 volts.

At 5, 6, 7 minutes, response at 20 volts.

At 8, 9, 10 minutes, response at 22 volts.

Tetanus well maintained at 2 and 5 minutes.

Tetanus poorly maintained at 10 minutes.

Relaxation: Began at 50 seconds.

Satisfactory at 90 seconds.

T 43. Age: 44. Sex: Male. Weight: 140 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O².

Succinylcholine 50 mg. given.

Response to stimulation after anaesthesia:

Minimal at 20 volts.

25 mg. d-tubocurarine given.

At 30, 45, 60 seconds, response at 18 volts.

At 90, 120 seconds, response at 18 volts.

At 3, 4 minutes, response at 20 volts.

At 5 minutes, response at 25 volts.

At 6, 7 minutes, response at 30 volts.

At 8, 9, 10 minutes, response at 35 volts.

Relaxation: Satisfactory at 80 seconds.

T 44. Age: 29. Sex: Female. Weight: 160 pounds.

Operation: Cholecystectomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal at 15 volts.

20 mg. d-tubocurarine given.

At 30, 45, 60 seconds, response at 12 volts.

At 90, 120 seconds, response at 15 volts.

At 3, 4 minutes, response at 18 volts.

At 5 minutes, response at 25 volts.

At 6, 7 minutes, response at 28 volts.

At 8, 9, 10 minutes, response at 28 volts.

Tetanus well maintained at 2, 5, 10 minutes.

Relaxation: Satisfactory at 60 seconds.

T 45. Age: 48. Sex: Female. Weight: 130 pounds.

Operation: Laparotomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O², succinylcholine 50 mg.

Response to stimulation after anaesthesia:

Minimal at 24 volts.

20 mg. d-tubocurarine given.

At 30 seconds, response at 24 volts.

At 45, 60 seconds, response at 22 volts.

At 90, 120 seconds, response at 25 volts.

At 3 minutes, response at 25 volts.

At 4 minutes, response at 26 volts.

At 5, 6, 7, 8 minutes, response at 28 volts, phase 2.

At 9, 10 minutes, response at 32 volts, phase 2.

At 20 minutes, response at 28 volts, phase 1.

At 30 minutes, response at 24 volts, phase 1.

Prostigmine given.

At 40 minutes, response at 22 volts,

Operation over.

Tetanus not maintained at 5, 10 minutes.

Tetanus not maintained at 20, 30 minutes.

Tetanus maintained at 40 minutes.

Relaxation: Began at 45 seconds.

Satisfactory at 60 seconds.

T 46. Age: 29. Sex: Female. Weight: 100 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O².

Response to stimulation after anaesthesia:

Minimal at 18 volts.

20 mg. d-tubocurarine given.

At 30 seconds, response at 16 volts.

At 45, 60, 90, 120 seconds, response at 15 volts.

At 3 minutes, response at 18 volts.

At 4, 5, 6, 7, 8 minutes, response at 20 volts.

At 9, 10 minutes, response at 18 volts.

Another 5 mg. d-tubocurarine given.

At 5 minutes, response at 22 volts.

At 10 minutes, response at 25 volts.

At 15 minutes, response at 23 volts.

Another 5 mg. d-tubocurarine given.

At 5 minutes, response at 25 volts.

At 10 minutes, response at 32 volts.

At 25 minutes, response at 20 volts.

At 35 minutes, response at 18 volts.

At 50 minutes, response at 18 volts.

At 75 minutes, response at 18 volts.

Tetanus maintained at 2, 5 and 10 minutes.

Tetanus poorly maintained 5 minutes after second dose, and five minutes after third dose of relaxant.

Tetanus maintained 25, 50 and 75 minutes after third dose of relaxant.

Relaxation: Satisfactory at 30 seconds and throughout.

Additional doses of relaxant were given so that the effects could be studied.

T 47. Age: 32. Sex: Male. Weight: 144 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Thiopentone 0.5 gramme, N²O and O², succinylcholine 50 mg.

Response to stimulation after anaesthesia:

Minimal at 18 volts.

20 mg. d-tubocurarine given.

At 30, 45, 60, 90, 120 seconds, response at 20 volts.

At 3, 4 minutes, response at 25 volts.

At 5, 6 minutes, response at 30 volts.

At 7 minutes, response at 31 volts.

At 8, 9, 10 minutes, response at 32 volts.

Another 10 mg. d-tubocurarine given.

At 5 minutes, response at 48 volts.

At 10 minutes, response at 48 volts.

At 20 minutes, response at 48 volts.

Tetanus maintained at 2, 5 minutes.

Tetanus fairly maintained at 10 minutes.

Tetanus poorly maintained after second dose of relaxant.

Relaxation: Satisfactory at 45 seconds and throughout.

T 48. Age: 51. Sex: Male. Weight: 128 pounds.

Operation: Gastro-enterostomy.

Anaesthetic: Pethidine 50 mg., thiopentone 0.5 gramme, N²O and O₂,
succinylcholine 50 mg.

Response to stimulation after anaesthesia:

Minimal at 12 volts.

20 mg. d-tubocurarine given.

At 15, 30, 45, 60 seconds, response at 9 volts.

At 90 seconds, response at 10 volts.

At 2, 3 minutes, response at 11 volts.

At 4, 5, 6, 7, 8 minutes, response at 13 volts.

At 9, 10, 15 minutes, response at 15 volts.

Another 10 mg. d-tubocurarine given.

At 30, 45, 60, 90, 120 seconds, response at 13 volts.

At 3 minutes, response at 16 volts.

At 4, 5 minutes, response at 18 volts.

At 10, 15 minutes, response at 60 volts.

Prostigmine given.

At 16, 17 minutes, response at 30 volts.

At 18 minutes, response at 25 volts.

At 19 minutes, response at 15 volts.

At 20, 25 minutes, response at 14 volts.

Operation ends.

Tetanus maintained at 5, 10 minutes.

Tetanus poorly maintained after second dose of relaxant.

Tetanus maintained after prostigmine.

Relaxation: Began at 60 seconds.

Satisfactory at 75 seconds and throughout.

T 49. Age: 29. Sex: Male. Weight: 164 pounds.

Operation: Partial gastrectomy.

Anaesthetic: Pethidine 75 mg., thiopentone 0.9 gramme, N²O and O²,
succinylcholine 50 mg.

Response to stimulation after anaesthesia:

Minimal at 15 volts.

20 mg. d-tubocurarine given.

At 30, 45, 60 seconds, response at 13 volts.

At 90 seconds, response at 15 volts.

At 120 seconds, response at 17 volts.

At 3, 4, 5, 6, 7 minutes, response at 20 volts.

At 8, 9, 10 minutes, response at 25 volts.

At 15 minutes, response at 28 volts.

At 20 minutes, response at 25 volts.

Another 10 mg. d-tubocurarine given.

At 30, 45, 60 seconds, response at 22 volts.

At 90 seconds, response at 30 volts.

At 120 seconds, response at 35 volts.

At 3, 4, 5, 10 minutes, response at 50 volts, phase 2.

At 25, 40, 55, 70 minutes, response at 50 volts, phase 2.

At 75 minutes, response at 30 volts, phase 2.

Prostigmine given.

At 76 minutes, response at 31 volts, phase 1.

At 77 minutes, response at 23 volts, phase 1.

At 78, 79, 80 minutes, response at 15 volts, phase 1.

Operation ends.

Tetanus maintained at 2, 5 minutes.

Tetanus poorly maintained at 10 minutes.

Tetanus not maintained at 15 minutes, or after second dose of relaxant.

Tetanus maintained 1 minute after giving prostigmine.

Relaxation: Began at 55 seconds.

Satisfactory at 65 seconds and throughout.

In nearly every case examined, immediately after the injection of the relaxant drug, there was a slight fall in the voltage at which a minimal response to stimulation of the ulnar nerve could be elicited. This fall persisted until after satisfactory relaxation for upper abdominal surgery had been attained. Although a rise frequently occurred later, in only one case (T 47), was the onset of abdominal relaxation associated with a rise in the threshold-voltage. The threshold-voltage frequently did not attain its maximum value for about ten minutes after the injection of the relaxant. This has been noted in earlier studies.

The effect of relaxants on the ability of the muscles supplied by the ulnar nerve to maintain tetanus was also slow in appearing. The maximal effect was frequently not observed for ten minutes. Relaxation satisfactory for upper abdominal surgery is compatible with a well-maintained tetanus in the muscles supplied by the ulnar nerve.

Six of the cases (G 16, T 40, 46, 47, 48 and 49) are illustrated in Figs. 17 - 22.

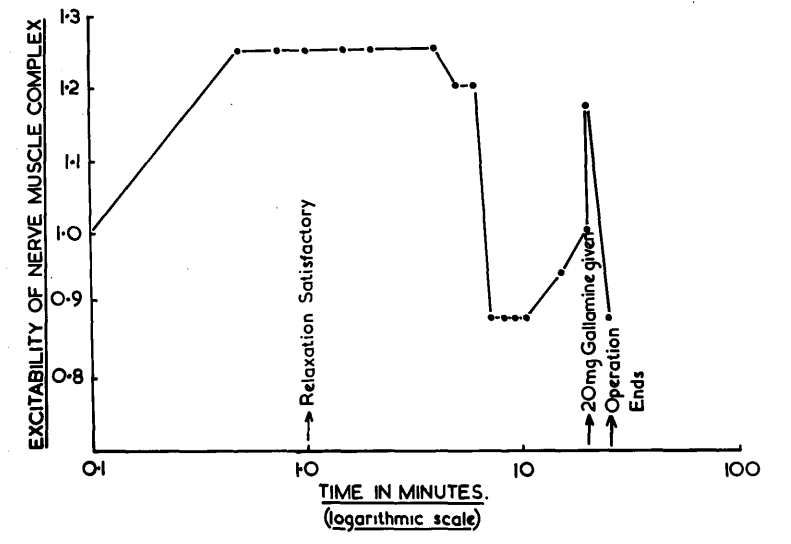
The variation in threshold-voltage has been expressed as the excitability of the nerve-muscle complex. This was calculated as:

Threshold-voltage in anaesthetised patient.

Threshold-voltage in curarised patient.

A logarithmic time-scale has been used. For purposes of illustration, it is assumed that no alteration occurs in the threshold-voltage in the first six seconds after injection of the relaxant.

FIG. 17. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.



G 16. Age: 43. Sex: Female. Weight: 130 pounds.

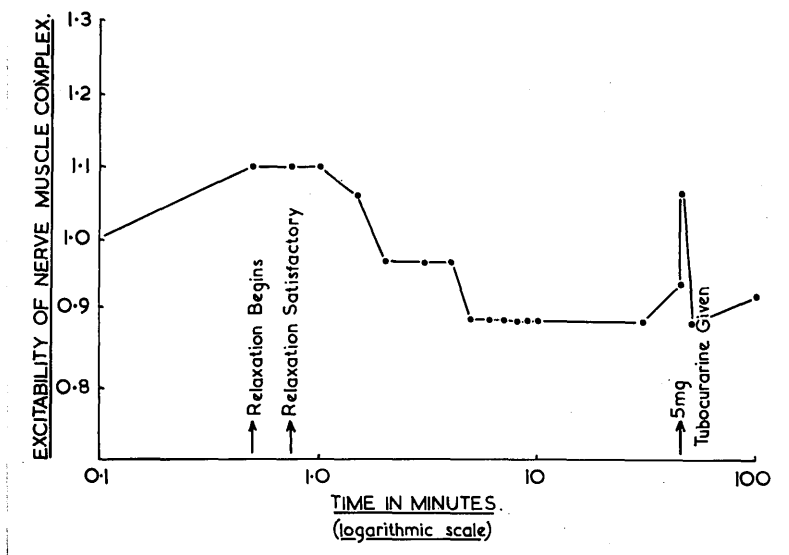
Given 80 mg. gallamine.

The ulnar nerve was stimulated, and the voltage necessary just to produce a standard minimal response was taken as "threshold."

Excitability is calculated as the ratio of the threshold-voltage before giving a relaxant drug to the threshold-voltage at the time considered.

It is assumed, for purposes of illustration, that no change in excitability occurs during the first six seconds after injection of the initial dose of relaxant.

FIG. 18. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.

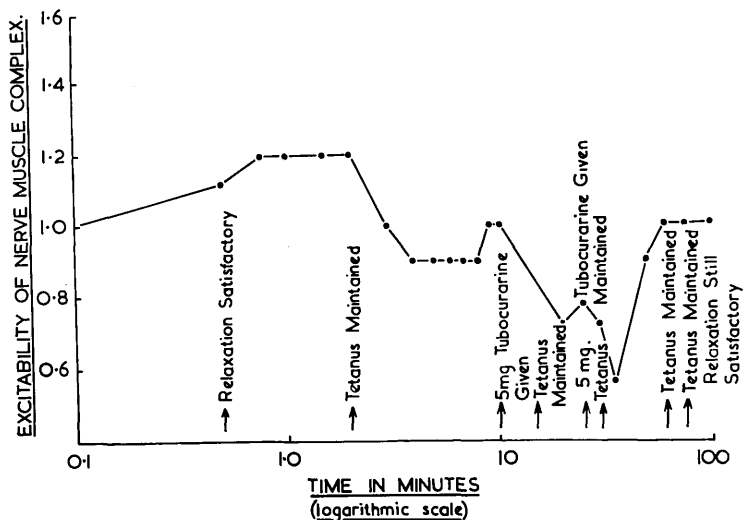


T 40. Age: 52. Sex: Male. Weight: 123 pounds.

Given 20 mg. d-tubocurarine.

For explanations, see Fig. 17.

FIG. 19. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.



T 46. Age: 29. Sex: Female. Weight: 100 pounds.

Given 20 mg. d-tubocurarine. Additional doses given to observe effects.

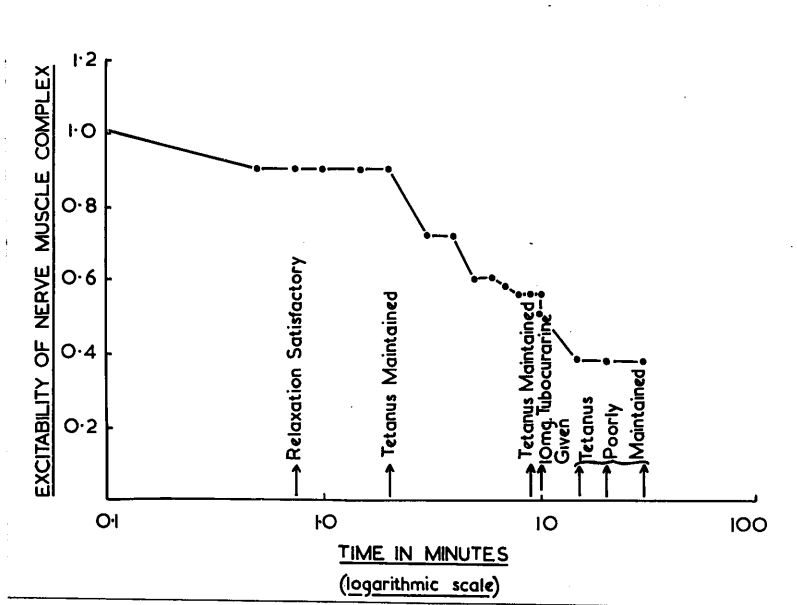
In this patient, and in all subsequent patients, observation was made of the response not only to single, minimal shocks, but also to tetanising, supramaximal shocks.

The ulnar nerve was stimulated, and the voltage necessary just to produce a standard minimal response was taken as "threshold."

Excitability is calculated as the ratio of the threshold-voltage before giving a relaxant drug to the threshold-voltage at the time considered.

It is assumed, for purposes of illustration, that no change in excitability occurs during the first six seconds after injection of the initial dose of relaxant.

FIG. 20. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.

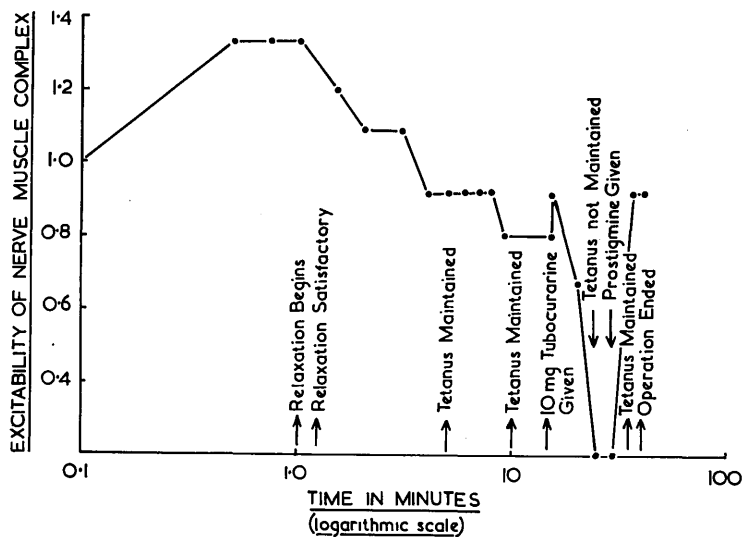


T 47. Age: 32. Sex: Male. Weight: 144 pounds.

Given 20 mg. d-tubocurarine. Another 10 mg. was given to study its effect.

For other explanations, see Fig. 19.

FIG. 21. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.

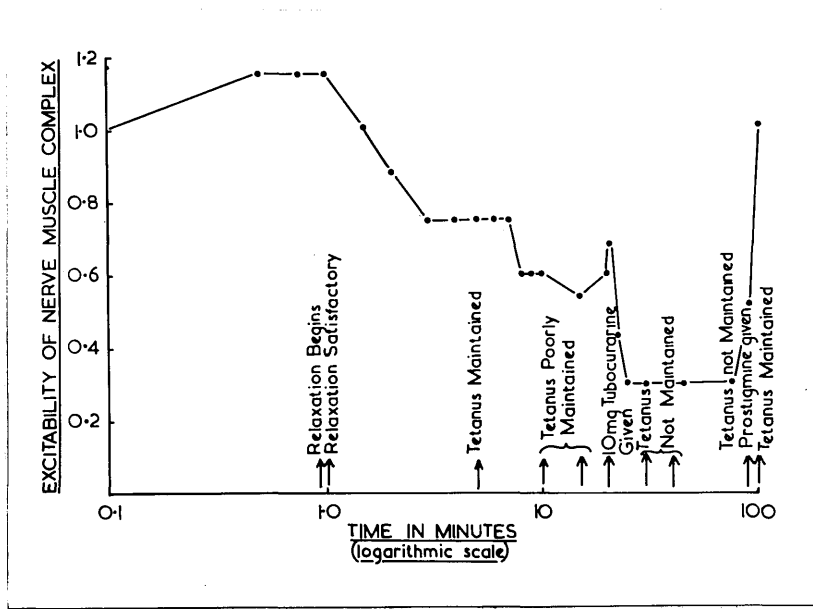


T 48. Age: 51. Sex: Male. Weight: 128 pounds.

Given 20 mg. d-tubocurarine. An additional dose was given after fifteen minutes in order to study its effects.

For other explanations, see Fig. 19.

FIG. 22. THE TIME-COURSE OF THE CHANGE IN EXCITABILITY FOLLOWING ADMINISTRATION OF RELAXANT DRUGS.



T 49. Age: 29. Sex: Male. Weight: 164 pounds.

Given 20 mg. d-tubocurarine. Another 10 mg. was given after 20 minutes in order to study its effects.

For other explanations, see Fig. 19.

Respiration.

Little useful information has been gathered in this investigation on the level of curarisation at which spontaneous respiration is abolished. This is because:

(1) The type of anaesthesia used included the use of many central respiratory depressants. e.g. papaveretum, scopolamine, pethidine, thiopentone.

(2) Controlled respiration by a mechanical pump, with a carbon-dioxide absorption, was usually employed when the patient was transferred to the theatre.

These factors made it impossible to draw conclusions from failure of respiration in curarisation, or from maintained apnoea. Conclusions were valid only in the few cases in which respiration persisted until the first dose of relaxant was fully active. The effect of relaxants on respiration is noted, where of interest, in Table 10, and elsewhere, but no conclusions will be drawn from this slender evidence.

DISCUSSION.The effect of anaesthesia on the tendon-jerks and on the response to nerve-stimulation.

It has been shown that the tendon-jerks are abolished in a somewhat unreliable fashion when di-ethyl ether or "Trilene" are used. The technique of general anaesthesia, adopted, however, seldom has any effect on the tendon-jerks. It is therefore safe to assume that alterations occurring in the tendon-jerks after the administration of relaxant drugs, are, in fact, associated with these drugs and not with the accompanying anaesthesia.

The response to nerve-stimulation in ether anaesthesia was of interest. In the cases examined here, the rise in threshold to stimulation was insignificant in the levels of ether anaesthesia usually employed. A rise in threshold certainly occurred in some patients at deeper levels of anaesthesia, but not in all. In no case was a change of phase of response found.

It is known that ether potentiates curare-like activity. Auer and Meltzer (1914) and Gross and Cullen (1943) attributed to ether a peripheral curare-like action. Gross and Cullen found that the contraction of the gastrocnemius muscle which is elicited by intra-arterially injected acetylcholine, or by electrical stimulation of the nerve, is less in dogs anaesthetised with ether, tribromethanol, or thiopentone, than in dogs anaesthetised with cyclopropane or ethylene. Clinically, there is no doubt that ether does potentiate the action of curare. The evidence of Gross and Cullen would attribute this to a peripheral action. The evidence of the present study is not considered to be sufficiently striking to confirm or deny this view.

The response to inadequate anaesthesia.

The first sign of surgical anaesthesia is usually the institution of regular, automatic, respiration. Correspondingly, the first sign of inadequate anaesthesia is usually the beginning of irregular respiration. If this sign were ignored, movements of the hand, the arm, the head, the leg, might follow. In the anaesthetised, lightly curarised subject, the response to inadequate anaesthesia is somewhat modified. If spontaneous respiration is retained, the first sign of inadequate anaesthesia, may, again, be the beginning of irregular respiration. If, however, respiration is controlled, the first sign of inadequate anaesthesia is usually a slight movement of the small muscles of the hand or face. Very rarely, a more marked response may occur, involving contraction of the larger muscles of the arm or the leg. The lesser degree of response is compatible with relaxation satisfactory for upper abdominal surgery. At least one patient, not included in this series of studies, showed marked protesting movements in the lower limbs, apparently due to inadequate anaesthesia, and yet his abdomen was perfectly relaxed. The few patients in this series of studies who have shown reflex indications of slightly inadequate anaesthesia have, at that time, also shown a response to stimulation of the ulnar nerve of phase 1 type.

The tendon-jerks have been chosen as convenient examples of reflex activity. It has been shown that, with the anaesthetic technique used in this investigation, they are little affected by anaesthesia, and any changes which occur in the anaesthetised subject on injection of a relaxant drug, may be taken as due to the activity of the relaxant drug.

The effect of relaxant drugs on the tendon-jerks.

The tendon-jerks have been chosen as convenient examples of reflex activity. It has been shown that, with the anaesthetic technique used in this investigation, they are little affected by anaesthesia, and any changes in the jerks which occur in the anaesthetised subject on injection of a relaxant drug, may be taken as due to the activity of the relaxant drug.

In the case of decamethonium iodide, the inhibition of the tendon-jerks is not a useful gauge of the effectiveness of the relaxant on abdominal muscles. The tendon-jerks may be abolished in the presence of relaxation quite inadequate for surgical purposes.

With d-tubocurarine however, changes in the tendon-jerks are a useful gauge of the effectiveness of the relaxant. The presence or absence of tendon-jerks forms the dividing line between the stage of Bremer, and the stage of Vulpian. There is no sign available clinically for the earliest appearance of the stage of Bremer, and it has been shown to be unnecessary to abolish the tendon-jerks completely to secure surgical satisfaction. There is no certain sign of the stage of Bremer until the tendon-jerks start to fail at its border, with the stage of Vulpian. Perfectly satisfactory relaxation may, however, occur in association with unaltered or even enhanced tendon-jerks. In this connection it is interesting to note the ankle clonus which frequently appears during curarisation. This sign seems to be a fore-runner of the abolition of the jerk. It may be useful as a sign of adequate curarisation, when it is present.

Stages of "curarisation."

Stages of "curarisation" have been described in relation to curare by Bremer, Vulpian, and Claude Bernard. The stage of Bremer is best indicated clinically by failing tendon-jerks at its border with the stage of Vulpian. The stage of Bremer seems to correspond with part of the phase 1 response. The stage of Vulpian follows the stage of Bremer. It is known that Vulpian used an interrupted current of low voltage for nerve-stimulation, but the periodicity of the interruption is not known. As he did not describe the phenonemon later known as Wedensky inhibition, it is presumed that the stage of Vulpian is also associated with the phase 1 response. The stage of Claude Bernard obviously corresponds with phase 3. The phase 2 response, which is a very definite phenonemon in ulnar-nerve stimulation, and which is an instance of Wedensky inhibition, then falls between the stage of Vulpian and the stage of Claude Bernard. Bremer et al., (1935), however, appear to associate Wedensky inhibition with the "stage of Bremer."

These stages are in no way applicable to decamethonium. It is difficult to see any signs which could be used to judge adequate dosage with decamethonium before an operation starts, as both tendon-jerks and response to stimulation of the ulnar nerve may show marked alterations without the abdominal relaxation necessarily being adequate.

Comparison of relaxants.

Decamethonium iodide was used only in a short series of cases. It was not so successful as d-tubocurarine in procuring satisfactory conditions for upper abdominal surgery. (Table 9). This result confirms the findings of Vetten and Nicholson (1950). In each case, although three minutes were allowed for the full relaxant effect, endotracheal intubation was relatively difficult. Decamethonium is known to be less effective than d-tubocurarine in relaxing pharyngeal and laryngeal muscles. (Paton 1953).

The use of decamethonium has been recommended on the theoretical grounds that this drug affects skeletal muscle more than respiratory muscle; that it has only a slight blocking action on the autonomic ganglia; and that it has little tendency to liberate histamine or heparin. (Paton and Zaimis 1948). With the anaesthetic technique adopted, it was not possible to draw any conclusions about a "respiratory-sparing" effect. For the purposes of major surgery, however, a relative sparing effect on the respiratory muscles is no longer considered an advantage. (Gray and Rees 1952). If there is such a "respiratory-sparing" effect, decamethonium may well be useful in shorter surgical interventions in the lower abdomen; it is, however, considered unsatisfactory for upper abdominal surgery. It would be an advantage to have a relaxant of competitive-block type which did not have the histamine and heparin liberating properties of d-tubocurarine.

Gallamine triethiodide, as might be expected from its competitive-block action, had actions very similar to those of d-tubocurarine. It seemed more difficult, with this agent, to obtain complete neuro-muscular block. This may perhaps be due to its relatively short action.

The effect of relaxants on the response to stimulation of nerves.

The general pattern of the response to stimulation of the ulnar nerve on patients given relaxant drugs was shown in Tables 7, 8, 9 and 10. Decamethonium seemed to give, as might be expected, a pattern of response somewhat different from that given by d-tubocurarine and gallamine. Only the pattern of response given by these latter relaxants will be considered in this section of the discussion.

A degree of relaxation satisfactory for abdominal surgery was usually accompanied by a slight rise in the threshold of response to stimulation of the ulnar nerve. (The changes in the threshold immediately following the injection were not examined in these cases). Larger doses of a relaxant brought about a considerable rise in the threshold of response, and alterations in the nature of the response. These were expected findings in view of the known peripheral blocking action of d-tubocurarine.

Other features of the results were not expected. It was found that after small doses of relaxant had procured satisfactory relaxation, the accompanying slight rise in threshold-voltage might not be maintained. Satisfactory relaxation might then be associated with a voltage-threshold no higher than that found before the injection of the relaxant.

After larger doses of relaxant, the full peripheral blocking action might not be shown until about ten minutes after the injection. When the phase of response was altered by a large dose of the relaxant, a phase 2 or phase 3 response might persist for as long as an hour, and until after the return of spontaneous respiration.

The peripheral block, as judged by the response to stimulation of the ulnar nerve, seemed slow to appear, and slow to disappear. At the end of an operation, a patient might have a persistent phase 2 response. He might lie inert, apnoeic, without reflexes and unconscious. When a dose of prostigmine was given, the neuromuscular block seemed to give way suddenly. The patient breathed, coughed, moved, recovered his reflexes. He might even open his eyes, and answer questions at this stage. At the same time, the response to stimulation of ulnar nerve returned to a more normal level.

The frequent slow appearance of the full effect of a dose of a relaxant on the voltage-threshold, led to an investigation of the early stages of the effects of d-tubocurarine and gallamine. From this work, it appears that relaxation satisfactory for upper abdominal surgery starts within 45 - 90 seconds of the time of the injection. The full effect of a relaxant on the voltage-threshold may take much longer. Further, when a dose is employed, which is just sufficient for the patient, satisfactory relaxation may occur with no rise in the voltage-threshold. Relaxation, may indeed, be obtained in an initial hyperexcitable phase, when the threshold is temporarily lowered. This initial hyperexcitable phase has been described by Rosenblueth et al. (1936).

The question now arises whether these results are peculiar to the muscles supplied by the ulnar nerve, or whether they have a more general application. The small muscles which are involved in a response to stimulation of the ulnar nerve are said to be more susceptible to the action of d-tubocurarine than are the abdominal muscles in which anaesthetists are particularly interested. (Paton and Zaimis 1950).

If this is true, it would not be justifiable to assume that a degree of neuromuscular block found in the hand muscles would be associated with a similar degree of block in the abdominal muscles. It would, however, be justifiable to assume that a lesser degree of neuromuscular block existed in the abdominal muscles than was found in the hand muscles. It was, therefore, thought useful to compare the degree of neuromuscular block existing in the hand muscles with that in the abdominal muscles, when the abdominal muscles were known, from surgical evidence, to be relaxed. The effects of ulnar and intercostal stimulation in the curarised subject provide such a comparison.

The results of stimulating an intercostal nerve have seemed, up to a point, to parallel the results of stimulating the ulnar nerve. It was not possible to compare variations in the threshold-voltage for reasons given on p.51, but a change of phase in the response of one nerve was associated with a change of phase of response in the other nerve.

Paton and Zaimis (1952) have also claimed that a muscle partially paralysed by d-tubocurarine cannot maintain a tetanus at its initial strength. This is contrasted with the response to decamethonium. The work here reported suggests that there may, in the case of d-tubocurarine and gallamine, be an intermediate stage. In this stage, satisfactory abdominal relaxation may occur while it is still possible to show well-maintained tetanus in the muscles supplied by the ulnar nerve, and even in the muscles of the abdominal wall.

Conditions suitable for abdominal surgery.

Surgical intervention in an unanaesthetised patient would be hindered by strong movements of protest, both consciously directed and reflex. One of the objects of the anaesthetist is to prevent these movements. Light anaesthesia will abolish both the conscious and the reflex response to cutting the skin. It will not, however, usually abolish the reflex response to peritoneal or muscular traction in abdominal surgery. With certain techniques of anaesthesia, other reflexes, such as the tendon-jerks, may also be retained.

To facilitate abdominal surgery, relaxant drugs are used, in association with light anaesthesia, to abolish the reflex response to peritoneal and muscular traction. It is desirable to achieve a level of "curarisation" in which the patient retains the power of indicating the onset of inadequate anaesthesia, while the abdominal muscles are satisfactorily relaxed, for surgical intervention.

It has been shown that with d-tubocurarine and gallamine, a level of "curarisation" corresponding with the "stage of Bremer" provides such conditions - the abdominal muscles are satisfactorily relaxed, although they are able to respond to stimulation of an intercostal nerve, and even to maintain a tetanus: the tendon-jerks are intact: respiration may be spontaneous, if this is allowed: lightening anaesthesia is revealed by slight movements of the muscles of the hand or the face. It is suggested that this is the safest stage of "curarisation" for general adoption in clinical practice.

The mode of action of specific relaxants.

The action of curare has been attributed since the time of Claude Bernard to its effect at the neuro-muscular junction. Research with the alkaloid d-tubocurarine chloride has shown that it also possesses powers of ganglionic block. (Gross and Cullen (1945), Guyton and Reeder (1950)). Paton (1953) has recently said that the ganglion-blocking power of the drug is not far short of its neuro-muscular effect, and is of the same competitive character.

If the relaxant effect of d-tubocurarine is due solely to its effect at the neuro-muscular junction, one would expect that, after an injection of a dose of the drug effective in producing relaxation, the threshold to stimulation of the ulnar nerve would be raised. Yet this is not always true. A satisfactory relaxant effect can be obtained with the threshold unaltered, or even slightly lowered. This suggests that the relaxant effect of d-tubocurarine is not wholly due to its peripheral blocking action.

There is a conflict of evidence as regards the action of d-tubocurarine on the central nervous system. It has been shown by Prescott et al. (1946), Smith et al. (1947), and Kellgren et al. (1946), that when the alkaloid is injected into the conscious patient there is no narcotic or hypnotic effect.

It has been claimed by Burman (1938, 1939, 1940) and by Bennett (1940, 1941, 1943), that the injection of curare in the conscious subject results in some narcosis, but this evidence must be regarded with caution, as an extract of curare was used, not the pure alkaloid. Whitacre and Fisher (1945) have operated on patients using large doses of "Intocostrin" - a standardised curare extract

from chondrodendron tomentosum - without general anaesthesia. The patients were supplied with oxygen, and the authors claim that there was no clinical evidence of anoxia. Unconsciousness supervened suddenly when a sufficiently large dose had been given, with no preceding stage of analgesia.

Fegler (1942) has shown that when curare is injected into anaesthetised dogs, there is an inhibition of respiration as shown by depression of respiratory frequency and amplitude. During this inhibition, sensory stimuli which normally augment respiration (central sciatic stimulation) and diminish it (central vagal stimulation) become ineffective in these respects. He concludes that the slowing of respiratory rhythm, and progressive depression of response to reflex excitatory and inhibitory stimuli, seem to prove that curare influences the respiratory centre before the full development of the peripheral action.

Pick and Unna (1945), experimenting on frogs, found that d-tubocurarine inhibited and suppressed electrical activity in the frog's brain. They interpreted this as inhibition of central synaptic transmission of d-tubocurarine.

Pick and Richards (1947) have shown that there is a synergism between d-tubocurarine and curare-like alkaloids, and anaesthetic agents such as ether, sodium phenobarbitone, and sodium thiopentone. They found that sub-effective doses of d-tubocurarine and other curare-like alkaloids, had a paralytic effect on mice and cats premedicated with these anaesthetic agents. They found a reciprocal relation between the dose of alkaloid and the dose of premedication. They did not find an enhanced anaesthetic effect with any of the animals treated with d-tubocurarine, but this effect was noted in

cats treated with dihydro-~~β~~-erythroidine and sodium thiopentone.

Ever since the introduction of relaxant drugs, anaesthetists have had a strong clinical impression that it is possible to maintain anaesthesia, when using relaxants, with smaller doses of anaesthetic agents than would otherwise be necessary. Gray and Halton (1946) tried to show that this impression was justified, and that d-tubocurarine potentiated the effect of thiopentone. In later work, Gray et al. (1951) abandoned this view. After a series of controlled experiments involving the comparison of the length of narcosis after the administration of thiopentone plus d-tubocurarine, with the length of narcosis after thiopentone alone, they came to the conclusion that d-tubocurarine did not potentiate thiopentone narcosis when respiration was not controlled. Dundee (1952) later showed that there was a statistically significant lowering of the thiopentone requirements of patients when respiration is controlled. Gray and Rees (1952) therefore concluded that apnoea should be regarded as an important feature of the technique of anaesthesia for major surgery. Apnoea, which is initiated by paralysis of the respiratory muscles, is largely maintained by controlled respiration, by regular cyclical inflation of the lungs (Burstein 1949), and by the establishment of a normal or low carbon-dioxide level in the blood. It is also considered that apnoea facilitates relaxation by abolishing the alterations in tone of the abdominal muscles which result from spontaneous respiratory movements.

It is certainly true that the relaxant drugs examined have a peripheral action at the neuro-muscular junction. It is, however, necessary to explain the occurrence of relaxation satisfactory for upper abdominal surgery while the response to stimulation of the ulnar

nerve is unaltered or is even enhanced and while tetanus is well-maintained. It is necessary to explain why tetanus may be maintained even by the abdominal muscles while relaxation is satisfactory. It is also necessary to explain the peculiar association between unconsciousness and the apnoea following "curarisation."

It is suggested that these findings could be more readily understood on the basis that d-tubocurarine possessed a central action in addition to its peripheral action. We might then suppose that a small dose of d-tubocurarine produced its relaxant effect, at least initially, by its hypothetical central action. A degree of peripheral block might well follow. Larger doses of d-tubocurarine have an obvious effect at the neuro-muscular junction, clearly reflected in the rising threshold of response to nerve-stimulation, in the type of response, and in the impaired power of maintaining an imposed tetanus.

In the first part of the thesis, it was concluded that the purpose of relaxant drugs was to maintain relaxation unimpaired by protective reflexes. The relaxant drugs are presumed to block these reflexes at some point. While a purely peripheral blocking action may seem an adequate mechanism for this effect in the case of decamethonium, it does not seem to provide an adequate explanation in the case of d-tubocurarine and gallamine. The present series of studies, however, has not provided information which would localise any central action. It does, however, show that the onset of relaxation is compatible with apparently intact neuro-muscular transmission.

CONCLUSIONS.

(1) A diminution in the tendon-jerks after the administration of d-tubocurarine chloride or gallamine triethiodide is a good clinical indication of adequate curarisation. The appearance of ankle clonus has a similar significance.

(2) When small doses of d-tubocurarine or gallamine are given, relaxation adequate for upper abdominal surgery is initially obtainable without any increase in the threshold of response to stimulation of the ulnar nerve, and while it is possible to occasion well-maintained tetanic contraction in both hand and abdominal muscles.

(3) When decamethonium iodide has been given, a diminution in the tendon-jerks or a rise in the threshold to stimulation of the ulnar nerve is not necessarily accompanied by relaxation adequate for upper abdominal surgery.

(4) When large doses of d-tubocurarine have been given, there is a slow rise in the threshold-voltage, and well-defined phases of response to stimulation of ulnar nerve. An altered phase of response may persist until after the return of spontaneous respiration. This effect is reversed by prostigmine. Consciousness does not [appear to] return until this stage.

(5) The relaxant effect of d-tubocurarine and gallamine seems to occur before the development of a peripheral block at the neuro-muscular junction. This suggests that both these drugs produce their initial relaxant effect at a more central site. No evidence is provided to localise any such central action.

SUMMARY.

A brief historical survey of the concept of muscle-tone is given. Muscle-tone is defined as: "the capacity of a muscle to resist extension," An instrument, the Tonometer, working on the "hardness" principle, is described and assessed. It is shown to provide an effective measure of differences in muscle-tone. It is further shown that measures of tone based on "hardness" and based on "resistance to extension" may, under limited conditions, give equivalent results.

Clinical work is described in which the effect on muscle-tone of ether anaesthesia and of relaxants is assessed by the Tonometer. It is found that the increase in tone common in second stage anaesthesia may persist into the first plane of the third stage. No decrease in tone below the level in the relaxed conscious patient was shown to occur with anaesthesia. (Objects (1) and (3), page 1). No decrease in tone below the level found in the relaxed, conscious patient was shown to occur with relaxants. (Objects (2) and (3), page 1). It is concluded that the purpose both of anaesthesia and of relaxant drugs is, not the obtaining of muscular relaxation, but its maintenance by preventing reflex increases in tone.

Part 2 of the thesis is devoted to a consideration of the effects of relaxants and the way in which reflex increases in tone are prevented. This is an expansion of object (2). As relaxants produce no decrease in muscle-tone beyond that found in the relaxed conscious patient, the activity of the drugs was judged by the effect on the tendon-jerks; the effect on the response to stimulation of peripheral nerves; and by the presence or absence of conditions satisfactory for upper abdominal surgery. It is shown that tendon-jerks are gradually abolished

under the influence of relaxants. When d-tubocurarine or gallamine are used, abdominal protective reflexes may be abolished while the tendon-jerks are still present. (Stage of Bremer). This is not true in the case of decamethonium.

Relaxation satisfactory for upper abdominal surgery may begin while the threshold for response to stimulation of the ulnar nerve is unaltered, or is even temporarily lowered, and while both hand and abdominal muscles can still maintain an imposed tetanus. It is concluded that the peripheral blocking action of d-tubocurarine and gallamine is not sufficient to explain the abolishing of protective reflexes by these drugs, but no site is assigned for any central action which might be responsible for this effect.

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