DISORDERED RESPIRATION

IN

D Y S T R O P H I A   M Y O T O N I C A

BY

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P R E F A C E

The purpose of this investigation is to endeavour to find an explanation for the high morbidity and mortality that occurs in patients suffering from dystrophia myotonica, in relation to anaesthesia, and to ascertain whether there exists a specific hyper-sensitivity to thiopentone.

The natural history of the disease is reviewed in some detail, surveying many of its features, including the muscular wasting and myotonia, which might well affect the muscles of respiration.

10 cases of the disease and a series of controls are investigated.

Some tests of lung function are performed, and the effects of thiopentone on respiration are studied under various conditions. The earlier experiments make use of a simple recording spirometer for studying the possible respiratory depressant effects of the drug on ventilation; but later, with the aid of a Jerkin plethysmograph, it is also possible to inspect the pattern of respiration.

Five of the 10 cases of dystrophia myotonica display profound and prolonged respiratory depression, after injection of 50 - 100 mg. thiopentone, and irregular respiration is induced or accentuated in three of these cases. The drug has little effect on the remaining patients and controls.

PREFACE

The maximum expiratory pressure in all cases is reduced to a level that is significantly lower than the controls, while other tests such as the maximum breathing capacity is within the normal range in 90% of the patients.

It is concluded that there exists in dystrophia myotonica, respiratory dysfunction which varies with the severity of the disease, and which may not be evident until a respiratory depressant drug is given.

The prolonged and profound respiratory depressant effect of thiopentone depends on the presence of pre-existing respiratory insufficiency, which appears to be due to muscular wasting and not myotonia.

The reduction in maximum expiratory pressure implies a decreased ability to cough, which in the presence of pharyngeal and laryngeal weakness may lead to the inhalation of secretions into the bronchial tree.

The response to thiopentone is not specific, but can be produced by other respiratory depressant drugs. It is impossible to predict the effect on respiration by the use of simple tests of lung function.

The morbidity and mortality appears to be related not specifically to anaesthesia but to sedation of these patients, which accentuates any respiratory depression already present. With the reduced ability to cough, these

features represent a condition similar to that of bulbo-spinal poliomyelitis, with its attendant disabilities.

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INTRODUCTION

Dystrophia Myotonica, which was originally described by Batten and Gibb (1909), and Steinert (1909), is a disease characterised by the presence of muscular wasting, myotonia, endocrine dysfunction and cataract. Myotonia, which is the failure of relaxation after contraction of skeletal muscle, was first described by Thomsen in 1876. His name is given to myotonia congenita, a disease in which muscular hypertrophy is seen, as well as myotonia. Myotonia also occurs in paramyotonia, in which delayed relaxation occurs only in the presence of cold, and is accompanied by intermittent flaccid paralysis.

Thus three clinical entities, Dystrophia Myotonica, Myotonia Congenita a nd Paramyotonia have myotonia as a feature. Thomasen (1948) and De Jong (1956) believed that dystrophia myotonica and myotonica congenita are quite distinct diseases, whilst Maas and Paterson (1939, 1950), maintained that they are but variations of the same disease, and that if cases of the latter are closely observed, dystrophic signs are invariably seen. Paramyotonia was regarded by Thomasen (1948) as a variant of myotonia congenita, but Drager (1958) considered it to be a separate disease. Walton and Nattrass (1954) suggested that, though all the three entities may be regarded as clinical syndromes, they probably represent variations of a single disease process, which they called "the myotonic

syndrome". It is with the dystrophia myotonica form of the syndrome that this Study is primarily concerned.

INCIDENCE:

The incidence of dystrophia myotonica has been estimated to be 1 : 100,000 (Merritt 1959), so that at any one time there should be about 500 patients in this country. Onset, which is insidious, can occur at any age, varying between 5 and 60 years, with an average age of 18 years.

INHERITANCE:

The disease, the aetiology of which is unknown, is transmitted by an autosomal dominant gene, which is modified by the occurrence of "progressive inheritance". The onset of the disease is at an earlier age in succeeding generations, whilst the severity also increases in succeeding generations, (Ravin and Waring 1939).

MUSCULAR WASTING:

Muscular wasting is seen in the facial muscles, the masseters and the temporals, producing the expressionless myopathic facies, while profound atrophy of the sterno-mastoids and the trapezii produce the swan-like neck. As a result of the dystrophy of the sterno-mastoids, the patient may be unable to raise the head from the pillow. Ptosis is sometimes present, and spontaneous dislocation of the jaw is not unknown. There is also wasting of the forearm muscles and the dorsi-flexors of the feet, the wasting beginning distally and spreading proximally.

Wasting may be generalised, with a pronounced loss of weight. The muscles of the larynx, pharynx and tongue may be affected by the dystrophic process, resulting in a monotonous, weak or nasal voice, and articulation is often poor. Swallowing may be difficult. Fox (1908), described a case of the right abductor paralysis, as did Caughey and Barcley (1954), while Thomasen (1948) had one case of defective closure of the vocal cords.

Thomasen (1948) described the abdominal muscles as "slack and prominent", and notes that "difficulty with respiration is unknown but coughing may be of a paralytic nature". Buytendijk (1956), on examining patients with spirometry found the "function of the lungs not disturbed, and that vital capacity is fairly good".

Caughey and Gray (1954) reported 3 cases of unilateral elevation of the diaphragm. Two similar cases were reported (Caughey and Pachomov, 1959), and a biopsy specimen from the diaphragm of one patient was found to have definite histological changes of muscle dystrophy.

Bashour et al. (1955) described one case of dystrophia myotonica with cyanosis and polycythaemia, while Kilburn et al. (1959) reported another case with marked somnolence, cyanosis and Cheyne-Stokes respiration.

MYOTONIA :

Myotonia is an abnormality of muscular contraction that is provoked by voluntary movement, especially when

it is sudden or forceful. It is also produced by percussion or electrical stimulation of the affected muscle. Normally, contraction and relaxation of striated muscle takes less than a second, but in that affected by myotonia, the contraction persists, and relaxation is a lingering and prolonged process, sometimes lasting up to one minute. Repetitive movements diminish the myotonia, whilst sudden movement, fright, cold and neostigmine all aggravate it, (Kennedy and Wolf 1937).

Myotonia often precedes the muscular wasting, but is usually absent in the muscles, which have become atrophic.

Myotonia is commonly seen in the muscles of mastication, the tongue, in the thenar and hypothenar eminences, and in the muscles of the forearm and the legs. Stiffness of muscles is a common symptom, affecting grip, speech and swallowing. Walking and the climbing of stairs may be difficult, and falls are frequent.

During the period of delayed relaxation, action potentials can be seen on the electromyogram (Lindsley and Curnen 1936), (Denny-Brown and Nevin 1941). They can be recognised as bursts of oscillations which are of short duration, emitting on the loud-speaker the characteristic "dive-bomber" sound, (Buchthal and Clemmensen 1941: Kugelberg 1949: Walton 1952: Richardson and Wynn Parry 1957).

Brown and Harvey (1939) demonstrated in the congenital

myotonia of the goat that the abnormality was in the muscle fibre itself, and that the prolonged discharge of actions potentials was unaltered by nerve section or curarisation on direct stimulation of the muscle.

The repetitive response was increased by acetycholine and potassium ions, but only in concentrations which normally caused some contractions, (Denny-Brown and Foley 1949). The response to atropine of myotonic goat muscle did not differ from that of normal, but the response to acetylcholine and anticholinesterase agents, such as diisopropylfluorophosphate (D.F.P.) or physostigmine, was greater than normal (Tum-Suden and Stoufer 1958).

In man, neither Lanari (1946) using tubarine, nor Geschwind and Simpson (1955) using tubarine and decamethonium, were able to abolish myotonia.

In a severe case of myotonica congenita, Thomasen (1948) noted respiratory difficulty, which he called myotonic asthma, while Caughey (1958) in a similar case observed myotonia of the respiratory muscles on deep inspiration. One of the few cases of dystrophia myotonica with respiratory difficulty caused by myotonia is that described by Benaim and Worster-Drought (1954), whose patient had myotonia of the intercostal muscles and the diaphragm, observed on fluoroscopy, resulting in pulmonary hypoventilation, anoxaemia and secondary polycythaemia.

CARDIO-VASCULAR SYSTEM:

Numerous abnormalities have been recorded in the cardio-vascular system on electrocardiographic examination, despite the relative absence of symptoms and clinical signs. Evans (1944) and Spillane (1951) recorded. in their 13 and 16 cases respectively, the presence of a small pulse volume, low blood pressure, splitting of the mitral first sound, P-R interval prolonged greater than 0.2 sec., low voltage P waves, slurring of the Q.R.S. complex and left axis deviation. A review of the literature by Fisch (1951) showed a significant incidence of E.C.G. changes in dystrophia myotonica, the commonest being defects in conduction and/or disturbances of rhythm. Spillane (1951), and Fisch and Evans (1954) both reported one case of sudden death: the post-mortem account by the latter of a patient aged 41 revealed the presence in the papillary muscles of the left ventricle and in its wall, of diffuse fibrosis and separation of the muscle fibres by fairly dense fibrous connective tissues.

ENDOCRINE FUNCTION:

The presence of frontal baldness, gonadal atrophy, and a low basal metabolic rate in the disease led Caughey and Brown (1950) to investigate endocrine function. Out of a total of 10 cases, he found myxoedema in 2, gonadal atrophy in 5, while in all cases, a uniformly low ketosteroid excretion. Soffer et al. (1958) demonstrated a partial impairment of

adrenal function in that 24-hour 17 ketosteroid excretion was not increased after corticotrophin. Marshall (1959) found low urinary ketosteroids, reduced thyroid functions, testicular tubular degeneration, and suggested that the muscular and endocrine aspects of the disease are sequelae of a degenerative disorder, which involves many tissues, and that primary gonadal atrophy is an unlikely cause of the disease.

PHYSICAL DEFECTS:

Cataracts, diagnosed often only by means of the slit lamp, and frequently the only feature of the disease, present as small lenticular and refractile opacities in the anterior and posterior lamellae of the lens.

Congenital physical defects include changes in the skull with thickening of the calvarum, hyperostosis frontalis and a small pituitary fossa (Caughey and Barclay 1954).

MENTAL CHANGES:

Mental intelligence is low, initiative is lacking, and unsociable and paranoid characteristics are common, (Maas and Paterson 1937). Thomasen (1948) noted that patients with dystrophia myotonica were easily overcome by sleep, and are also difficult to arouse. Kilburn (1959) et al. described one patient who often fell asleep whilst driving a car, and had frequent naps during the day. Phemister and Small (1961) found marked hypersomnia and somnolence in 4 cases, one of whom could sleep for 48 hours at a stretch.

All patients exhibited a tendency to drop off to sleep during the day, despite the fact that all slept well at night.

PATHOLOGY:

Histological changes are seen in the atrophic muscle in the early stages of the disease. They are internal migration of the nuclei from the periphery to the centre of the muscle fibre, without change in fibre size. Later there is severe atrophy of the fibre, a marked increase in connective tissue, and some fatty infiltration. Sarcoplasmic masses are commonly seen, while inflammatory reactions are rare, (Wohlfart 1951: Adams et al 1953: Greenfield et al 1957).

By means of the intra-vital methylene blue staining technique which they developed, Coers and Woolf (1959) have shown in biopsy specimens of muscle that the intramuscular nerve fibres are normal but that the more distal nerve fibre reveals an unusual profusion of sprouting of the subterminal nerve fibres. The end plates are increased in size. MacDermot (1961) by a similar technique, as well as by using silver staining, found the calibre of the nerve fibre to be reduced in size, and that there are similar abnormalities not only in the distal nerve fibres but also in the intramuscular fibres.

Of 5 cases examined at autopsy by Black and Ravin (1947) three were found to have extensive broncho-pneumonia, while De Jong (1956) noted lower lobe collapse in one out

of 3 cases.

Studies of potassium content of muscle biopsy specimens revealed this to be low, but increased after the injection of neostigmine (Cumings 1939). Serum potassium was elevated after excercise (Cumings and Maas 1939). Blood cholinesterase levels were normal (Poncher and Wade 1939). Creatinuria, with diminished creatinine excretion, does occur but is an inconstant feature (De Jong 1956), and may depend on the extent of muscular wasting (Merritt 1959).

PROGNOSIS:

Death is usually precipitated by intercurrent pulmonary infection. Mental and physical debility may be protracted for many years, though very few patients appear to be in excess of 50 years of age, (De Jong 1956).

TREATMENT - MYOTONIA:

Quinine sulphate has for many years been the drug of choice in the treatment of myotonia (Smith 1937: Kennedy and Wolf 1937, 1938: Kolb et al 1938). Its efficiency is somewhat diminished by its toxic effects and it has been replaced by procaine amide (Geschwind and Simpson 1956). Cortisone and corticotrophin (Liversedge and Newman 1956) also reduce the period of myotonia. Mertens and Gruttner (1955) and Tompkins et al (1959) favoured the use of potassium exchange resins which are effective, but only at the expense of reducing the serum

potassium level. Leyburn and Walton (1960), however, found them to be of no practical value in the treatment of myotonia. A controlled clinical test by Leyburn and Walton (1959) found both procaine amide and prednisone to be equally successful, but preferred the former drug because of the undesirable effects of the long-term administration of steroids.

DYSTROPHY:

Drug therapy at present is of no avail in the treatment of the dystrophic process within the muscle, there being no means of restoring the diseased muscle to its former condition, nor even of halting any further degeneration. Moreover, unaffected muscles may develop weakness because of disuse, and physiotherapy (including isometric exercises) is helpful in improving the patient's strength, (Lenman 1959).

ANAESTHESIA IN DYSTROPHIA MYOTONICA:

Dundee (1952) was the first to report sensitivity to thiopentone in dystrophia myotonica, this sensitivity taking the form of prolonged apnoea or profound respiratory depression. In one case, having a minor gynaelogical operation, 10 minutes apnoea and 30 minutes respiratory depression resulted after 500 mg. thiopentone, whilst in the case of another patient, being operated on for ptosis, 3 minutes apnoea and 40 minutes respiratory depression occurred after the administration of 250 mg.

of the drug. Morphine or papaveretum had been administered before the thiopentone when the patient was premedicated. The effect of 50 mg. thiopentone was studied on the spirometer in the case of a third patient: this resulted in a 48% reduction in minute volume in the first and second minutes after injection, with no loss of consciousness, while in six controls subjected to a similar dose, there was a transient stimulation of respiration of 30% in minute volume in the same period of time. (Neither the third patient nor the controls had received any opiate previously). Administration of carbon dioxide to the first patient failed to stimulate respiration, and the giving of nikethamide (2ml. of 25% solution) to the third case did not result in marked increase in minute volume.

Dundee (1952) concluded from this evidence that the overaction of thiopentone is peripheral, and that it acts on abnormally sensitive muscles. Dundee (1956) suggested that the dose of thiopentone should be restricted to 100 mg. as a maximum.

Bourke and Zuck (1957) reported the case of one patient (having a cataract extraction) who suffered 2 hours complete apnoea after 500 mg. thiopentone. In addition to this, the patient had also received 20 mg. papaveretum pre-operatively, 50 mg. suxamethonium after induction of anaesthesia for intubation, 4% lignocaine to the vocal

cords and 20 mg. pethidine, and nitrous oxide and oxygen during the operation. Inhalation of carbon dioxide and 2 ml. nikethamide produced no respiratory response 45 minutes after induction, but 2 hours later respiration commenced, being regular, slow, and shallow. 5mg. of the morphine antagonist, nalorphine, injected 3½ hours after induction produced adequate respiration, and until this time, respiration was maintained by artificial ventilation. The patient did not recover consciousness for some time, and 12 hours later developed pulmonary oedema from which he recovered.

At a later date, this patient's respiratory response to drugs was studied by means of spirometry. 50 mg. thiopentone produced apnoea for one minute, whilst 10 mg. of pethidine reduced the respiratory rate from 15 per minute to 8 per minute, for a period of 8 minutes. In one control the same dose of thiopentone increased the depth of respiration for one minute, whilst the same dose of pethidine produced no respiratory change at all.

Lodge (1958) reporting one case of "thiopentone sensitivity and dystrophia myotonica" stated that 100 mg. thiopentone produced apnoea for 20 minutes, respiratory depression for a further 20 minutes and complete muscular flaccidity. Previous to this, the patient had received 100 mg. pethidine as premedication.

Pachomov and Caughey (1958) described anaesthesia for

one case of dystrophia myotonica - of a child aged 12 - for correction of ptosis. Anaesthesia consisted of 130 mg. quinalbarbitone as premedication, 200 mg. thiopentone for induction, then ethyl chloride, ether and oxygen. Anaesthesia was uneventful: 30 minutes after the operation had been completed, breathing ceased, and despite resuscitative measures, the patient died. The cause of death was attributed to the following factors:-

" (a) Undue sensitivity of the skeletal musculature

(b) Damaged myocardium

(c) Possible inter-relationship of the metabolism of pentothal and certain enzyme deficiencies in dystrophia myotonica."

McClelland (1960) described one case of dystrophia myotonica having a hysterectomy. Amongst the drugs she received was 50 mg. pethidine for premedication; and thereafter, 300 mg. thiopentone, 20 mg. tubarine, 80 mg. pethidine, nitrous oxide and oxygen. Respiration was maintained by artificial ventilation. Atropine and neostigmine were given, at the end of the operation, to antagonise the action of tubarine and failed to terminate the apnoea, but nalorphine did produce a return of spontaneous respiration, which only became satisfactory 3½ hours after the induction of anaesthesia. McClelland (1960) suggested that "the cause for the respiratory depressant response to thiopentone was obscure" and that

"thiopentone was contraindicated in dystrophia myotonica".

Hunter (1960) noted that, in a patient given morphine premedication, thiopentone, suxamethonium, tubarine (for a hysterectomy), the most successful drug in improving respiration after prolonged apnoea was nalorphine. Despite this, respiration was not considered to be adequate, and artificial ventilation had to be maintained for four days.

Klein (1957). who has examined over 500 cases of dystrophia myotonica at the Geneva Eye Clinic, where the patients attend for the treatment of their cataracts, was unable to recollect any instance of sensitivity to drugs used in general anaesthesia. A further hundred case notes from the collection of the late Dr. Maas were inspected personally, and of the 10 patients who had had operations, one died in the immediate post-operative period, but the details of this were not available.

Kaufman (1960) collected 79 cases of myotonia, 71 of dystrophia myotonica and 8 of myotonia congenita. Of the cases of dystrophia myotonica, 30 had been given oral barbiturates and no abnormal response was noted but neither respiratory depression nor prolonged sleep were specifically observed, and may in fact have occurred. 15 patients had cataract extractions, under local anaesthesia,without incident. 24 patients did not undergo surgical treatment, but of these, two were admitted to hospital with broncho-pneumonia. 32 patients had been submitted to operation but

details were only available in 25 cases. Thiopentone had been used on all occasions, preceded by morphine or pethidine as premedication. 9 of the patients developed complications during or immediately after operation, representing a morbidity of 36% - a very high complication rate. 15 had prolonged respiratory depression varying from 30 minutes to 2 hours. Of the 4 patients who died in the immediate post-operative period, one recovered satisfactorily from operation, only to succumb after the administration of morphine; but another patient died, after ether anaesthesia, in which no specific cause for death was found at autopsy. Two patients who had received barbiturates for the induction of anaesthesia, which was without incident, died respectively 8 and 11 hours post-operatively, being unable to cough up profuse bronchial secretions. Autopsy in one of these cases revealed the presence of an elevated diaphragm, while the lungs were full of fluid and almost airless.

Persistant myotonia, under general anaesthesia, has also been reported in one case of dystrophia myotonica by Talmage and McKechnie (1959) but this did not affect the muscles of respiration. Grund (1919) and Kennedy and Wolf (1937) both recorded one case each of myotonia produced by mechanical stimulation, which was not abolished by spinal anaesthesia, while Buchthal and Clemmensen (1941) noticed this, too, after brachial plexus nerve block.

The natural history of dystrophia myotonica has been reviewed in some detail, surveying as many aspects as possible, in a search for any explanation that would offer an answer for the cause of the high morbidity and mortality, and to assess whether the response to thiopentone was a specific idiosyncrasy. Thiopentone has been administered with ill effect in some cases, but without complications in others; but no prior tests of lung function were performed. In other investigations (Bashour et al 1955: Kilburn et al 1959), lung function has been extensively studied, but the effects of an accompanying sedative have not received the same examination. The following investigation attempts to co-ordinate some of these aspects of dystrophia myotonica, and to endeavour to discover whether inherent abnormality is to be found in the disease or the drug.

METHOD AND MATERIALS:

Studies of pulmonary ventilation were performed on 10 known cases of dystrophia myotonica, and 22 controls, who were healthy men and women. Their ages and weights were all recorded. Before the investigation began, the nature of the tests was explained to the subjects, so that they would not be unduly apprehensive.

The following tests of pulmonary ventilation were carried out, (measurements were all at A.T.P.S.) : - vital capacity, maximum breathing capacity, maximum expiratory pressure,

and estimation of the resting mixed venous carbon dioxide tension. Whenever it was possible fluoroscopy of the chest was performed. The effect of carbon dioxide on ventilation was also studied, and the effect, in some instances, before and after the administration of 50 - 100 mg. thiopentone.

(1) Forced Vital Capacity (F.V.C.) was performed, with the subject sitting in a comfortable upright posture, and wearing a nose clip. Measurement was on a light-weight spirometer (Bernstein et al 1952) and the speed of the recording drum was 2 cm/second. From the forced vital capacity (F.V.C.) the forced expiratory volume over one second was measured. The forced expiratory volume over one second (F.E.V.i), when multiplied by 35, gives an indirect measure of maximum breathing capacity (M.B.C.) in litres/minute. (Gandevia and Hugh Jones 1957).

(2) On the spirometer, the direct maximum breathing capacity (M.B.C.) was recorded - this is the maximum pulmonary ventilation in litres/minute determined in our cases over a 5 second period. The subject was in an upright posture and wearing a nose clip. The subject was instructed to breath in and out as deeply and as fast as possible. Normally, it is performed over 15 seconds, but in the present cases it was limited to 5 seconds as it was felt that it might lead to respiratory distress over the longer period. This test was not performed routinely as it demands the maximum co-operation of the

subject, and depends a lot on his incentive.

(3) Maximum expiratory pressure (M.E.P.) was measured by asking the subject (who was seated in an upright posture and wearing a nose clip) to make a maximal effort to blow up and sustain the column of mercury of a sphygmomanometer adapted to take a mouthpiece. A small leak was present in the mouthpiece so that pressure could not be maintained by glottic closure. The result was measured in mm. Hg. and was performed on all subjects. In three instances, in dystrophia myotonica patients, the M.E.P. was verified by recording oesophageal pressures by means of a water-filled polythene tube connected to a capacitance manometer. In all cases, 3 recordings of F.V.C. and M.E.P. were made, and the best of these adopted.

(4) The mixed venous CO_2 tension was estimated by the re-breathing method as described by Campbell and Howell (1960), using a two-litre re-breathing bag containing oxygen, and standard times of 90 seconds and 20 seconds for equilibration. The CO_2 content of the rebreathing bag was determined by analysis in a Scholander dry gas analyser or by an infra-red gas analyser (Hartman and Braun Capnograph).

This was done in 7 cases of dystrophia myotonica.

(5) RESPIRATORY RESPONSE TO BREATHING ENDOGENOUS CO_2

The effects of CO_2 on pulmonary ventilation was studied in 3 cases of dystrophia myotonica and 7 controls. In this procedure, the subject was seated comfortably in an upright posture, wearing a nose clip and breathing in to

a Palmer 5 litre spirometer, which had previously been filled with oxygen. There was no soda lime canister in the circuit, so that endogenous CO_2 was allowed to accumulate during the 5 minute period of the test. The inspiratory tubing to the patient was connected to the spirometer by means of a non-return valve and mouthpiece. On the expiratory tubing a continuous sample of gas was drawn off near the mouthpiece into the CO_2 infra-red analyser, and then returned to the spirometer. Measurements of the end tidal CO_2 tensions were recorded continuously by means of an ultra-violet recorder (N.E.P.) Recording of pulmonary ventilation was by pen on the spirometer (Speed 24 mm. per minute).

(6) The effect of thiopentone on respiration was studied using the following methods:

METHOD 1:

Subjects: 5 cases of dystrophia myotonica*

3 controls

(* Four of these patients consented to undergo respiratory tests with the jerkin plethysmograph. The tests are recorded under Method 111)

In this method the subject was seated in a comfortable upright position wearing a nose clip. Using the same spirometer as in (5), which had been previously filled with oxygen but without the CO_2 analyser, the patient re-breathed for a period of 5 minutes accumulating endogenous CO_2. Ventilation was measured during this period by pen (Spirometer speed 24 mm/minute).

The patient was allowed to rest for 10 minutes, to allow ventilation to return to normal, after which 50 mg. of 1.25% thiopentone was injected intravenously over a period of 2 minutes. The thiopentone was administered with the subject in a recumbent posture, except for one patient (D.H.), who was seated. The rebreathing of endogenous CO_2 was repeated as before.

METHOD 11:

Subjects: 1 case of dystrophia myotonica
2 controls

In this test, the subjects were all recumbent, breathing 5% CO_2 in air from a Donald single 100-litre box-bag spirometer (Donald and Christie 1949) via a mouthpiece, whilst wearing a nose clip. Pulmonary ventilation was recorded by pen on the spirometer (speed 24 mm. per minute). After 4 minutes, 50 mg. thiopentone (1.25% solution) was injected and the effect studied.

METHOD 111:

Subjects were fitted with a jerkin plethysmograph, described by Heaf et al(1961). The jerkin, which is a double-layer garment filled with air, was put on the patient and adjusted to fit comfortably round the trunk. During respiratory movement the inner layer of the jerkin moves freely as the volume of the trunk alters, while the outer layer moves less. The change in jerkin pressure produced by these movements is related to change in trunk volume during respi-

ration. The pressure in the jerkin was adjusted so that the swing of pressure during deep expiration to deep inspiration was of the order of 2 - 6 cm. H_2O. The change in pressure in the jerkin was measured with a differential electro-manometer (Scott & Willims 1960). The mean of the positive pressure was applied to the back of the diaphragm of the transducer from a reservoir so that the average swing during respiration was 2 - 3 cm. H_2O. Recording was on a Schwarzer direct-writing multi-channel recorder, the paper moving at the speed of 5 cm. per minute. The frequency of the system was greater than 25 cycles per second. Calibration was performed twice at least - at the commencement and at the end of the experiment. Calibration was performed by asking the subjects to breathe into a mouthpiece connected to a Donald box-bag spirometer filled with air. Each breath on the spirometer was readily identified with the corresponding breath on the Schwarzer direct-writing recorder. During the tests, the subjects were all in a recumbent position in bed and encouraged to relax and fall asleep.

(i) 5% CO_2 and 50 mg. thiopentone.

Subjects: 2 cases of dystrophia myotonica

1 control

In this method, after the subjects had settled, they breathed 5% CO_2 in air as in Method 11. 50 mg. thiopentone (1.25% solution) was injected rapidly, and the effect studied.

(ii) Air and 100 mg. thiopentone

Subjects: 6 cases of dystrophia myotonica

Subjects: 1 case of motor neurone disease
(contd.) 10 controls

In this method, the subjects were allowed at least 20 minutes to settle, to allow ventilation to reach resting level as soon as possible. 100 mg. of 1.25% thiopentone was injected within 30 seconds, but the injection did not commence until any stimulating action of respiration caused by the pain of venipuncture had passed. The patient was unaware of the precise moment that the drug was injected. The subject remained in the jerkin for at least another 30 minutes after the injection.

The only occasion that the subject had any apparatus in direct contact with his face or mouth was when calibration was carried out, or when attempts were made to measure mixed venous CO_2 concentrations by the rebreathing method (Campbell and Howell 1960).

MISCELLANEOUS CASES:

In four other cases of myopathy F.E.V.i, F.V.C. and M.E.P. were measured prior to operation for muscle biopsy, and the results also recorded (Table xi, appendix).

LIMITATIONS OF METHODS:

The methods chosen were restricted by the necessity that studies had to be conducted on potentially ill patients who, because of the mental aspects of their disease, were not necessarily co-operative. The tests had to be safe and simple, and so conducted as to produce the minimum of discomfort. The direct maximum breathing capacity (M.B.C.)

was not used as a routine after the initial experiments, because it proved exhausting, and hence probably not very reliable under these circumstances. The oesophageal tube for measuring maximum expiratory pressure (M.E.P.) was most unpopular with patients, and its use was discontinued.

The multiplicity of the methods used is the reflection of some of the difficulties encountered in the study. At the beginning of the study which was conducted for a period of over two years, some of the apparatus for the investigation was not yet available, and also the number of patients was limited by the rarity of the disease. It was only possible in a few instances to repeat the injection of thiopentone on a further occasion with improved techniques and apparatus. It was not possible to subject these patients to daily respiratory tests, increasing the dose of thiopentone, nor, as some were out-patients, was it felt justifiable to use other drugs such as morphine, which might have a more prolonged effect.

Inhalation of CO_2 was used in the initial studies. Eckenhoff and Oech (1960) have restated the view of Loewy (1890) that the effects of narcotics upon respiratory rate and minute volume were not uniform without this stimulus because any depression in respiration produced by drugs effected the level of arterial pCO_2, and limited the extent of respiration depression. It was found to be too powerful a stimulus, except in the case of two very ill patients,

abolishing any abnormal pattern of respiration and its use was discontinued. The use of a mouthpiece also had disadvantages. (See below under Method 111).

METHOD 1:

The rebreathing of endogenous CO_2 was chosen because of its simplicity but suffered from the disadvantage of the lack of continuity of recording, in that the patient had first to be moved for the injection of thiopentone, and then attached again to the spirometer. In one case (W.H.) who was given thiopentone in the sitting position, in an attempt to maintain some continuity, there was a profound effect on respiration, probably due to hypotension.

The CO_2 analyser was not yet available, so that it was impossible to record continuously either the concentration of CO_2 inhaled or the end tidal pCO_2.

METHOD 11:

In this method of breathing of 5% CO_2, recording had to be interrupted periodically while the single 100 litre box-bag spirometer was refilled.

Neither of the above two Methods gave a complete picture of the pattern of respiration.

METHOD 111:

The jerkin plethysmograph proved to be the most satisfactory method for continuous and prolonged recording and it was found possible to continue the investigation for about an hour in most cases. The patient did not have to be

moved during the investigation, so that a constant response to the drug could be obtained. Artifacts from coughing, snoring, movement in the bed, or talking were easily recognised on the direct writing recorder. Respiratory patterns could also be observed with this Method, but irregular respiration usually reverted to normal with the administration of CO_2 or even with the stimulus of insertion of a mouthpiece.

The dose of thiopentone was increased to 100 mg., and given rapidly to produce a profound effect within a short space of time. This was acceptable as 50 mg. given slowly in two cases in previous tests produced little effect. The larger dose was therefore given to all subjects in Method 111, who were not given 5% CO_2 to inhale.

NOTE ON JERKIN PLETHYSMOGRAPH: (Limitations and accuracy)

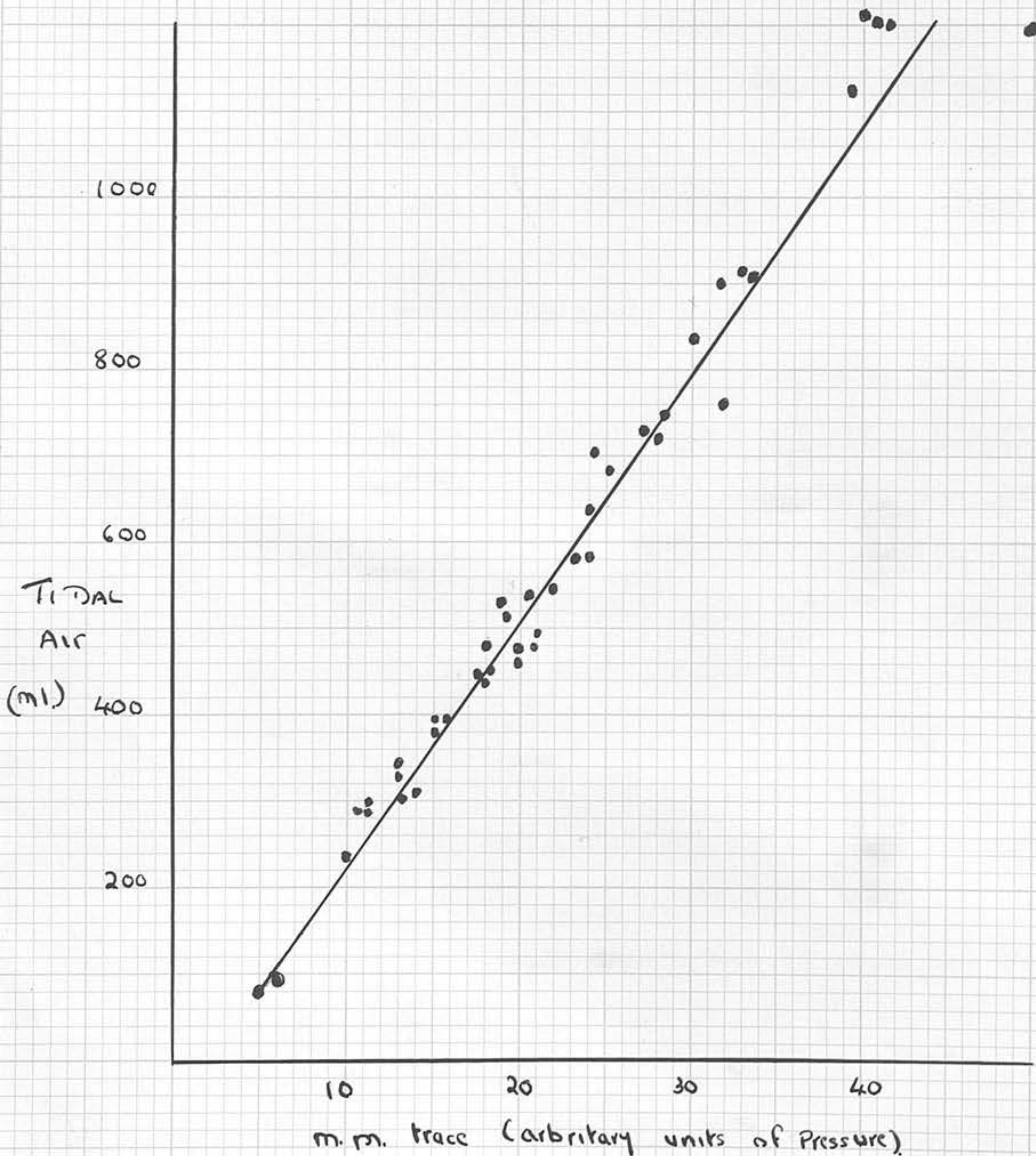
Greene and Coggeshall (1933) described the use of a body plethysmograph enclosing the chest and abdomen only; the outer layer of this plethysmograph was fairly rigid, and the volume of air displaced from it was recorded by means of a spirometer. With large breaths the accuracy of this Method was $\pm$ 8.3%, but difficulty with calibration was encountered with obese subjects, who had shallow respirations.

The outer layer of the jerkin plethysmograph, described by Heaf et al (1961), is not rigid and the change in pressure is much less than could be the case if it were rigid, but it does not interfere with the patients' respiratory movements. The change in pressure in the jerkin was measured

Fig. 1a.

Calibration of Jenkin Plethysmograph showing relationship of the volume of air inspired to changes in Jenkin Pressure.

(subject - control ♀, aged 24, wt 7st 6 lbs, Ht 5'6")



by means of a differential electromanometer (Scott and Williams 1960).

The jerkin plethysmograph was calibrated for linearity between respiratory volume response and pressure change in the jerkin in 6 controls, of various body builds, and two cases of dystrophia myotonica. (Figs. la and lb in the text, and lc to lh in the appendix).

The calibration was performed with the patient enclosed in the jerkin as in Method 111, and pressure changes in the jerkin measured by the electromanometer, were recorded on the Schwarzer recorder or N.E.P. ultra-violet recorder. At the same time, the patient breathed into a Donald box-bag spirometer,* and the individual breath on the spirometer identified with the pressure change produced by the same breath. The pressure change-volume relationship appeared to be linear (within $\pm$ 10%) within the range of tidal air of 200 ml. - 1000 ml.

The accuracy of the plethysmograph is affected by such factors as adiabatic expansion of the air in the jerkin; and by hysteresis of the plastic material of which the jerkin is made.

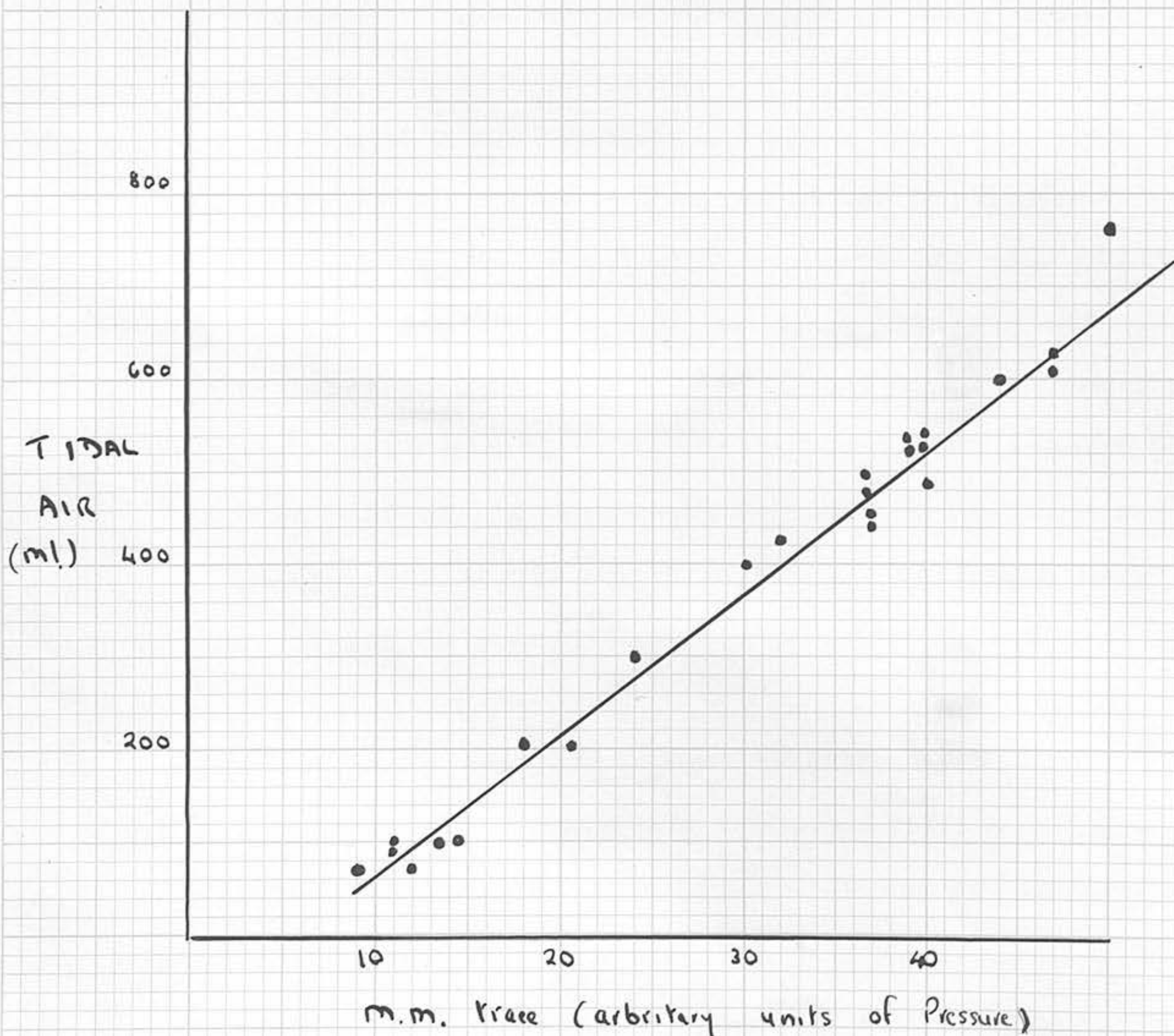
Movement of the patient during thiopentone experiments may upset the calibration, but these movements are easily recognised on the direct-writing recorder, and may result in base shift. To obviate any difficulty created by this, repeated calibrations were performed during experiments.

The volumes of tidal air used to calibrate the jerkin

* Filled with air.

Fig I b

Calibration of Jerkin Plethysmograph, showing relationship of the volume of air inspired to changes in Jerkin Pressure (subject - case of Dystrophia Myotonica - W.H.)



during thiopentone experiments under Method 111 were about 500 ml., which can be seen from Figs. 1a - 1h are on a section of the graph where the pressure change-volume relationships are quite linear (within ± 10%). At low tidal volumes it can be seen that for the calibration curves (Figs. 1a - 1h) that the line joining the points is no longer straight, and probably curves to reach zero. In the calibration during the experiments tidal volumes at approximately 500 ml. were used, plotted, and a straight line drawn to zero. Thus at low tidal volumes, the pressure changes tend to over-estimate the volume. Thus the readings of low tidal volumes in the experiments are probably greater than they are in fact. Thus any decrease in pulmonary ventilation associated with low tidal volume in the present method would be minimised rather than exaggerated.

Studies of neuromuscular conduction were attempted during the respiratory investigation, to assess the possible peripheral effects of thiopentone. This was done by stimulating the ulnar nerve at the wrist, and recording action potentials at isometric tension for the abductor digiti minimi (Grob et al 1956), but the discomfort produced by the supramaximal nerve stimulation disturbed the resting ventilation. Furthermore, the myotonia in the hands produced by the nerve stimulation made it impossible to assess the effect of any drug peripherally, unless it were to have a specific effect on myotonia, and this procedure was abandoned.

RESULTS

The ages, weights, F.E.Vi., F.V.C. and F.E.Vi/F.V.C. % of age, M.B.C., M.E.P. for the patients suffering from dystrophia myotonica are shown in Table 1, and the corresponding information for the controls appears in Table 11. Similar data on a group of patients suffering from other myopathies appears in Table xi (Appendix). Case reports of all the patients suffering from dystrophia myotonica also appear in the Appendix.

A statistical analysis of the ages, weights, M.B.C. and M.E.P. has been prepared and appears in Table iii. A difference between the means of the respective groups of more than two standard errors (2 S.E.) was regarded as probably significant, and that of three (3 S.E.) as highly significant.

There was a tendency for the mean of the ages of the cases of dystrophia myotonica to be higher than that of the controls (difference between means was greater than 2 S.E. but not 3.S.E.), but there was no significant difference for that of their weights. There was no significant difference between the means for M.B.C., but for M.E.P. there was a highly significant difference between that of the cases of dystrophia myotonica and the controls.

A study of the M.B.C. and M.E.P. within the group of cases of dystrophia myotonica reveals that the M.B.C. of one case (O.B.) was significantly low. Her M.B.C. was 38.5 litres per minute, which is more than three standard deviations

TABLE i

Ages, Weights and Pulmonary Function tests of 10 cases of Dystrophia Myotonica.

Patient	Age	Wt. St.	lbs.	FEV1 ml.	FVC ml	$\frac{FEV1}{FVC}$ %	Direct MBC L/min	Indirect MBC L/min	MEP mm. Hg.	MEP Oesophageal cm. H_2O
C.J.	35	8.	4	2800	3150	90	74	102	10	15
J.H.	43	13	0	2300	2500	92	-	80.5	30	
D.H.	41	8.	10	2580	2800	92	75	91	20	
H.N.	46	10	4	2050	2600	78	66	71	10	
R.B.	38	7	7	2700	2950	92	-	94.5	30	
W.H.	42	10	6	1900	2400	90	84	66.5	40	55
J.S.	45	9	12	3400	4900	70	100	119	20	
T.B.	50	10	0	2000	2630	76	90	70	20	
J.G.	32	8	4	3000	3600	83	75	105	20	20
O.B.	49	10	2	1100	1500	73	-	38.5	25	

Mixed venous pCO_2 (mm. Hg.) in 7 cases of Dystrophia Myotonica.

D.H.	45	W.H.	45		
H.N.	44.7	J.S.	47	J.G.	52.5
R.B.	42	O.B.	44		

TABLE ii

Ages, Weights and Pulmonary Function Tests of Controls.

Subject	Age Years	Wt. St.	lbs	FEVi ml.	FVC ml.	FEVi/FVC %	Indirect MBC L/min.	MEP mm Hg.
L.W.	38	9	10	2700	3300	82	94.5	80
E.S.	30	9	11	3550	3800	93	123	70
C.Y.	35	10	4	3800	4800	80	130	100
B.C.	27	13	0	3500	3800	92	122.5	90
M.P.	32	13	6	4650	5650	82	163	160
J.N.	37	6	12	2900	3900	74	101.5	45
J.J.	64	11	4	1550	1850	84	52.5	50
D.S.	33	8	4	2550	3300	77	87.5	60
R.K.	36	9	8	2400	3550	70	96	75
D.SH.	43	9	12	1300	2100	62	45	45
R.S.	52	9	0	2400	2900	83	96	45
A.W.	35	10	2	3400	4000	85	119	90
W.A.	47	10	3	3200	4200	76	100	112
B.D.	21	10	0	3000	4330	70	110	105
F.E.	20	10	11	3800	5100	75	95	133
W.I.	30	10	0	2700	3500	77	60	94.5
W.T.	49	9	2	3150	3700	85	70	120
S.M.	34	10	0	3950	4900	80	90	138
J.T.	26	11	0	4500	5400	83	90	157
D.P.	47	9	7	3200	4400	73	80	112
J.M.	29	10	9	3000	3700	80	95	105
L.H.	23	9	3	3200	4300	74	90	112

TABLE iii

The Means, Standard Deviation for Age, Weight, M.B.C. and M.E.P. of Cases of Dystrophia Myotonica and Controls. Standard Error of Difference between Cases and Controls. is shown, with the significance.

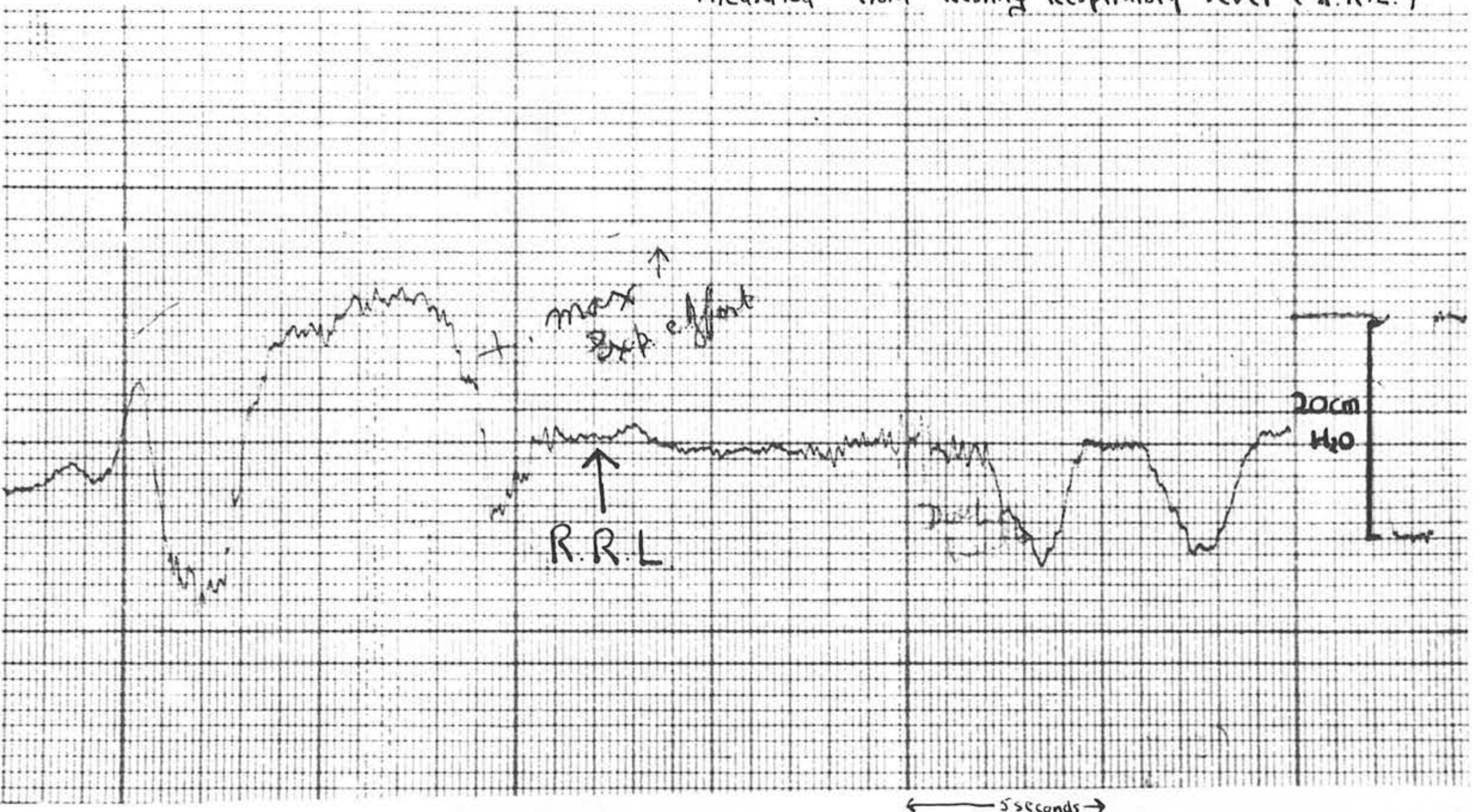
	Subjects	Mean	S.D. (±)	Standard error of diff. (S.E)	Significance
Age Years	10 cases of D.M.	42	5.2	-	
	Controls	36	10.6	2.8	>2 but <3 S.E.
Wt.	10 cases of D.M.	9st. 9	20lbs		
	Controls	10st.1	18.9lbs	7.5lbs	<2 S.E.
M.B.C. L/min	10 cases of D.M.	84	7		
	Controls	100	26.4	8.9	<2 S.E.
M.E.P mm. Hg	10 cases of D.M.	22.5	8.7	-	
	Controls	81.3	25.7	6.0	>3 S.E.

Significance: >2 S.E. between means = Probably significant

>3 S.E. between means =Highly signifcant.

Fig. 2.

Measurement of oesophageal pressure in a case of Dystrophia Myotonica.



(S.D.) from the mean of the group. One patient (W.H.) had an M.E.P. of 40 mm. Hg., which is just two standard deviations from the mean of the group.

The maximum expiratory pressure (M.E.P.) was measured by means of an oesophageal tube in three cases (C.J., W.H., J.G.) and found to be similar to the results obtained by means of the sphygmomanometer (Table i). A recording of M.E.P. for C.J. is seen in Fig. 2, showing this to be 15 cms. H_2O from the resting respiratory level.

The results of the re-breathing Method of measuring pCO_2 are also shown in Table i, showing this to be elevated in only one case (J.G.) when it was 52.5 mm. Hg. The normal range of mixed venous pCO_2 by this method is from 42 - 50 mm.Hg. (The mixed venous pCO_2 is about 6 mm. Hg. more than the arterial pCO_2 at rest). (Campbell 1960). Fluoroscopy of the chest failed to reveal any myotonica of the diaphragm. (C.J., D.H., J.H., J.C.).

<u>RESPIRATORY RESPONSE TO BREATHING ENDOGENOUS CO_2</u>:

Most of the control cases showed a maximum increase of minute ventilation of 160 - 300% at the end of the 5th. minute of breathing endogenous CO_2, compared with the ventilation during the 1st. minute. The respiratory rate per minute increased by 5-41% (although one control showed no change in respiratory rate) and an increase in their tidal air by 100-200%. Two of the cases of dystrophia myotonica were respectively able to increase their pulmonary ventilation by 172% and 190%; the respiratory rate 24% - 46%

Fig 2a

Respiratory Response to rising end-tidal pCO_2 in 3 cases of Dystrophia myotonica

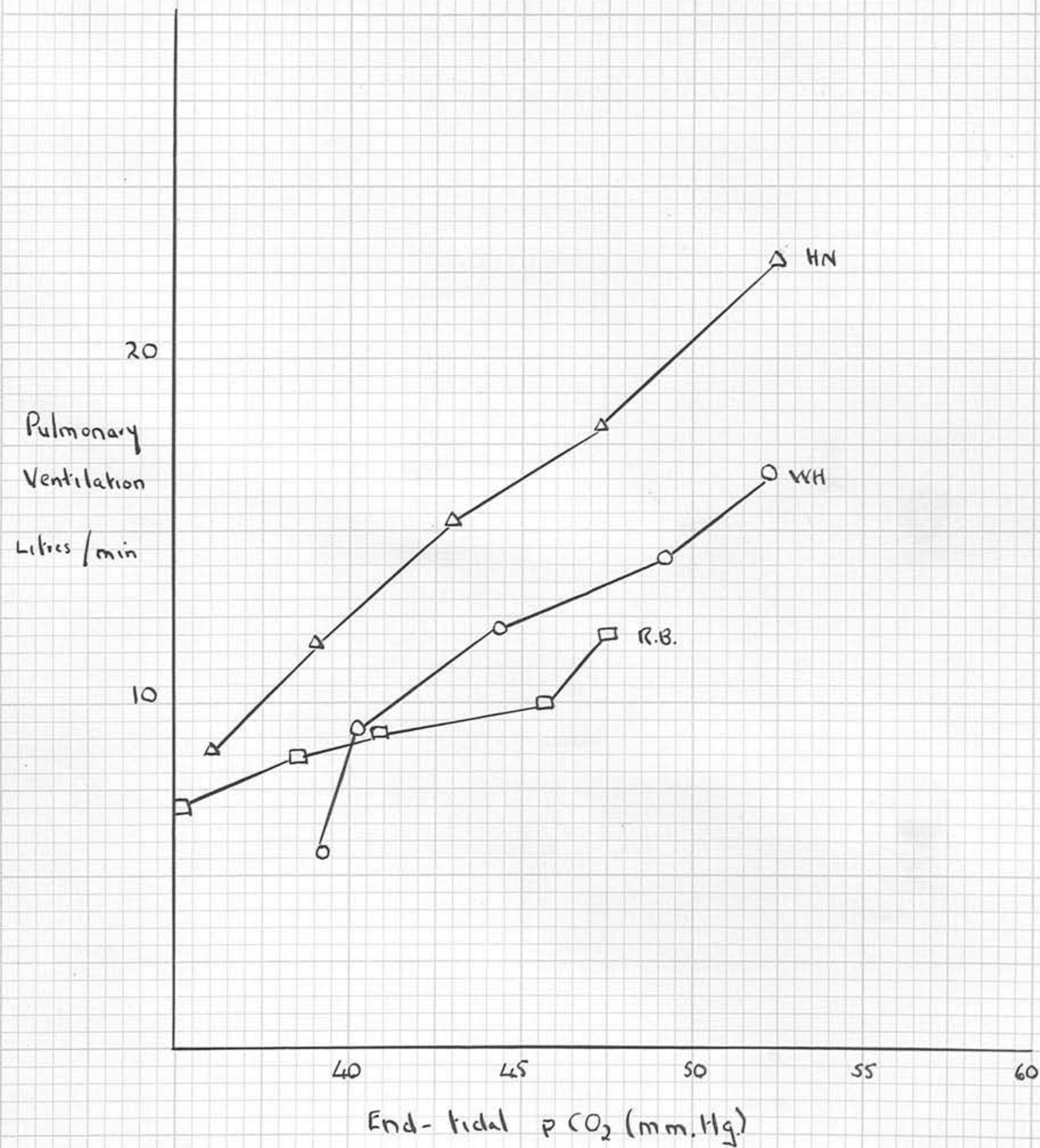


TABLE iiia

Respiratory response to rising end-tidal CO_2 tension in 3 cases of Dystrophia Myotonica.

Subject	Minutes of CO_2	Tidal Volume ml.	Resp. Rate	Ventil L/Min.	End Tidal* pCO_2 mm. Hg.	% increase of Ventil.
W.H.	1	450	13	5.8	38.4	
	2	650	14	9.1	40.4	57
	3	750	15	12.1*	44.4	109
	4	800	17	14.4*	49.3	150
	5	900	18	16.8*	52.2	190
H.N.	1	700	15	8.5	36	
	2	700	17	11.9	38.9	40
	3	850	18	15.3	42.8	80
	4	1100	18	18	47.2	110
	5	1100	21	23.1	52.5	172
R.B.	1	400	18	7.2	34.5	
	2	500	17	8.5	38.4	18
	3	550	16	8.8	40.4	20
	4	500	20	10	45.5	40
	5	600	20	12	47.3	66

* Includes 1 breath of 1.5 L. *The end-tidal pCO_2 was measured at the middle of each minute.

Fig 2b

Respiratory Response to rising end-tidal pCO_2 in 7 controls.

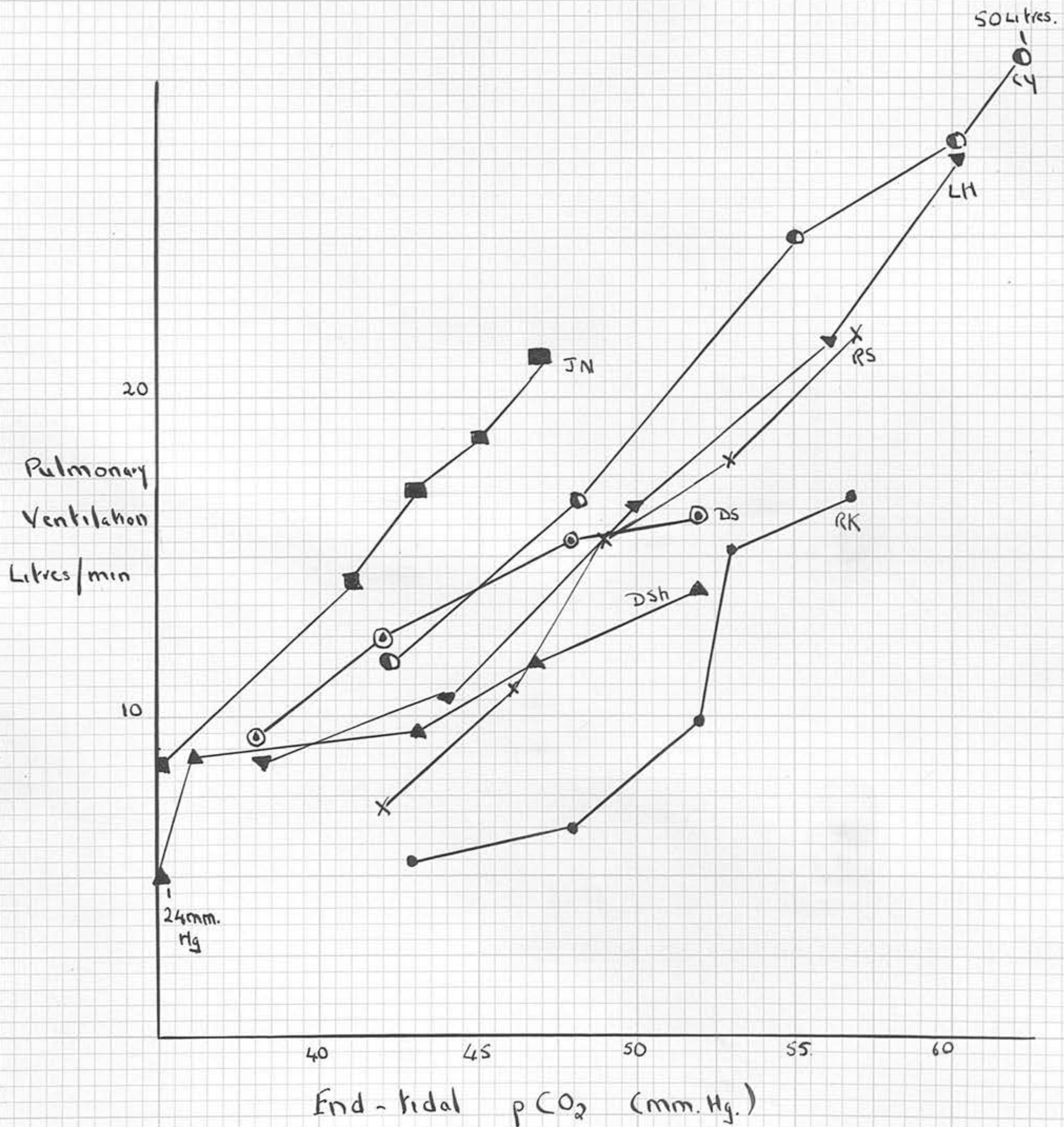


TABLE iiib

Respiratory response to rising end-tidal CO_2 tension in 7 controls.

Subject	Minutes of CO_2	Tidal Volume ml.	Resp. Rate	Ventil. L/Min	End-tidal pCO_2 mm.Hg.	% Increase In Ventil.
	1	350	16	5.6	43	
	2	400	16	6.4	48	16
R.K.	3	550	18	9.9	52	77
	4	850	18	15.3	53	174
	5	850	20	17	57	200
	1	450	19	8.4	35	
	2	650	22	14.3	41	70
J.N.	3	800	21	16.8	43	100
	4	850	22	18.7	45	122
	5	900	24	21.6	47	160
	1	400	13	5.2	24	
	2	750	12	9	36	54
D.SH.	3	800	12	9.6	43	84
	4	900	13	11.7	47	124
	5	1050	13	13.9	52	170
	1	800	15	12	42	
	2	1200	14	16.8	48	40
C.Y.	3	1600	16	25.6	55	113
	4	2000	14	28	61	133
	5	2500	20	50	63	317
	1	600	12	7.2	42	
	2	800	14	11.2	46	56
R.S.	3	1050	15	15.7	49	85
	4	1100	16	17.6	53	144
	5	1300	17	22.1	57	207
	1	450	20	9	37	
	2	500	22	11	44	22
L.H.	3	700	23	16.1	50	79
	4	850	25	21.2	56	135
	5	1000	28	28	62	210
	1	450	21	9.5	38	
	2	550	23	12.6	42	33
D.S.	3	700	22	15.4	48	62
	4	750	22	16.5	52	72
	5	Unable to continue with test.				

The end-tidal pCO_2 was measured at the middle of each minute.

and the tidal air by 60% and 100%. One case (R.B.) was able to reach a maximum increase of 66% only, of minute ventilation; an increase of respiratory rate of 11%, and an increase of tidal air of 50% 1½ times. Results are shown in Tables iiia, iiib and Figs. 2a and 2b, showing the increase of pulmonary ventilation in relation to end tidal pCO_2.

METHOD 1: The results of Method 1 (breathing endogenous CO_2) are summarised in Table iv and Figs. 2c and 2d.

There was a pause of about 5 minutes after the injection of thiopentone, before ventilation was again recorded. Two patients (H.N. and R.B.) showed little change respectively in ventilation rates before and after the administration of thiopentone, after 5 minutes CO_2. W.H. was unable to continue for more than 4 minutes of CO_2, but again there was no marked change in ventilation rates at the end of this time. D.H. had a period of apnoea for 2 minutes after the thiopentone - the drug being injected whilst he was sitting. But he was able to record a ventilation rate of 25 litres per minute, comparable with the 23 per minute that he attained before the injection.

C.J. became distressed after 3 minutes of re-breathing CO_2, the ventilation rate reaching 25 litres per minute with a tidal air of 1250 ml. and a respiratory rate of 20 per minute. After the dose of thiopentone, she was able to continue for four minutes without any subjective discomfort, but after this period her ventilation rate only rose to 14 litres per minute, with tidal air of 1200 ml. at a rate

Fig. 2C.

Respiratory Response to Endogenous CO_2 before and after 50mg. Thiopentone (method I) in 5 cases of Dystrophia myotonica

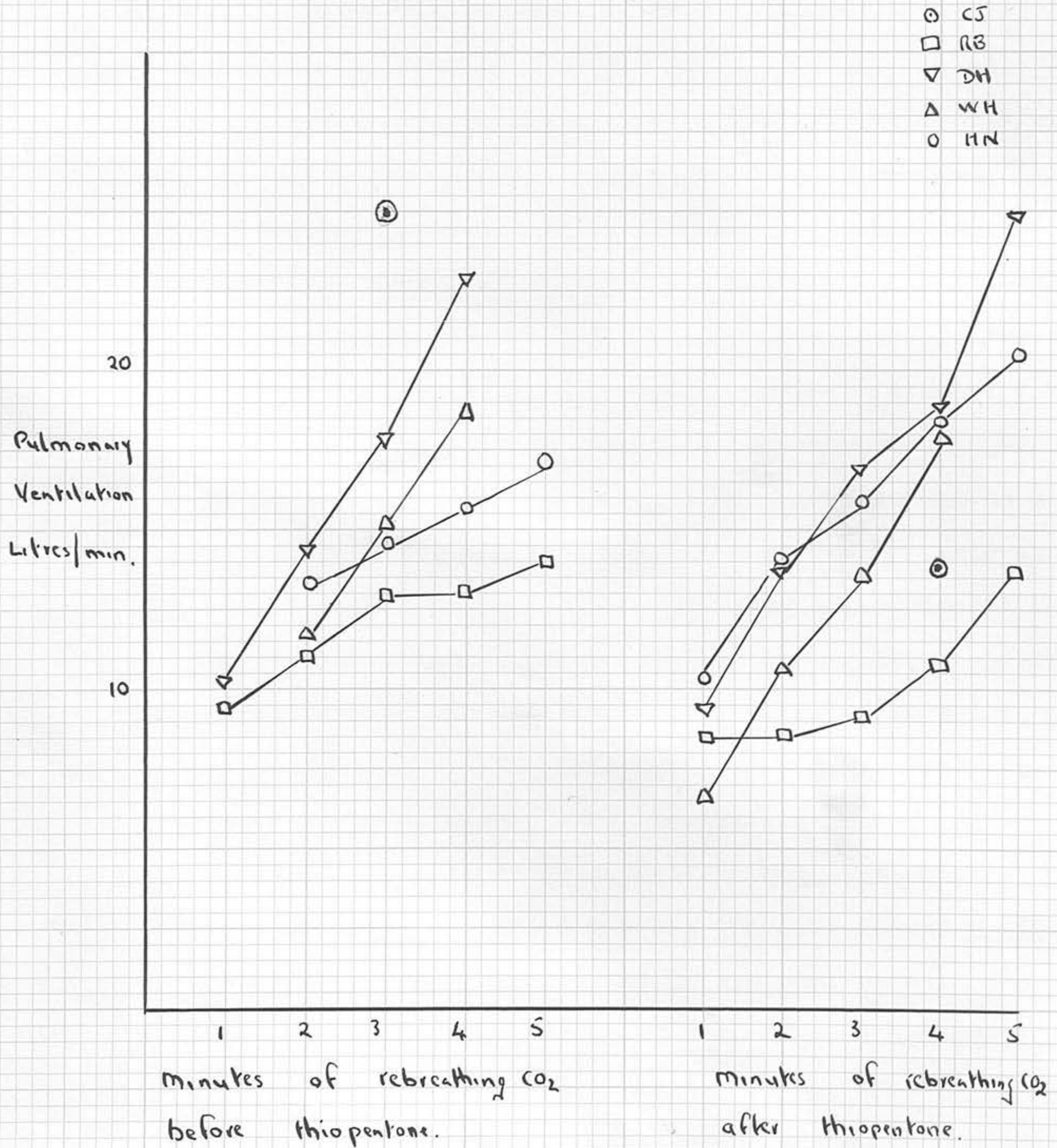


Fig 2 d.

Respiratory Response to Endogenous CO_2 before and after 50 mg. Thiopentone (Method I) in 3 controls

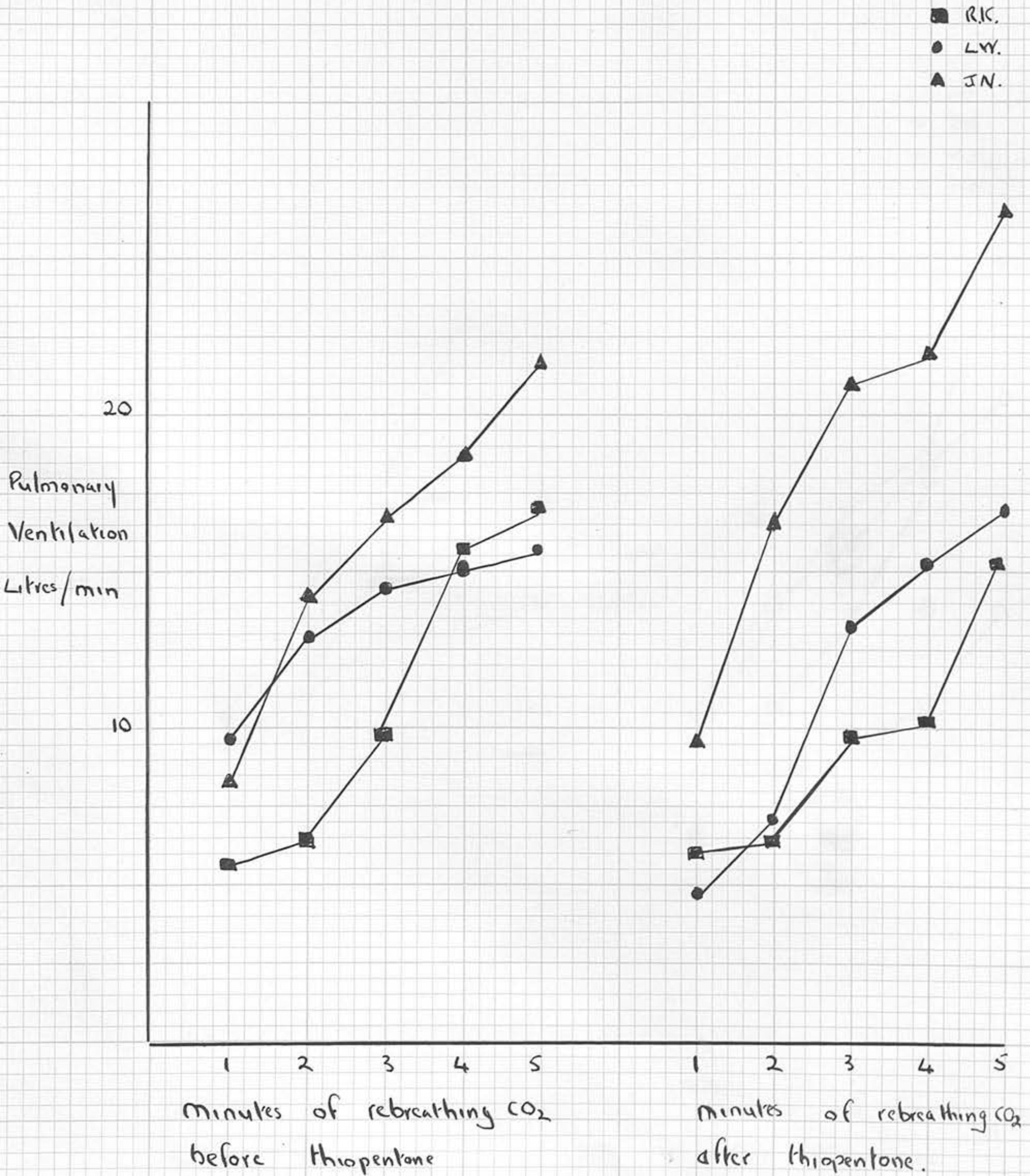


TABLE iv

Ventilation in 5 cases of Myotonic Dystrophy and 3 Controls. Method 1 (Endogenous CO_2)

Subject	Minutes of Rebreathing CO2	Pulm Vent L/Min Before Thiopentone	Pulm Vent L/Min After Thiopentone	Subject	Minutes of Rebreathing CO2	Pulm Vent L/Min Before Thiopentone	Pulm Vent L/Min After Thiopentone
H.N. Dystro. Myoton.	1	–	10.4	R.B. Dystro. Myoton.	1	9.4	8.5
	2	13.3	14.2		2	11	8.5
	3	14.7	16		3	13	8.8
	4	15.7	18.7		4	13	10.8
	5	17.1	20.9		5	14	13.6
W.H. Dystro. Myoton.	1	–	6.6	D.H. Dystro. Myoton.	1	10.2	9.5
	2	12.3	10.6		2	14.4	13.6
	3	15	13.5		3	18	17
	4	19	18		4	23	18.9
					5	–	25
C.J.* Dystro. Myoton.	1			L.W. Control	1	9.8	4.8
	2				2	13.3	7
	3	25*			3	14.7	13.3
	4		14*		4	15	15.3
	5				5	16	17
R.K. Control	1	5.6	6	J.N. Control	1	8.4	9.9
	2	6.4	6.75		2	14.3	16.5
	3	9.9	9.6		3	16.8	21
	4	15.3	10.2		4	18.7	22
	5	17	15.2		5	21.6	26.4

* Due to a technical fault it was not possible to obtain recordings of complete minutes apart from these two ventilation rates. (Patient C.J.).

Fig. 2e

Respiratory Response to Thiopentone in 1 case of Dystrophia myotonica and 2 controls while breathing 5% CO_2 in Air.
(Method II)

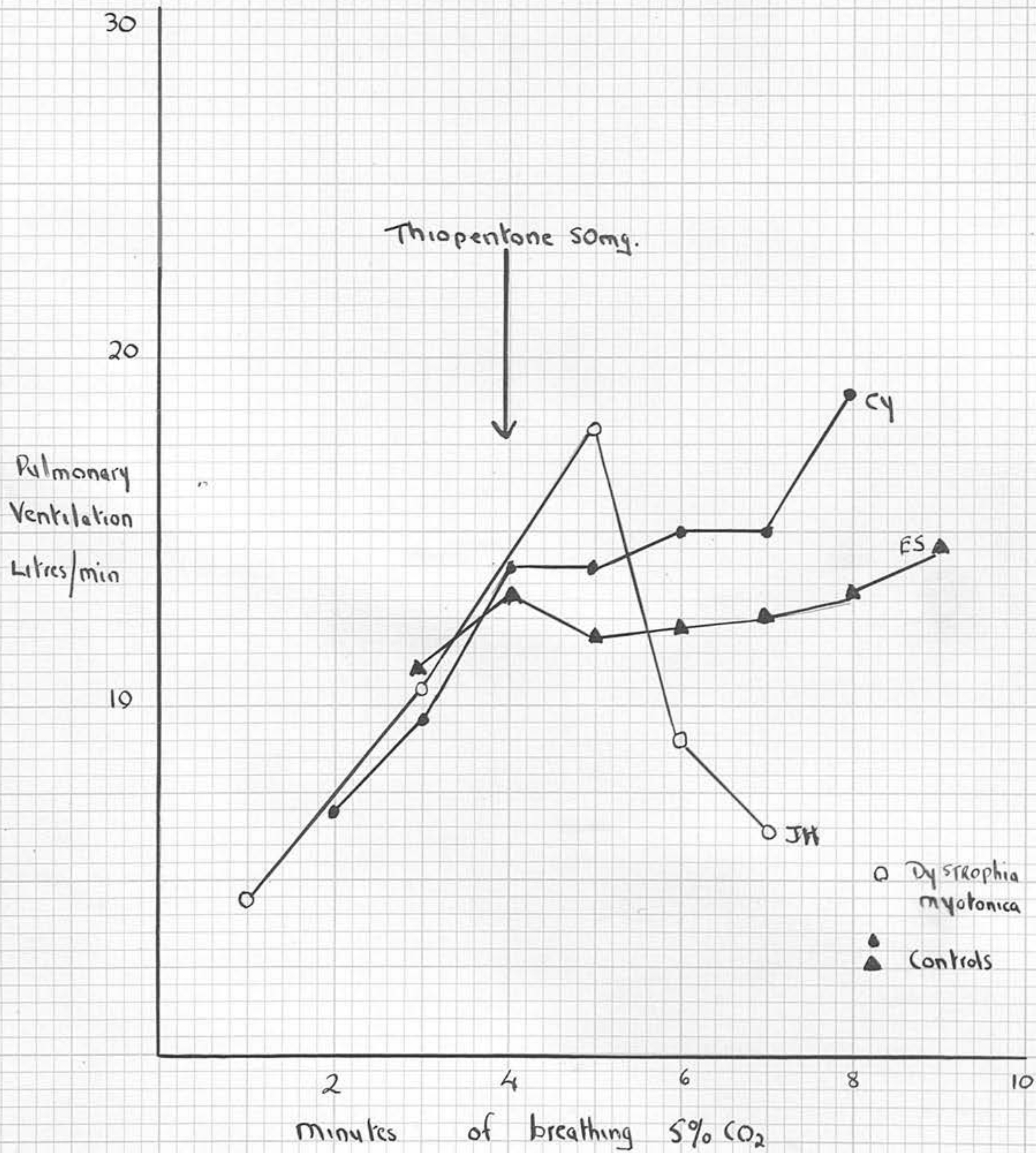


TABLE v

Ventilation in 1 case of Dystrophia Myotonica and 2 controls.

Method 11 - 5% CO_2 in air.

Subjects	Minutes of 5% CO_2	Tidal Volume ml.	Resp. Rate	Ventil. L/Min
	2	400	18	72
	3	450	21	95
C.Y.	4	700	20	14
Control	Thiopentone 50 mg.			
	5	700	20	14
	6	750	20	15
	7	750	20	15
	8	1050	18	19
	3	750	15	11.25
	4	1080	13	14
E.S.	Thiopentone 50 mg.			
Control	5	925	13	12
	6	880	14	12.3
	7	900	14	12.6
	8	950	14	13.3
	9	1050	14	14.7
	1	350	13	4.5
	2			
J.H.	3	500	21	10.5
Dystro.	4			
Myoton.	Thioopentone 50 mg.			
	5	600	30	18
	6	300	30	9
	7	300	22	66

of 12 per minute. This was in marked contrast to the 3 controls and the other 4 cases of dystrophia myotonica.

The value of this test was limited because the concentration of CO_2 inhaled was unknown in the earlier experiments. The pulmonary ventilation of R.B. was lower than the rest of the group of cases and controls, but this may have been due to the fact that the concentration of CO_2 that she inhaled was less than in the other cases.

METHOD 11: The results in Method 11 (breathing 5% CO_2) are summarised in Table v and Fig. 2e.

Two control cases showed little drop in ventilation after thiopentone. The ventilation of J.H. (the case of dystrophia myotonica) rose initially with inhalation of 5% CO_2, with an increase of respiratory rate and tidal volume. After thiopentone, both respiratory rate and tidal air dropped markedly. (The initial rise after the thiopentone was probably due to slow circulation time).

METHOD 111: Jerkin plethysmograph, breathing 5% CO_2; thiopentone 50 mg. The results of the ventilation studies, in 2 cases of dystrophia myotonica and one control are shown in Figs. 3, 4 and 13.

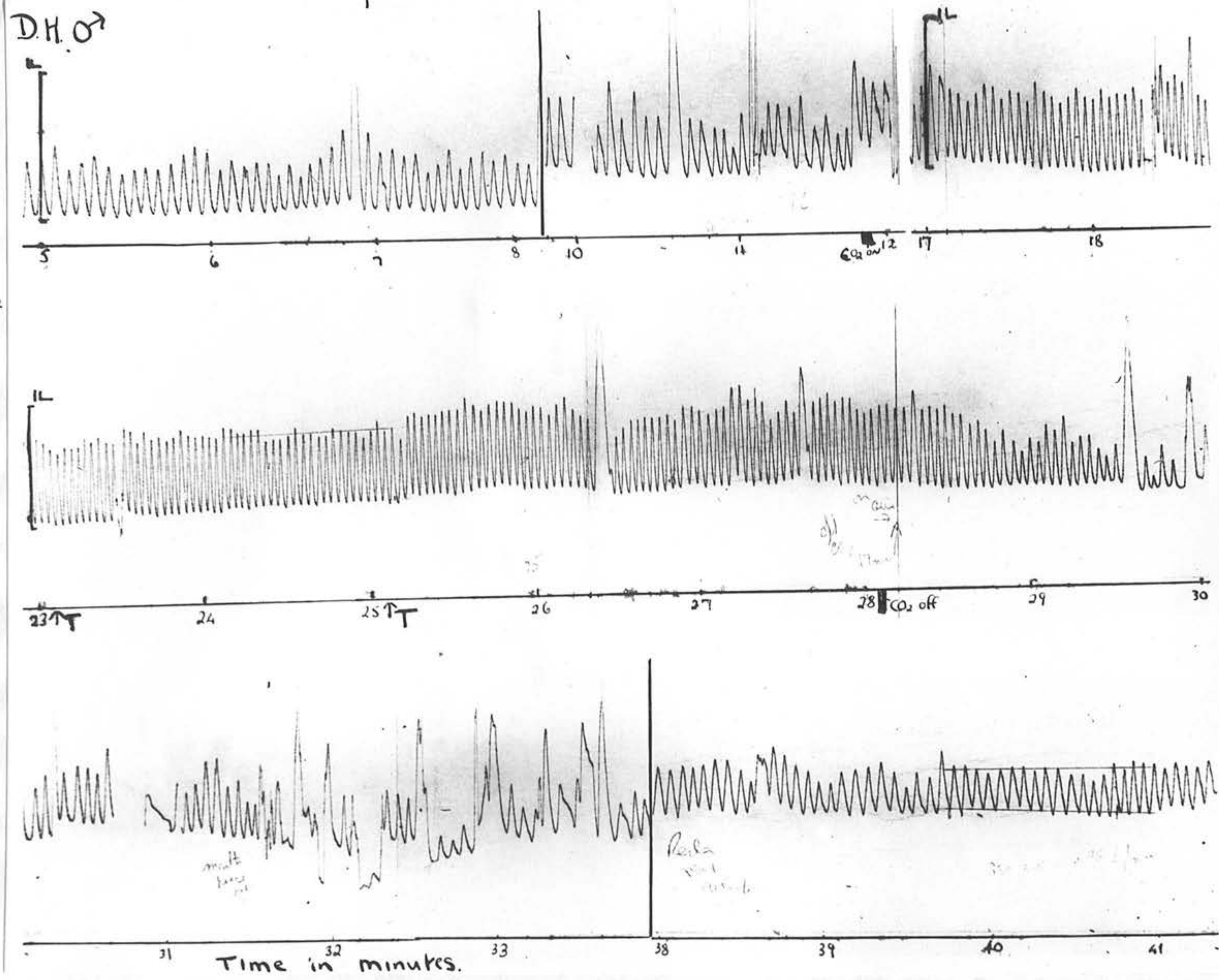
The resting respiratory pattern of D.H. (Fig. 3) was seen to be irregular, but this was abolished with CO_2. The thiopentone given in 2 doses of 25 mg. (because of the marked effect when 50 mg. was given, whilst he was sitting,

Fig. 3

Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica. Method III - (breathing CO_2)

Key:-
inspiration in upward direction.
Calibration:-
1L = 1 Litre

T = 25mg Thiopentone with ↑ at end of injections



Note:- Upper and Lower tracings are not continuous.

LEGEND TO FIG. 3

Key	Minutes after begin. of exp.	Pulm Vent in L/Min	Resp. Rate /Min.
Resting Resp.	(5-6)		
Irregular	(7-8)	4	12
		3.8	12
Resting Resp.			
Irregular	10-12		
CO_2 on	12		
Resp. Regular	17-18	12.4	20
25mg Thiopen.	23		
	24-25	13.7	23
25mg Thiopen.	25		
	25-26	14.1	23
	26-27	13	20
CO_2 off	28		
	28-29	10.6	17
Note period	29-30	7	20
of irregular	33-34	5.8	11
resp. at 31-33 after CO_2 off and mouthpiece removed			
Resp.Regular	40-41	5	15

Note little effect of thiopentone on ventilation
Total time of CO_2=16 mins.
Thiopentone injected after 12 minutes of CO_2

Age 41 Wt. 8st 10
FEVi 2580 FVC 2800
$\frac{FEVi}{FVC}$ 92%
MBC Direct 92 L/Min
MBC Indirect 91 L/Min
MEP 20 mm Hg.

Fig. 4

Recording of Pulmonary Ventilation in a Control.

Method III - (breathing CO_2)

LEGEND TO FIG. 4

Key	Minutes after begin.exp.	Pulm Vent L/Min	Resp.Rate /Min
CO2 on	15		
	16-17	19.2	24
	18-19	20.9	22
Thiopentone 50mg inject	19-		
	19-20	20.9	22
	20-21	20.9	22
	39-40	24.2	22
CO2 off	40		
	41-42	9	16
	42-43	12.7	16
Note little effect of thiopentone on ventilation.			

Total CO2 time 25 minutes.
Thiopentone injected after 4 minutes.

Age 35 Wt. 10st.2
FEVi 3400 FVC 4000
$\frac{FEVi}{FVC}$ 85%
MBC indirect 119 L/Min
MEP 90 mm Hg.

in Method 1 in a previous experiment), produced no pronounced effect on ventilation, but respiration became irregular after the CO_2 was discontinued and the mouthpiece removed. The effect of the thiopentone on the control (A.W.) was minimal (Fig. 4).

The tracing of H.N. (Fig. 13 in Appendix) showed irregularity of respiration prior to the administration of CO_2. No appreciable depressant effect on ventilation was seen after the thiopentone injection. Respiration again became irregular after CO_2 was discontinued.

METHOD 111: Jerkin plethysmograph, breathing air; 100 mg. thiopentone. The effects of the 100 mg. thiopentone were studied in 6 cases of dystrophia myotonica, one case of motor neurone disease and 10 controls.

Two aspects of the respiratory response to thiopentone were considered. (i) alterations in respiratory pattern (ii) respiratory depression.

RESPIRATORY PATTERN: The pattern of respiration fell into two main groups, one with fairly regular respiration, and the other, irregular respiration, of rate and depth.

In the present context, the term "periodic respiration" refers to periods of irregular respiration, occurring at more or less regular intervals, as seen in T.B. (Fig. 10 26 -32 minutes of tracing) and W.A. (Fig. 12, 33 - 37 minutes of tracing. This periodic respiration is not synonymous with Cheyne-Stokes respiration, which refers

to a series of respirations which gradually increase in depth from a hardly perceptible movement to a maximum, and progressively declines in a period of apnoea.

REGULAR RESPIRATORY PATTERN: Group l. There was no marked irregularity of respiration before or after the thiopentone in one case, R.B. (Fig. 5). W.H. showed (Fig. 6) some before the injection, while J.S. (Fig. 7) did have some irregularity afterwards, but in neither case was it pronounced. R.B. showed hardly any change in pulmonary ventilation.

Nine of the controls, of which the only tidal volume recording shown is that of B.D. (Fig. 8), revealed little if any alteration in the respiratory pattern after the thiopentone.

IRREGULAR RESPIRATORY PATTERN: Group ll. The remaining 3 cases, T.B. (Fig. 9), O.B. (Fig. 10), and J.G. (Fig. 11), demonstrated marked periodicity of respiration after the thiopentone until they were disturbed for calibration or awakened.

The irregular respiration recurred when stimulation was removed, the irregularity often being present until almost the end of the experiment. Two of these patients did show some irregularity of respiration before the thiopentone, and this appeared to be more pronounced after the injection. Only one control case (W.A.) showed a similar pattern of respiration after injection, despite which there was a marked drop in ventilation for only one

minute after the drug was given (Fig. 12).

RESPIRATORY DEPRESSION: The mean resting ventilation rate for the controls was 5.1 litres per minute (S.D.= ± 1.7) whilst that of the cases of dystrophia myotonica was 4.5 litres per minute. There was no significant difference between the mean of these groups. (The mean resting ventilation rate was calculated from the mean of the 5 minutes prior to the injection of thiopentone).

Table vi showed the % decrease in ventilation after the thiopentone, compared with the resting ventilation, and also the drop in respiratory rate after the injection, both for the cases and the controls. The % decrease in pulmonary ventilation for the individual cases and the individual controls is shown in Figs. 3a, 3b. Fig. 3c showed the mean % decrease in pulmonary ventilation for the controls and the cases of dystrophia myotonica, demonstrating the more prolonged and more pronounced drop in ventilation in the latter. (Figs. 3a,b and c are based on Table vi).

Respiratory depression occurred in some of the cases of dystrophia myotonica after the injection of thiopentone. After 2 minutes, three of the cases of dystrophia myotonica (R.B., W.H., and J.S.) had little change in ventilation rate per minute. Depression persisted in the other cases (J.G., O.B. and T.B.), where after 5 minutes the depression was 50%, 22% and 62% respectively. This was accompanied in two of the cases (J.G., T.B.) by a marked

Fig. 3a

Percentage Decrease in Minute Ventilation in 6 cases of Dystrophia Myotonica after Thiopentone (Method III)

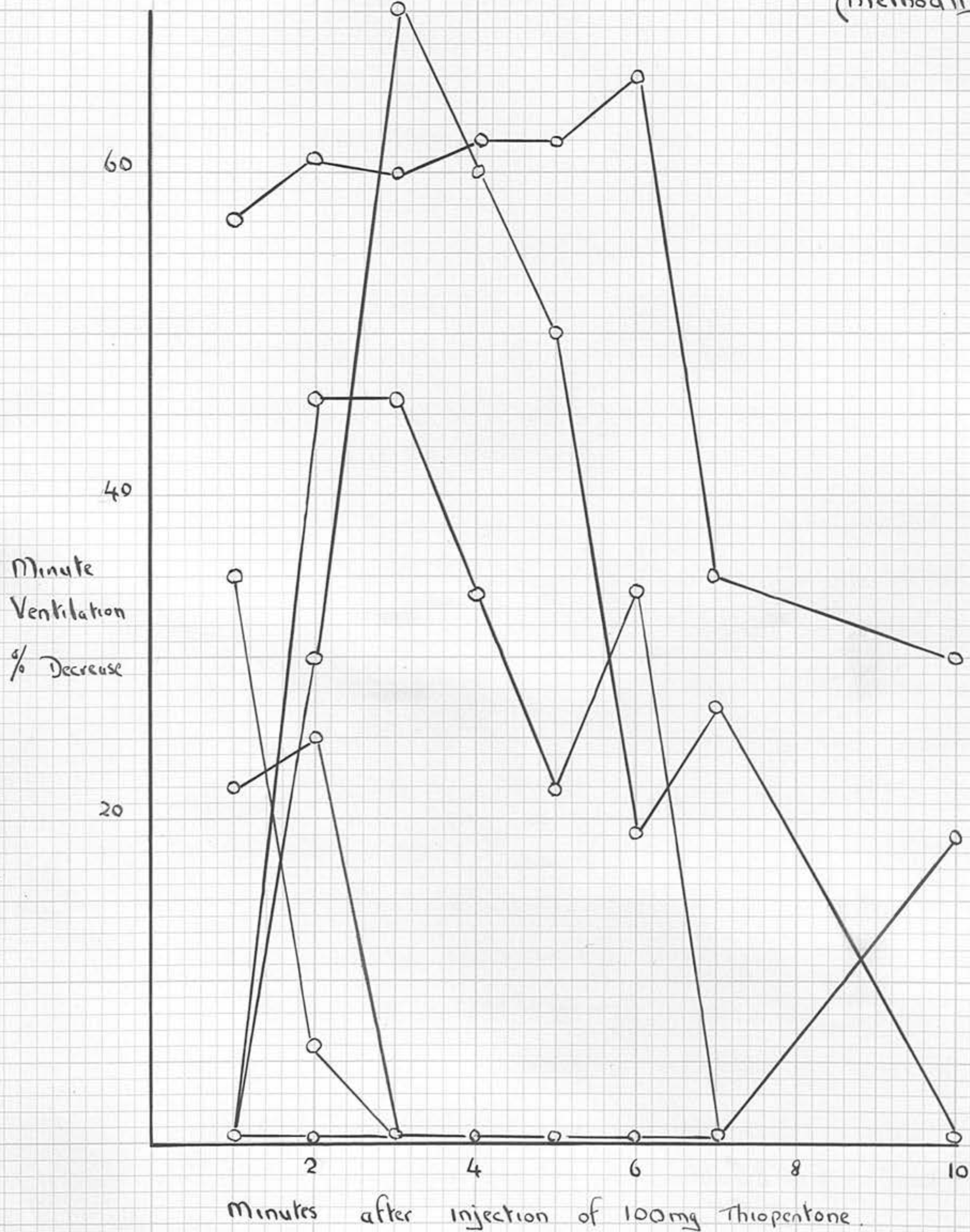


Fig 3b

Percentage Decrease in Minute Ventilation in 10 controls after Thiopentone (Method III)

60

40

Minute Ventilation % Decrease

20

2 4 6 8 10

Minutes after injection of 100mg Thiopentone

Fig 3c

Mean Percentage Decrease in Minute Ventilation
In Dystrophia myotonica and Controls after Thiopentone
(Method III)

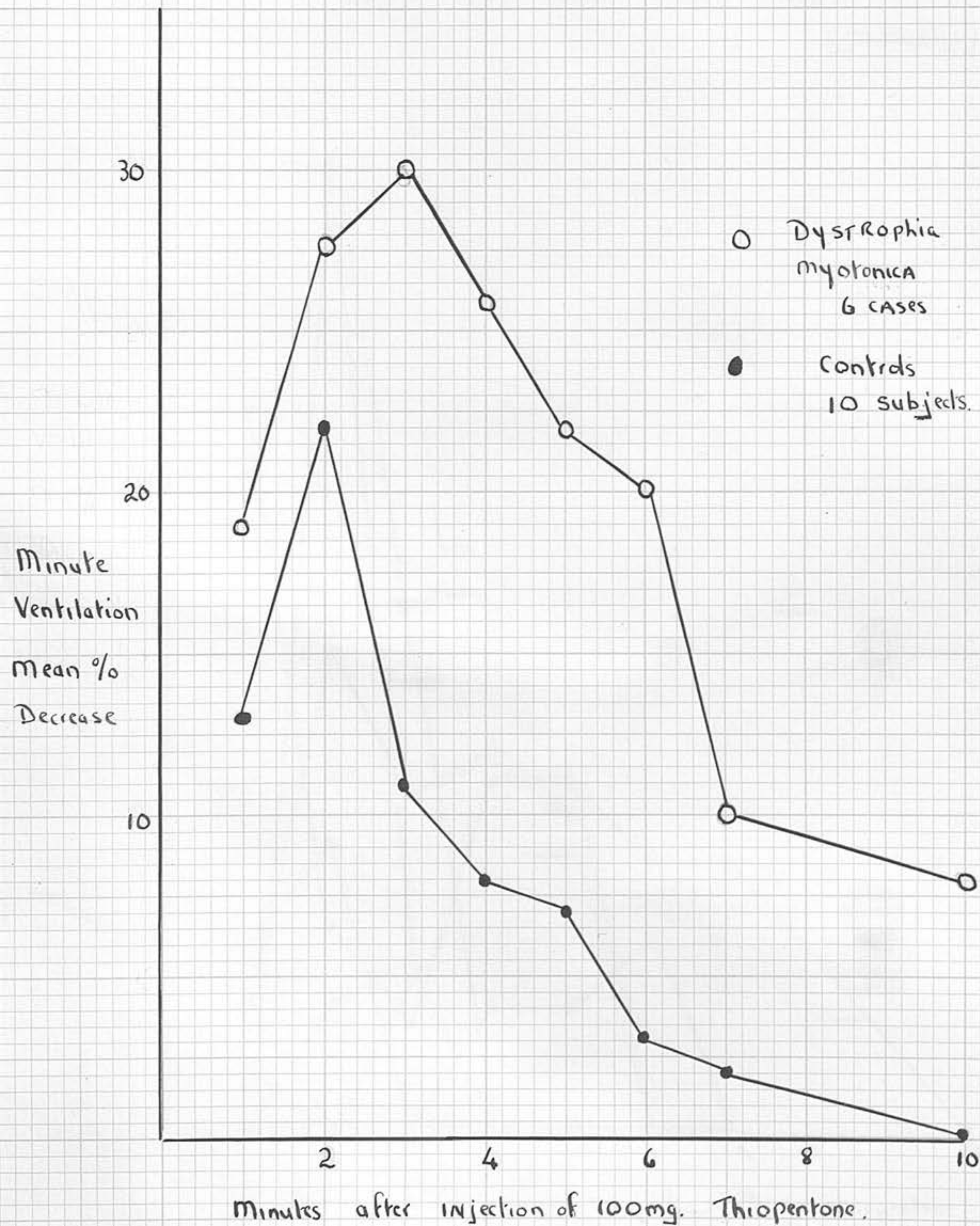


TABLE vi

Percentage Decrease in Minute Ventilation and Decrease in Respiratory Rate after 100 mg. Thiopentone, (Method 111 - Breathing air), in 6 Cases of Dystrophia Myotonica and 10 Controls.

	CONTROLS										CASES OF D.M.					
Subjects	S.M	D.P	L.H	F.E	W.T	J.M	W.I	W.A	B.D	J.T	R.B	W.H	J.S	J.G	O.B	T.B
Average Resting Vent L/min	5	3.9	4.7	5.1	3.8	5.1	4	10	5.5	4.3	3.5	4	5.1	3.8	3.3	7.4
	PERCENTAGE DECREASE IN VENTILATION AFTER THIOPENTONE															
Thiopentone, minutes after																
1	–	13	4	–	–	41	8	45	7	7	–	22	35	–	–	57
2	–	18	–	60	8	57	–	13	30	30	–	25	6	30	46	61
3	–	–	10	30	11	10	–	7	21	21	–	–	–	74	46	60
4	–	–	–	–	–	–	8	22	23	24	–	–	–	60	34	62
5	–	–	–	–	–	–	8	22	20	20	–	–	–	50	22	62
6	–	–	–	–	–	–	12	–	–	17	–	–	–	19	34	66
7	–	–	–	–	–	–	–	–	–	17	–	–	–	27	–	35
10+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19	30
	DECREASE IN RESPIRATORY RATE AFTER THIOPENTONE															
Minutes after Thiopentone																
1	–	–	–	1	–	8	1	4	–	–	–	–	2	–	–	2
2	–	–	–	7	1	8	–	1	1	5	–	–	–	9	–	8
3	–	–	–	7	2	4	–	1	1	2	–	–	–	9	–	7
4	–	–	–	–	2	5	–	–	–	2	–	–	–	11	–	6
5	–	–	–	1	1	–	–	–	–	2	–	–	–	5	–	9

Average resting minute ventilation calculated from that of the mean of the 5 minutes preceding the injection of thiopentone.
Use of the symbol – indicates that ventilation has returned to resting level.

drop in respiratory rates per minute. In T.B. marked respiratory depression was still present after 25 minutes. Thus there are variations in response within the group of patients with dystrophia myotonica - some 3 cases showed little change in respiratory rate, minute volume and respiratory pattern. The other 3 cases (J.G., O.B., T.B.) showed profound depression of minute volume, two of these showed slowing of respiratory rate, but all three demonstrated marked periodicity of respiration.

With respect to the controls, after 3 minutes ventilation rate had almost returned to resting levels in 7 cases; two had a 20% drop until the end of 5 minutes; and another had a 17% depression for 7 minutes. Respiratory rate dropped markedly in 2 controls.

The effect of thiopentone on ventilation in the controls is shown in Fig. 8 for B.D., Fig. 12 for W.A., and Tables vii - x for the remaining eight controls, (Appendix). Respiratory studies of miscellaneous cases are shown in Table xi, showing one patient to have an F.V.C. of 700 ml.

DISCUSSION:

The observation was made by Dundee (1952) that patients suffering from dystrophia myotonica were sensitive to thiopentone; this sensitivity taking the form of prolonged apnoea or prolonged respiratory depression. Furthermore, it was postulated that the action of the drug was peripheral, exerting its effect upon the muscle itself. Many individual case reports followed, endorsing this view (Bourke and Zuck 1957: Lodge 1958: Pachomov and Caughey 1958). These opinions suggested that a specific anomalous response was present, such as occurs in acute intermittent porphyria after barbiturates. This interpretation is based on the fact that as the singular response follows the injection of thiopentone, it must be caused by it.

However, evidence conflicting with this view of the presence of a specific idiosyncracy to thiopentone, was presented when it was shown that thiopentone had been administered on 7 occasions without any undue complications. Furthermore, a death occurred in one patient after anaesthesia involving only ether, while another patient died after morphine had been administered in the post-operative period (Kaufman 1960). It is also known that sudden death can occur in the disease (Spillane, 1951: Fisch and Evans 1954) without the administration of any drug whatsoever.

It was also worthy of note that although Dundee (1952)

used prolonged apnoea or respiratory depression as signs of sensitivity to thiopentone, no attempt was made to assess respiratory function before the administration of the drug.

Attention was drawn to other neuromuscular disorders to ascertain if they exhibited any undue sensitivity to drugs. Rowland et al (1956) reviewed the causes of mortality in 39 cases of myasthenia gravis and found that 6 patients died after the administration of sedatives, the dosage being in the range for producing a "normal soporific effect".

The commonest cause of death in myasthenia gravis is respiratory failure due to weakness of the muscles of respiration and the inability to expel secretions from the lungs (Osserman 1958: Genkins et al 1961). Myasthenia gravis is believed to be due to defective neuromuscular transmission at the end plate situated at the myoneural junction, its main result being to produce muscular weakness, a prominent feature of dystrophia myotonica. Although study of myasthenia gravis offered an indication of the disability of the muscular dystrophy there has been no examination of lung functions for daily assessment, as there has been in the management of acute anterior poliomyelitis, where frequent measurement of vital capacity has been used to gauge the degree of respiratory paralysis, and the necessity for artificial assistance to respiration. (Spalding 1955). Lung function has been shown to be depressed in patients convalescing from acute anterior poliomyelitis with respiratory paralysis;

lowered vital capacity, lowered maximum breathing capacity, and hypo-ventilation were features of this depression (Lukas and Plum 1952).

In other neuromuscular diseases of more insidious onset, such as amyotrophic lateral sclerosis, Feltman et al (1952) described one case where the maximum breathing capacity was 38 litres per minute, and there was arterial oxygen unsaturation (73% oxygen saturation) and carbon dioxide retention (arterial pCO_2 84 mm. Hg.).

Similarly, Dreq Miller et al (1957) found 2 cases of progressive muscular atrophy, and one of amyotrophic lateral sclerosis, to have lowered vital capacity, ranging from 40% to 47% of normal, and maximum breathing capacity of 32, 42 and 57 litres per minute respectively.

In the survey of the natural history of dystrophia myotonia, whose onset is also insidious, muscle wasting was prominent and often generalised, so that the muscles of respiration might well be affected. The sterno- mastoids, considered to be the most important accessory muscles of respiration (Campbell 1958), are invariably involved in the wasting process, and often completely absent. The abdominal muscles normally are of great value in forced expiration, and these, too, are wasted, with resulting weakness.

Tests of pulmonary function in dystrophia myotonia have been reported in only 3 cases. Bashour et al (1955) described one case, with cyanosis, polycythaemia, vital capacity of 500 ml. and arterial pCO_2 of 56 mm. Hg.

They believed this to be due to under-ventilation, as a consequence of weak thoracic and diaphragmatic muscles. Kilburn et al (1959), whose patient, weighing 200 - 230 lbs. had Cheyne-Stokes respiration, marked somnolence, cyanosis, polycythaemia, anoxaemia and pulmonary hypertension, had a vital capacity of 2460 ml., M.B.C. 72 litres per minute, 80% oxygen saturation and arterial pCO_2 of 58 mm. Hg. Benaim and Worster-Drought (1954) also had a similar case, with polycythaemia, vital capacity of 100 ml., maximum breathing capacity of 40 litres per minute, oxygen saturation of 80.8% and arterial pCO_2 of 72 mm. Hg.

In the present series of cases of dystrophia myotonica, lung function tests revealed there to be no obstruction to air flow or air trapping in all cases and controls (except possibly one control(D.S.H., Table ii) because the F.E.V.i/ F.V.C.% was greater than 75%. There was no significant difference in M.B.C. between the means of the cases and that of the controls. The M.B.C. of the cases of dystrophia myotonica was also in the range of values reported by Comroe et al (1955) except that of O.B. She had a low vital capacity of 100 ml. and M.B.C. of 38.5 litres per minute. The mixed venous pCO_2 was elevated in only one patient (J.G.) when it was found to be 52.5 mm. Hg., indicating some degree of alveolar hypoventilation.

The patient described by Kilburn (1959) and to whom reference has already been made, had a resting arterial pCO_2

of 60 mm. Hg. indicating some degree of hypo-ventilation. The response to breathing 5% CO_2 for 5 minutes was to increase the minute volume from 6.3 litres per minute to 10.3 litres per minute; the rate from 13 to 17; and the end-tidal pCO_2 from 60 to 71 mm. Hg. The maximum % increase of minute volume was 70.

The response to breathing endogenous CO_2 in oxygen in two of the present cases of dystrophia myotonica was an increase in respiratory rate, tidal volume, and a maximum pulmonary ventilation increase of 170 - 190%. The maximum pulmonary ventilation increase of the controls was of the order of 160 - 200%. R.B., (Fig. 2a, Table 3a), however, had a maximum pulmonary ventilation increase of only 66%, which could be due to diminished production of CO_2 for stimulation of her respiration. Her final end-tidal pCO_2 was the lowest recorded in the cases and controls, being 47.3 mm. Hg. This compared favourably with the % increase in ventilation of D.S., who when the end-tidal pCO_2 was 48 mm. Hg. had a % increase of only 62, while the% increase of R.S. at 46 mm. Hg. end-tidal pCO_2 (2nd. minute of CO_2) was only 56. R.S., however, at the end of the 5th. minute of re-breathing CO_2, had a final % increase of ventilation of over 200% at 57 mm. Hg. (Fig. 2b, Table iiib.)

Similarly, although the maximum increase of tidal volume for R.B. was only 50%, that of D.S. at the similar level of end-tidal pCO_2 was 55%, and for R.S. 33%. Thus the respiratory response to CO_2 of the cases of dystrophia

myotonica appeared to be comparable to that of the controls.

The response to endogenous CO_2 of pulmonary ventilation of the cases of dystrophia myotonica compared favourably with the equivalent pCO_2 level in 5 cases (normals) described by Eckenhoff (1958), who used similar apparatus and techniques.

Severe respiratory depression after 50 mg. thiopentone occurred in one case (C.J.), who was breathing endogenous CO_2 (Method 1) but not in the controls nor in the other cases of dystrophia myotonica (W.H. and C.J.) who subsequently were given 100 mg. in Method 111 and showed little change in ventilation rate. In C. J. the ventilation rate fell from 25 litres per minute to 14 litres per minute, the tidal air remaining constant and the respiratory rate falling from 20 to 12.

The initial apnoea in D.H. was not significant because the conditions of the experiment were altered, and he was given the drug in the sitting position. When he was given a similar dose of thiopentone in Method 111, breathing 5% CO_2, there was no drop in ventilation rate compared with the control.

The only patient (J.H.) involved in Method 11 showed also a profound drop in ventilation rate, compared with that of the controls. Both the respiratory rate and tidal air were reduced.

Neither he, nor C.J. were able, because of increasing severity of their illness to return for measurements with

the jerkin plethysmograph. No indication of the pronounced depressant effect could be predicted from the pulmonary function tests performed before the experiment. In the case of C.J. it was known, however, that it was difficult to arouse her from sleep, especially when she had been sedated with barbiturates. (See Case Report in Appendix).

In Method 111, with the patient breathing 5% CO_2, no abnormal response occurred after 50 mg. thiopentone in one case, (D.H.) compared with the control (A.W.). But what is of interest is the irregularity of respiration seen during resting ventilation prior to CO_2, and the irregularity of respiration after it was discontinued (seen also in H.N., Fig. 13 in Appendix).

In the last six cases (Fig. 5,6,7,9,10 and 11) and 10 controls (Fig. 8,12, Tables vii - x) the CO_2 was discontinued because it was felt to be too strong a stimulus, and the dose of thiopentone increased to 100 mg., and from this investigation additional information was obtained about the characteristics of respiration. R.B. (Fig. 5) showed little change in respiratory pattern during the experiment. There was some irregularity in respiration in W.H. (Fig. 6), prior to thiopentone; and some irregularity with J.S. (Fig. 7) after the drug. All the controls, of which B.D. (Fig. 8) is an example, likewise showed little change in respiratory pattern, except W.A. (Fig. 12). All these cases, W.H., R.B. and J.S., and the controls (except W.A.) were considered as one group; and the other cases, J.G., T.B., O.B. and one

control (W.A.) as a second group.

Apart from minimal changes in respiratory pattern in Group l, ventilation of these patients was not markedly affected by the drug. R.B. shows little change in ventilation, although some slowing of the respiratory rate for one minute. W.H. showed 25% depression of minute volume for 2 minutes, as compared with her average minute ventilation before the injection. In the preliminary experiments, these patients also showed little respiratory depression. J.S. was not affected either for a long period.

With respect to the controls in this group, some showed a profound drop in ventilation rate, e.g. J.M., where it dropped 57% in the second minute, and is associated with a drop in respiratory rate. In most cases, ventilation was almost back to pre-thiopentone rates within 5 minutes, or, as in the case of J.T., it was still a little depressed after 8 minutes. It is interesting to note that the M.B.C. of this control was 157 litres per minute.

In Group 11, the respiratory pattern of T.B. (Fig. 10) showed no irregularity of respiration before thiopentone administration, whilst in that of O.B. (Fig. 9) and J.G. (Fig. 11) it showed marked periodicity. All these cases had marked periodicity of respiration after the injection. They also showed a drop in respiratory rate after the drug. With respect to J.G., his ventilation rate recovered to

pre-thiopentone level after 7 minutes of respiratory depression. (It was still only at 50% of its average pre-injection level after 5 minutes). The rate of respiration of T.B. dropped from 15 per minute to 6 per minute and the ventilation was not in the range of its pre-thiopentone level until the conclusion of the experiment - almost one hour later. O.B. had 5 minutes of ventilation rates with depression varying between 46 and 22% of pre-thiopentone level.

It can only be presumed that without direct measurement there was alveolar hypo-ventilation and CO_2 retention when resting ventilation rates of 2.9 litres per minute (J.G.) and 2.8 litres per minute (O.B.) were present. After the thiopentone, these rates dropped to one litre per minute and 1.8 litres per minute respectively. This resulted in J.G. (weight 116 lbs.) having a tidal volume of 166 ml. and alveolar tidal air of 50 ml., breathing at the rate of 6 per minute. Allowance of 1 ml. for 1 lb. of body weight was made for dead space (Radford et al 1954). As for O.B. (weight 142 lbs.), this would have resulted in a tidal volume of 150 ml., and alveolar tidal air of 8 ml., with respiratory rate of 12 per minute. The mixed venous pCO_2 was raised in J.G. whilst awake, and this would have been further increased with the marked decrease in pulmonary ventilation following the thiopentone. (The mixed venous pCO_2 was not measured in O.B.).

In this Group, the irregular respiration and respiratory depression seemed to co-exist. The periodicity was also present in one control case (W.A.) whose ventilation dropped from 9.5 litres per minute before injection to 5.5 litres per minute afterwards, with a drop in respiratory rate to 6, over one minute.

This periodicity has also been noticed in one case of motor neurone disease, A.B. (Fig. 14 in Appendix), whose ventilation dropped from 5.3 litres per minute to 2 litres per minute for 5 minutes, and the respiratory rate from 10 to 5 per minute.

The other feature of this periodicity is that it was abolished by the application of a mouthpiece to the patient for calibration, or for administration of CO_2. This may only be because they were awakened and when these procedures were concluded, they often lapsed again into the irregular pattern of respiration.

The dose of 100 mg. thiopentone that was administered was constant, irrespective of age or weight, but there was no highly-significant difference between the cases and the controls for the means of these factors. The resting ventilation rates of the cases and controls were also compared and there was no significant difference either between the means of these groups.

Helrich (1956) in a study of 12 normal subjects, found that thiopentone in a dosage of 5oo mg., given over 30 minutes, had minimal depressant effects on respiration com-

pared to that of morphine. There was some depression of tidal volume and minute volume, with an increase in respiratory rate. There was a diminished response to endogenous CO_2. The end tidal pCO_2 never increased by more than 2 mm. Hg. after the thiopentone. This would confirm the present findings of minimal respiratory depression to thiopentone in normal subjects, without the prior administration of any other drug, such as morphine.

When the cases of dystrophia myotonica and the controls are compared for the effect of thiopentone on respiratory depression, it can be observed that there are some which show little if any response at all, while in others the effect is more pronounced. However, the respiratory depression, when it occurs, is more profound and more prolonged in the cases of dystrophia myotonica than in the controls. (Table vi, Fig. 3c). This does not confirm the view of Dundee (1952) that a specific idiosyncrasy to the drug exists.

Thiopentone does have an action on the peripheral nerve and neuromuscular junction in the experimental animal only in high concentrations (Secher 1951: Kraatz and Gluckman 1954: Sirnes 1954: Quilliam 1955) but much smaller doses are more effective centrally (Goodman and Gilman 1955). Its central action may be prolonged if the basal metabolic rate is reduced, as it sometimes is in dystrophia myotonica. This would also apply to many of the other drugs administered in the cases that had prolonged effects during anaesthesia, including morphine, pethidine and lignocaine.

Kilburn et al (1959) and Benaim and Worster-Drought (1954) ascribed the hypo-ventilation and CO_2 retention present in their two cases to myotonia of the respiratory muscles. This was based on the evidence of the jerky movement as seen by fluoroscopy. However, the interpretation of diaphragmatic movement by fluoroscopy depends upon clinical as well as upon radiological findings, (Campbell 1958); movement of the peripheral part of the diaphragm before that of the dome may well result in jerky respiration in the healthy patient (Edwards, 1961). Caughey and Gray (1954) were unable to observe, on X-ray screening, any delayed relaxation of the diaphragm (to command) in one case of dystrophia myotonica, after the administration of 2.5 mg. of neostigmine, which usually leads to increase of any myotonia present.

In the related condition of myotonica congenita, where myotonia is a most prominent feature, Schultz (1960) had difficulty in ventilating one case under anaesthesia after the administration of suxamethonium, a muscle relaxant, which elevates serum potassium (Paton 1956), a factor known to increase myotonia (Brown and Harvey 1939).

However, Sekiya (1940) and Robinson et al (1950) were unable to show any abnormality of diaphragmatic movement in cases of myotonica congenita.

Caughey and Pachomov (1959) were able to show, in a biopsy specimen of the diaphragm, histological evidence of muscular wasting. In view of this information, and the fact

that diaphragmatic movement may be influenced by the effects of previous respiratory infection to which these patients are prone, myotonia of the diaphragm seems to be extremely unlikely in the conscious patient in dystrophia myotonica.

In the present series of cases, no dyspnoea was present, nor was myotonia observed in the intercostal muscles. On X-ray screening of 4 cases, no myotonia of the diaphragm was observed. The stimulus of CO_2 did not provoke an attack of myotonia of the respiratory muscles.

Furthermore, myotonia is usually improved with repetitive movement (working off), and this has not been reported in the case of myotonia of the respiratory muscles. Myotonia disappears as the atrophy of the muscle progresses.

Thus it would appear that muscle atrophy is the most likely cause of any pulmonary hypo-ventilation, and this varies with the severity of the disease.

Obesity has been known to cause alveolar hypo-ventilation (Burwell et al 1956), and in 4 cases reported by Sieker et al (1955) there were present the features of somnolence, Cheyne-Stokes respiration and polycythaemia, and right axis deviation on the E.C.G. Two of their cases fell asleep quite easily. They comment that obesity results in reduction of functional residual capacity. This, in addition to the somnolence present and decreased sensitivity of the respiratory centre, leads to periodic hypo-ventilation and hypoxia.

Bedell (1960) remarked that patients with alveolar hypo-ventilation do not have specific symptoms; weakness, somnolence,

cyanosis, dyspnoea and polycythaemia are the common features. Somnolence can occur without alveolar hypo-ventilation and vice-versa, and many patients with chronic CO_2 retention are mentally alert.

Phemister and Small (1961) described 3 cases of hypersomnia and somnolence in known cases of dystrophia myotonica, and similar symptoms brought a previously unrecognised case to light. Thomasen (1948) also commented on this, but neither he nor Phemister and Small offer any explanation of the cause, although Phemister and Small did mention that some of their cases were prone to sleepiness since early childhood, long before any signs of the disease were noted.

Dyspnoea was uncommon in the present series of cases of dystrophia myotonica, for physical activity was restricted by the disease, and none had signs of congestive cardiac failure. There was no evidence of polycythaemia in 8 of the cases (no haemoglobin levels were estimated in O.B. and T.B.). Cyanosis was not observed in any of the cases after the thiopentone. (It may have in fact been present but cyanosis is not consistantly observed until the arterial oxygen percentage saturation falls below 75% (Medd et al 1959). Three of the patients were obese, but only in two (O.B. and J.H.) was there a marked effect after the thiopentone. A profound response was also seen in C.J. and J.G., who were quite thin. Two of the patients had somnolence (C.J. and O.B.) and both of them exhibited a marked respiratory depressant effect after thiopentone.

Hypo-ventilation and irregular respiration may occur during sleep in normal subjects, and Magnussen (1944) has suggested that periodic respiration, irrespective of the type, signified the presence of interrupted sleep or sleep with marked variations in intensity. Reed and Kleitman (1925) observed respiratory patterns with the aid of thoracic and abdominal pneumographs, and found irregular respiration in 16 out of 30 experiments performed in 9 subjects aged 20 - 40 years, while they were asleep. Only in one subject was respiration regular in every experiment. As a general rule they found that respiration became irregular with somnolence, only to become regular again during sound sleep. On awakening, respiration again became irregular, or, in some instances, remained regular.

Kilburn et al (1959) found elevated arterial pCO_2 levels and reduction in oxygen % saturation prior to the onset of drowsiness in natural sleep, in normals; while in the case of dystrophia myotonica, the pCO_2 was 58.4 mm. Hg. and oxygen % saturation 80.6. Birchfield et al (1958) found in normals that elevation of arterial pCO_2 (never greater than 60 mm. Hg.) and the slight but significant decrease in arterial oxygen % saturation appeared with the earliest E.E.G. changes of drowsiness and persisted during deep sleep. Birchfield et al (1959) found that in 11 subjects the mean pulmonary ventilation was reduced from 7.2 litres per minute whilst awake to 6.6 litres per minute whilst asleep. The tidal volume dropped from 528 to 402 ml., and the arterial pCO_2 rose from 45.6 to

to 49.7 mm. Hg., differences which they claimed to be statistically significant. The respiratory response to breathing 5% CO_2 in air was also significantly diminished in these normal subjects. Robin et al (1958) in a study of pulmonary function during sleep found that in 13 normal subjects the mean pulmonary ventilation dropped from 7.9 litres per minute whilst awake to 5.8 whilst asleep. The alveolar ventilation dropped from 5.21 to 3.55, while the alveolar pCO_2 rose from 41 to 44.6 mm. Hg. (The lowest figure recorded of pulmonary ventilation in this series was 3.87 litres per minute, whilst asleep, from 6.12 litres per minute whilst awake).

Production of CO_2 and consumption of oxygen were diminished. The ventilatory response to4 - 6% of inhaled CO_2 was also diminished. Six out of their 13 patients "showed cyclic respiration" whilst asleep with periods of hyper-ventilation alternating with hypo-ventilation, rather than apnoea." This pattern of respiration never lasted more than an hour. They suggested that during sleep the number of afferent stimuli to the respiratory centre is miminished, and the responsiveness of the centre decreased. Birchfield et al (1958) also subscribe to the view that ventilatory function was dependent on the state of awareness and that hypercapnia and hypoxia during sleep may be due to diminished sensitivity of the respiratory centre or to a decrease in afferent stimuli.

Fink (1961) observed that awaking patients recovering from acute hypocapnia continued to breathe rhythmically whereas

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anaesthetised patients subjected to acute hypo-capnia develop apnoea. From these experiments he inferred that wakefulness is a powerful respiratory stimulus.

Purdon Martin (1949) in a review of "Consciousness and its Disturbances" has drawn attention to the fact that "consciousness is maintained by an awareness of the body and environment. Without afferent impulses producing sensory excitation, consciousness lapses".

Macintosh (1951) noted that if spinal analgesia extends upwards beyond the level of the thoracic region the patients become drowsy, there being less stimuli reaching the cerebral cortex. If now a very small amount of thiopentone was administered, unconsciousness and respiratory arrest resulted, an effect that would not have occurred in the absence of the spinal analgesia.

It was not possible to determine whether the patients of dystrophia myotonica and the controls were asleep or anaesthetised without disturbing them and interfering with the respiratory pattern after they had received 100 mg. thiopentone (Method 111: Jerkin plethysmograph, and breathing air). Even prior to the thiopentone, some patients had irregular respiration and pulmonary hypo-ventilation. After the thiopentone, which was in the range of dosage which normally produces a short period of anaesthesia, respiratory depression often resulted and periodic respiration was induced or accentuated. In only one control was periodic respiration induced, but associated with a high level of pulmonary ventilation. (W.A.).

It would appear that the respiratory pattern and the respiratory depression in dystrophia myotonica are but an accentuation of the normal sleep response. The awareness stimulus may be diminished even without sedation, as hypersomnia has been reported to be a feature of the disease. (Phemister and Small, 1960). Hypersomnia was also present in 2 of the present series of cases.

Respiration may be stimulated reflexly by afferent stimuli from muscle and joint receptors, in particular by the afferent impulses from the muscle spindles in the inspiratory muscles. Muscle wasting may result in the stimuli being lessened and hence account for the diminished awareness stimulus to respiration and the profound respiratory depressant response occuring in natural or drug-induced sleep. If muscle wasting is less profuse the respiratory depression will also be less, and this would account for the variable response to thiopentone, as seen in the present cases of dystrophia myotonica. Those with a more marked weakness would be more prone to develop periodic respiration and hypo-ventilation when asleep. This effect would not be specific to thiopentone but it could occur with other sedatives, for Helrich et al (1956) have shown that the respiratory depressant effect of thiopentone was much less than that produced by morphine.

It was also impossible to predict the effect of sedation on ventilation or respiratory pattern by investigating only F.E.V.i, F.V.C., M.B.C. and mixed venous pCO_2 unless, of course,

these values are low. The mixed venous pCO_2 was only raised in one patient in the present series, but this measurement was performed with the patient awake and may not necessarily be a true guide to the respiratory response that will occur with sedation.

C.J. had one of the highest M.B.C. in the group but suffered a profound effect on respiration after only 50 mg. thiopentone. Dripps and Comroe (1947) have pointed out that during strenuous exercise in normal subjects the maximum respiratory minute volume was never greater than 66% of their M.B.C., nor was the response to 7.6% CO_2 greater than 29% of the M.B.C. This may be due to fatigue of the respiratory muscles and which was not an important factor in the measurement of M.B.C., which was measured over 30 seconds in their experiments. Thus the M.B.C. in the present series would be of little value in assessing respiratory reserve power as the M.B.C. was calculated from a one second measurement (F.E.V.i).

The maximum expiratory pressure, (M.E.P.) was reduced in the cases of dystrophia myotonica; the mean of this group of cases was 22.5 mm. Hg. (standard deviation ± 8.7), which was significantly lower than that of the controls, when it was 81.3 mm. Hg. The only case of dystrophia myotonica with a comparatively high M.E.P. was W. H. whose reading of 40 mm. Hg. is just two standard deviations from the mean of the cases of dystrophia myotonica. Clinically, there appeared to be a good deal of air escape via

the nostrils from this patient, with poor movement of the palate, when she inflated her cheeks, but despite this, the M.E.P. was the highest in the Group.

Gross (1943), using a similar method of measurement found the M.E.P. in 30 normal patients to be of an average value of 119 mm. Hg., with the patient standing. He could find no apparent relation between vital capacity and M.E.P., noting that the latter depends on the strength of the expiratory muscles. Mills (1950) showed that the maximum intra-abdominal pressure that can be maintained for more than one to two seconds is about 110 mm. Hg. (Recording both mouth-pressure by mercury column and intra-abdominal pressure by intra-gastric balloon).

Steinert (1909) described dystrophic changes in the laryngeal muscles, and mentioned that patients "flung out the words by expiratory movements instead of using the glottis". Thomasen (1948) laryngoscoped 4 patients and found defective closure in one, but a number of his cases had hoarse, monotonous and weak voices, indicating muscle wasting or weakness of the larynx.

Cough is an inspiratory effort, with a wide-open glottis, followed by a sudden expiratory effort against a closed glottis, which opens to let the air rush out under pressure (Best and Taylor 1961). Thus there are two factors necessary for the production of cough; a high intra-abdominal pressure and closure of the larynx.by the adductor muscles. During coughing there is a brief period of marked activity of the

adductor muscles and inhibition of the abductors, an observation which has been confirmed by electromyograph (Faaborg and Anderson 1957).

In dystrophia myotonica, the abdominal muscles are wasted to some degree, and therefore the force necessary for coughing will be diminished.

When the larynx cannot be properly closed because of paralysis explosive cough is no longer possible (Negus 1949), and this would seem to apply to dystrophia myotonica where the weakness of the laryngeal muscles results in ineffective closure (Bramwell and Adis 1913).

Most of the cases in the present series had soft monotonous voices, and one complained of loss of volume.

Thus the measurement of reduced maximum expiratory pressure in most of the cases, due eithe r to weakness of the abdominal muscles or the adductors of the larynx, confirmed the view that the power of coughing is reduced. Thomasen's description (1948) is most apt: "The abdomen is slack, and prominent without becoming completely paretic. Coughing may be of a paralytic nature".

Swallowing difficulties and nasal speech are prominent features of the disease, and Thomasen (1948) commented on the wasting of the soft palate, with the presence of dried-up secretions at the back of the throat. In the present cases, the palate was noticed to be wasted in 2 patients, and quite a few of the patients had difficulty in swallowing, but no nasal regurgitation.of food.

Inhalations of secretions and food into the bronchial tree is further facilitated by the presence of laryngeal weakness.

The reasons for the high morbidity and mortality become more evident as the manifestations of the disease (which impose limitation of function on the patient) are revealed. These limitations are similar to the disability resulting from poliomyelitis or myasthenia gravis where there may be weakness of the muscles of respiration and the inability to prevent secretions being inhaled into the lungs. In dystrophia myotonica they are of a graver significance, for muscle once atrophic is no longer capable of recovering its power.

Once asleep, the patients are deprived of any possible assistance from the limited accessory muscles. Since the sterno-mastoids are invariably absent, movement of the head by these muscles, as in normals, is impossible, and this predisposes to respiratory obstruction. Secretions may accumulate in the back of the throat, because of the patient's inability to swallow, and be inhaled into the bronchial tree owing to the laryngeal weakness. Secretions cannot be coughed up, and the incidence of pneumonia is high, as can also be seen in the present cases. (Case Reports in Appendix).

Autopsy studies (Black&Ravin 1947: De Jong 1956) have confirmed the incidence of pulmonary complica tions. In two of the deaths reported (Kaufman 1960), the patients recovered from anaesthesia, and were completely awake, but unable to cough up secretions.

Profuse secretions after operation were also noted by Talmage and McKechnie (1959). These may be due to the inhalation of acid stomach contents, which produce acute pulmonary oedema (Mendelson 1946), and in one of the cases (Kaufman 1960), the lungs were almost completely oedematous. Pulmonary complications with respiratory crisis after operation has also been reported in patients with myasthenia gravis by Pennington and Edwards (1960).

The inability to cough, apart from that caused by the muscle weakness, may be further diminished by the pain of abdominal operation, for Anscombe (1957) has shown that vital capacity, maximum respiratory and expiratory flow rates are diminished for a period of up to 10 days in the post-operative phase in normal subjects.

Thus it would appear that sedation with barbiturates, opiate or any other hypnotic, of patients suffering from dystrophia myotonica, is fraught with hazards; for these drugs may well accentuate the pre-existing respiratory insufficiency. This insufficiency may not be apparent with lung function tests, until small doses of drugs, such as 100 mg. thiopentone, are administered and the responses measured.

Sedation also depresses the cough reflex, which is already diminished by muscular weakness. The measurement of maximum expiratory pressure appears to be helpful assistance in the assessment of the ability to cough

up secretions. Exposure to pulmonary infection is also a factor in precipitating failure.

The present studies could be extended to include further investigations. Respiratory response to other drugs, such as morphine, could be measured, using the jerkin plethysmograph. Studies of respiratory patterns during natural sleep and drug-induced sleep could be performed, ascertaining the depth of sleep by electro-e ncephalographic control, and estimating arterial pCO_2 and oxygen saturation by direct measurement to monitor the degree of alveolar ventilation.

Electromyographic recording of action potentials and isometric tension from respiratory muscles would be of value in this co-ordinated study of respiration. Simultaneous E.M.G. investigations of the laryngeal muscles and of the muscles of expiration might reveal which of these is important in the coughing mechanism, and which is of importance in disease of muscle.

From all these tests, with a prior study of pulmonary function, it might be possible to assimilate all the information so gleaned, to develop a simple method of assessment, and predication of the response to drugs.

The maximum expiratory pressure appears to be a simple test of the ability of the patient to cough, but gives no indication of ventilatory reserve. It is easy to perform, and its use could be extended to assess the degree of efficacy of the cough mechanism. Its use could

become routine in assessment of all patients before surgical operation, and in many diseases where there is weakness due to nervous or muscle dysfunction. This could include poliomyelitis, myasthenia gravis, and other myopathies, including those associated with carcinoma. This test could be used many times a day in order to assess the success of any treatment. Some tests of respiratory function, including one under sedation , have already been performed in other myopathies. (See Table xi, Appendix).

In this study only the risks of sedation have been considered, but other investigations are in progress assembling facts as to the aetiology of the disease. (Adams et al 1960). The cause may be related to an auto-immune antibody response, as has been suggested in myasthenia gravis (Simpson 1960), where similar changes in the intra-muscular nerve endings have been reported, as in dystrophia myotonica (Woolf et al 1956). Myotonia appears to be associated with an increased potassium leakage from cells (Krayer and Acheson 1946), which may lead to an unstable muscle membrane and de-polarisation (Grob et al 1957). In myasthenia gravis, biopsy specimens of intercostal muscles have been studied by means of intracellular electrodes, and in the majority of cases, the miniature end plate potentials were markedly decreased in frequency, but not in amplitude or time course. Increasing the potassium in the fluid around the muscle fibre membrane normally res ulted in an increase in the frequency, but this was not so in

myasthenia, even in muscles which were not clinically abnormal, (Dählback et al 1961).

Investigation of this nature in a co-ordinated study of neuro-muscular function, with observation of the distortion of histology at the myo-neural junction, measurement of enzyme dysfunction, and electromyographic study, may finally reveal the true nature of this disease, as well as that of many other myopathies, and indicate the principles of treatment.

CONCLUSIONS

(1) A study of dystrophia myotonica reveals the presence of respiratory insuffiency, which may not be evident on clinical examination, or be detected by the simple tests of lung function. The respiratory insufficiency is most likely to be due to wasting of the muscles of respiration, and not due to myotonia.

(2) Profound and prolonged respiratory depression may occur after the administration of respiratory depressant drugs, and periodic respiration may be induced or accentuated by it.

(3) In dystrophia myotonica, the administration of 50 - 100 mg. thiopentone does not give rise to a specific response, but its effect on respiration is amplified in the presence of pre-existing respiratory insufficiency.

(4) The maximum expiratory pressure is reduced to a level which is statistically well below that of the controls. This implies a reduced ability to cough because of weakness of the muscles of expiration.

(5) The increased morbidity and mortality in dystrophia myotonica does not appear to be related specifically to anaesthesia, but to sedation in general, which further aggravates the respiratory disability. With ineffectual coughing, weakness of pharyngeal and laryngeal muscles, secretions are more liable to be inhaled into the bronchial tree.

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A P P E N D I X

Fig 1c

Calibration of Jerkin Plethysmograph showing relationship of volume of air inspired to changes in Jerkin pressure.

(subject - control ♀ age 21, wt 7st 3lbs Ht 5'3")

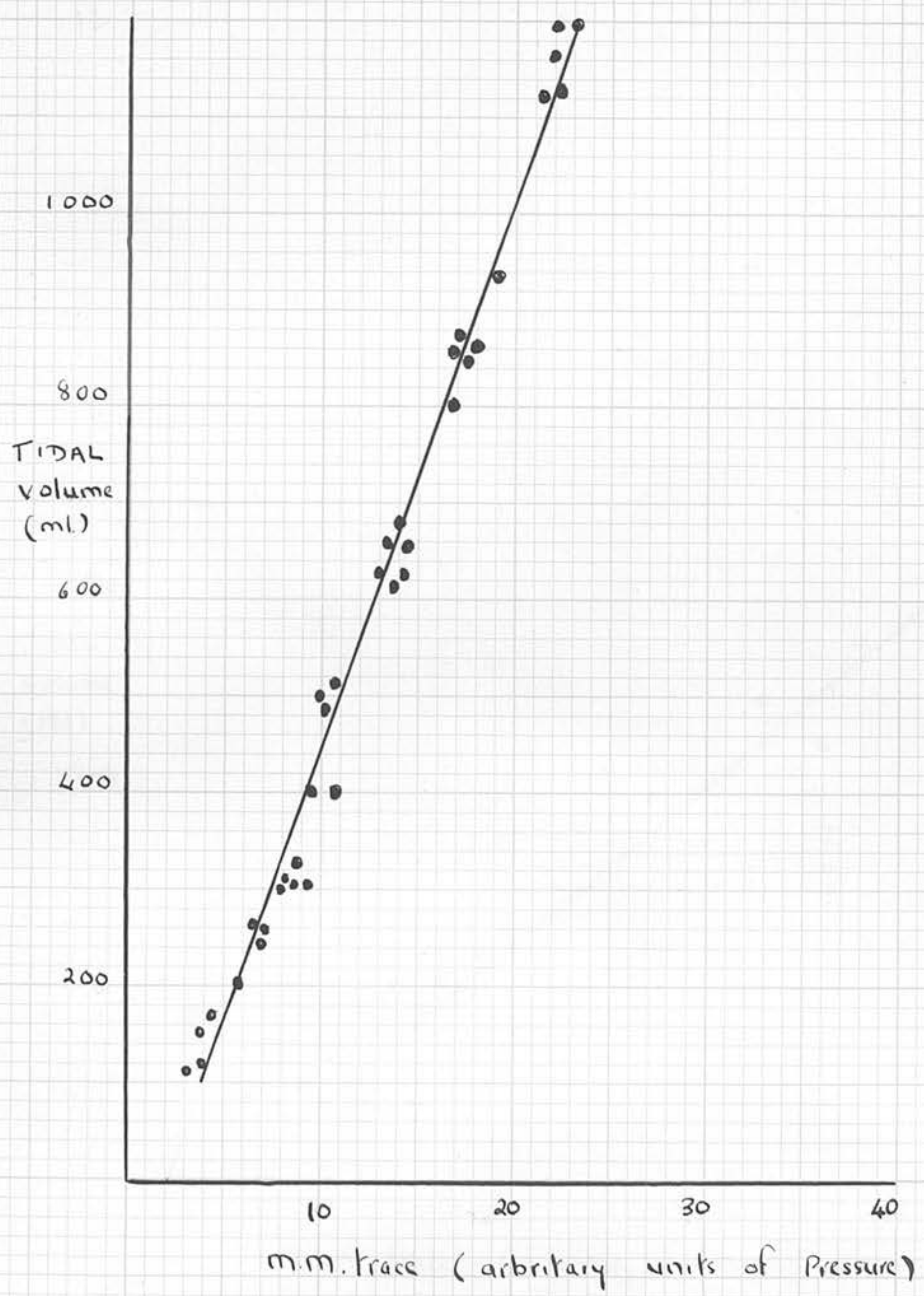


Fig 1d

Calibration of Jerkin Plethysmograph showing relationship of volume of air inspired to changes in Jerkin Pressure.

(Subject – control ♂, age 45, wt. 12 st. Ht 6')

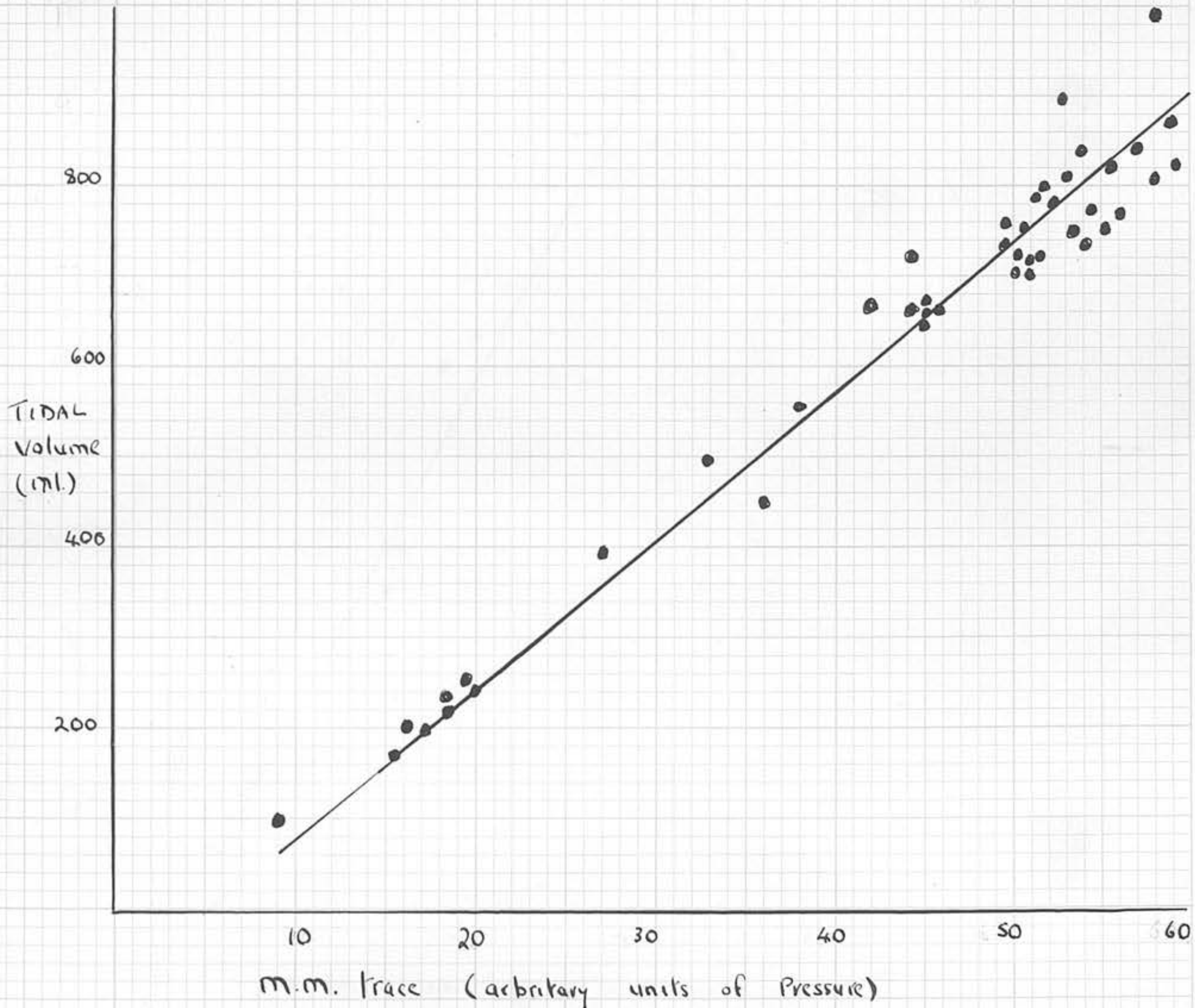


Fig 1e

Calibration of Jerkin Plethysmograph showing relationship of volume of air inspired to changes in Jerkin Pressure.

(Subject – control ♂ age 35, wt. 13 st. Ht 5'8")

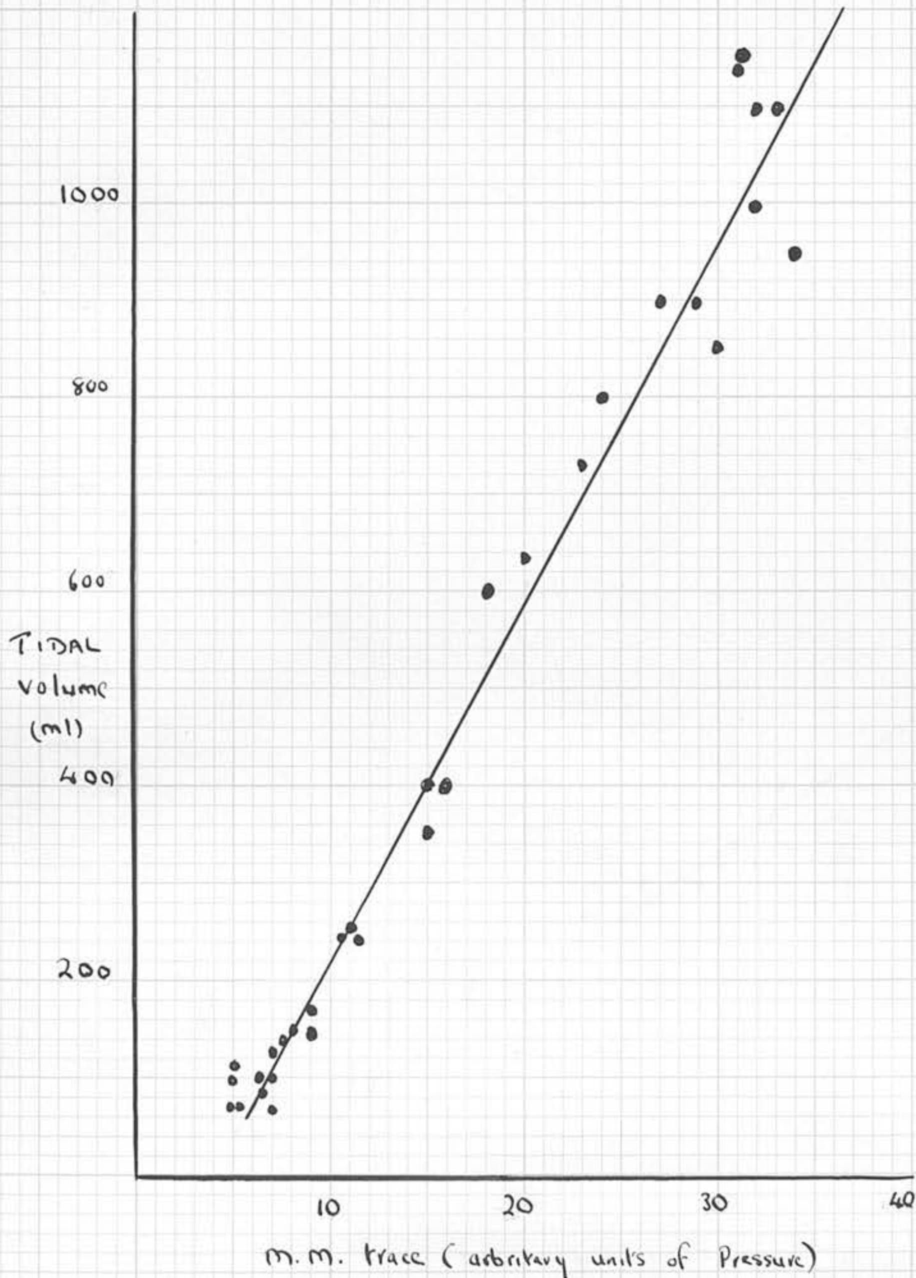


Fig 1f.

Calibration of Jerkin Plethysmograph showing relationship of volume of air inspired to changes in Jerkin Pressure.

(Subject :- Case of Dystrophia Myotonica R.B.)

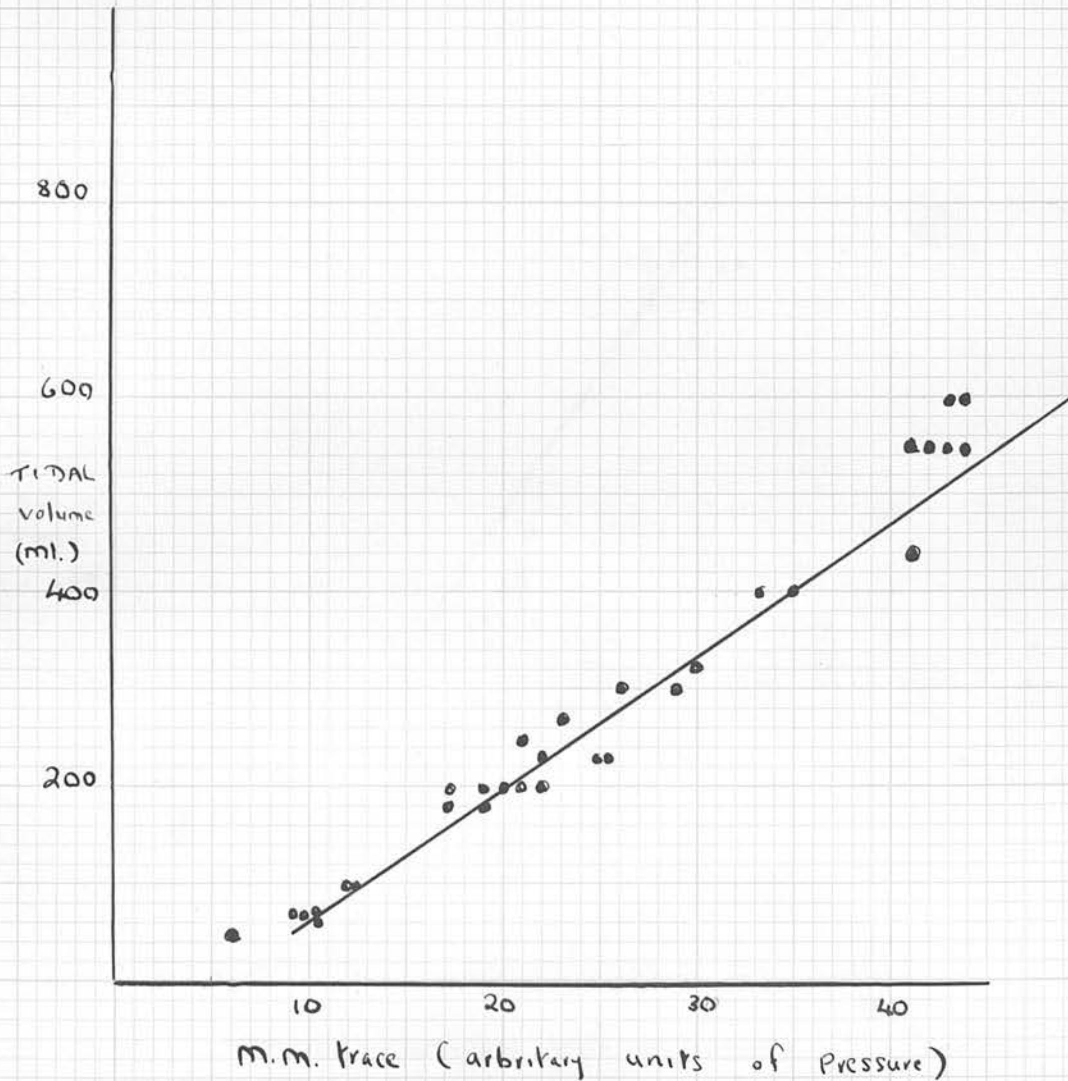


Fig. 1g.

Calibration of Jerkin Plethysmograph

Showing relationship of volume of air inspired to changes in Jerkin pressure

(Subject :- control, ♂ aged 62, wt 11st. with marked degree of Emphysema)

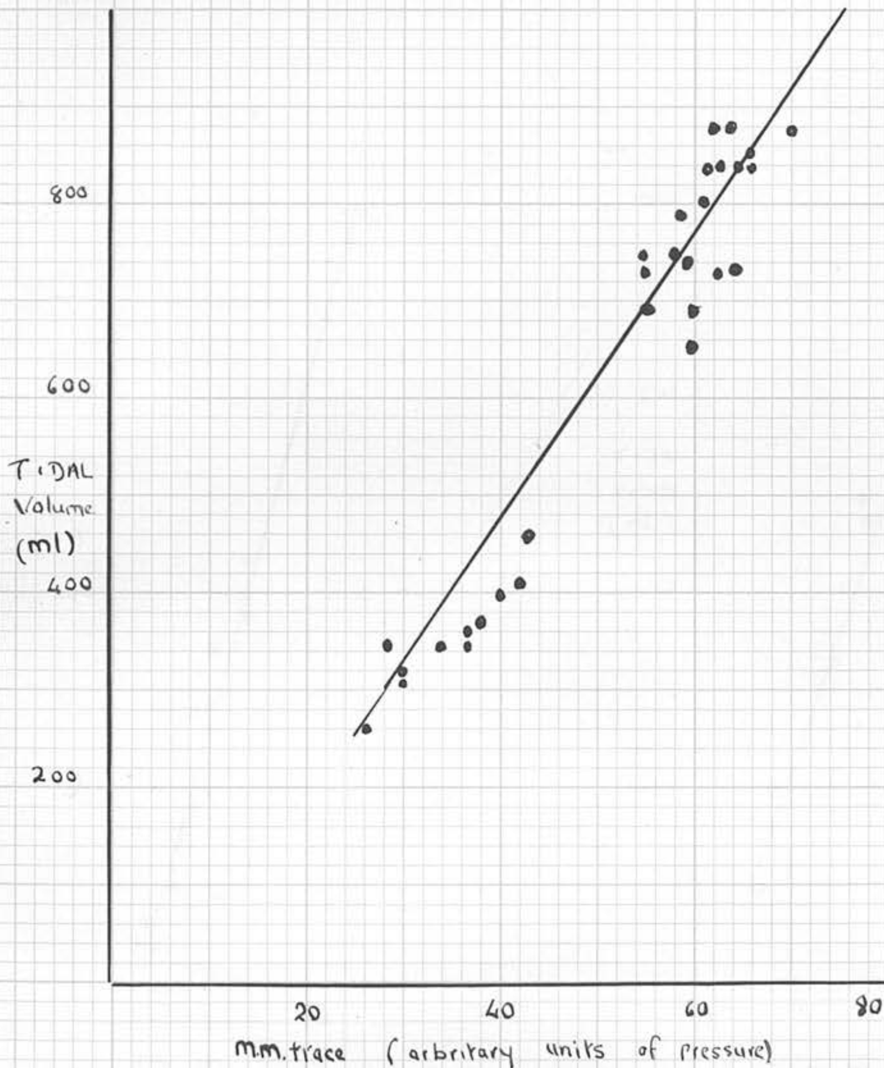
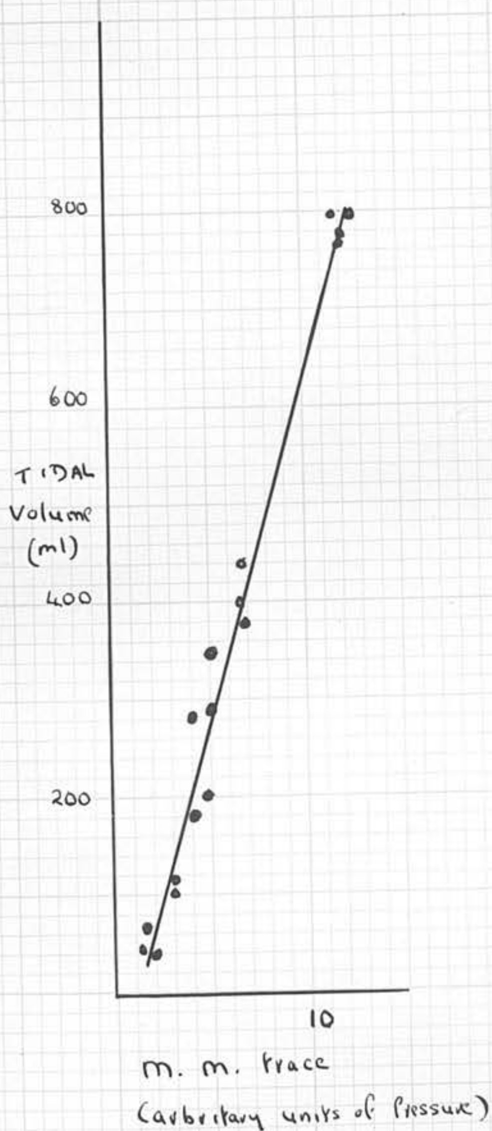


Fig. 1 h.

Calibration of Jerkin plethysmograph

Showing relationship of volume of air inspired to changes in Jerkin Pressure

(Subject:- Control ♀ aged 62, wt. 13st. Ht. 5'2", with Cheyne-Stokes Respiration)



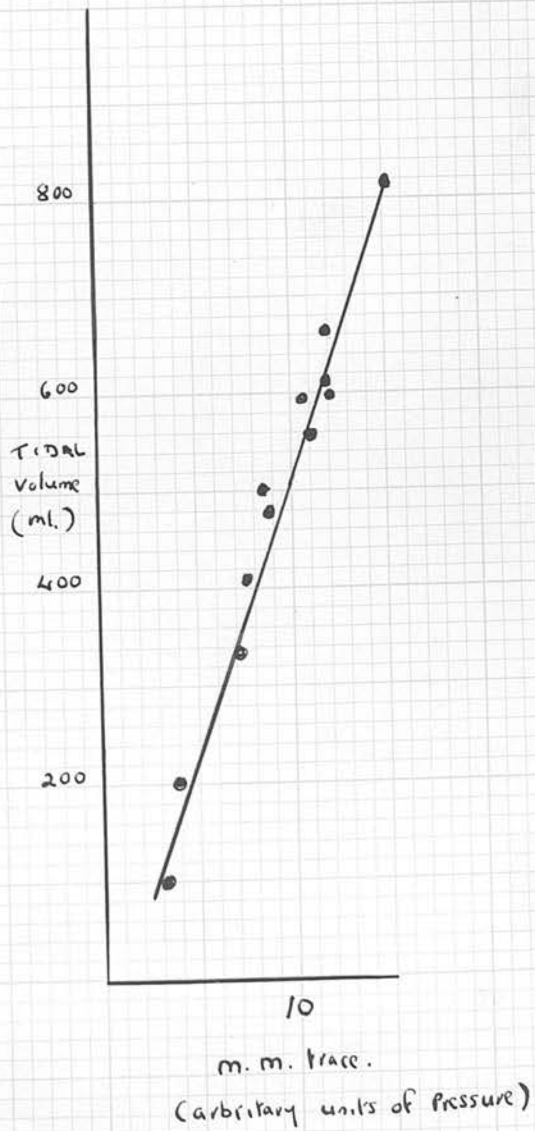
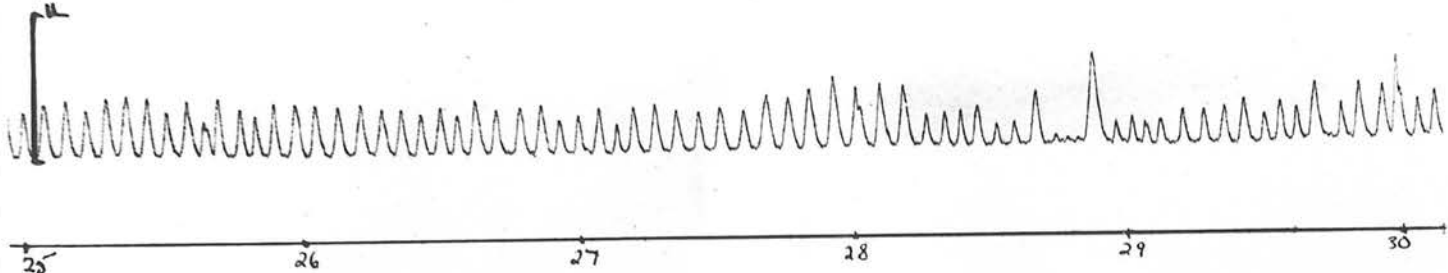
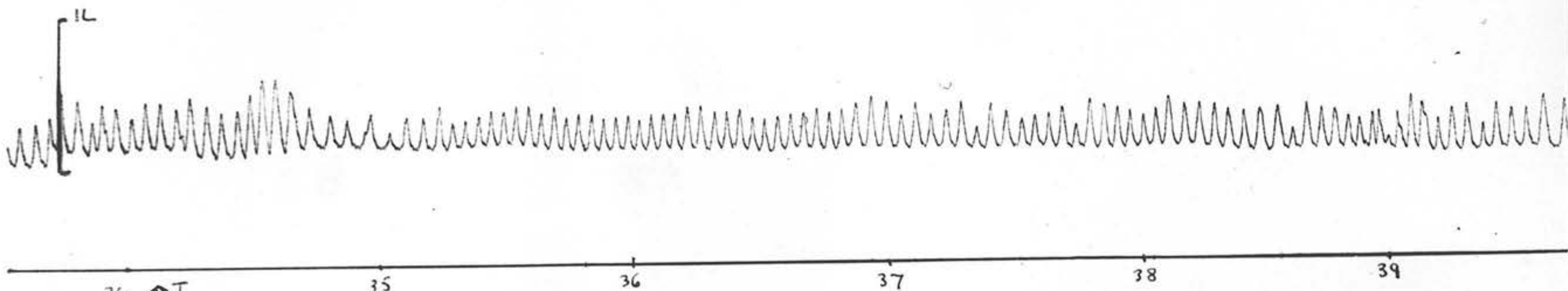


Fig. 5

Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica.

Method III - (breathing air)





Key:- Inspiration in upward direction. Calibration on tracing with 1 L = 1 Litre.
T = 100 mg Thiopentone with ↑ at end of injection.

LEGEND TO FIG. 5

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
15-16	3.5	13
16-17	3.6	15
26-27	3.8	13
28-29	2.9	12
29-30	3.7	16
34	Thiopentone	
34-35	4	16
35-36	3.9	20
36-37	3.9	20
37-38	3.8	18
40-41	3.9	18

EXPLANATORY NOTE

Minutes after begin. of exp.	
25-30	Respiration regular except for short period at 28-29
34-39	Note little change in ventilation rate after thiopentone

Age 36
Wt. 8st. 2lbs
FEVi 2800 ml
FVC 2900 ml
$\frac{FEVi}{FVC}$ 97%
MBC Direct 94 L/Min
MBC Indirect 102 L/Min
MEP 30 mm Hg.

Fig 6

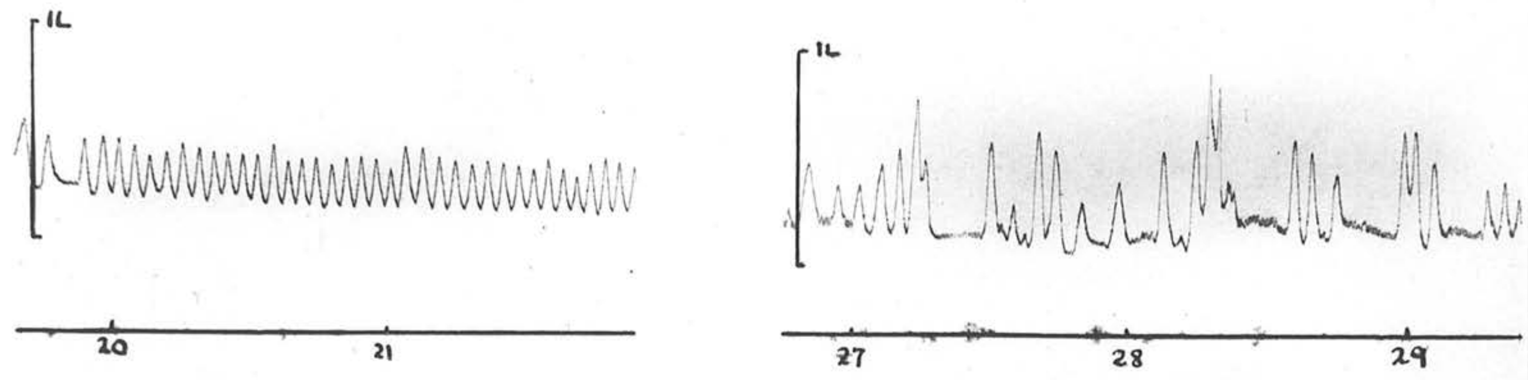
Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica.

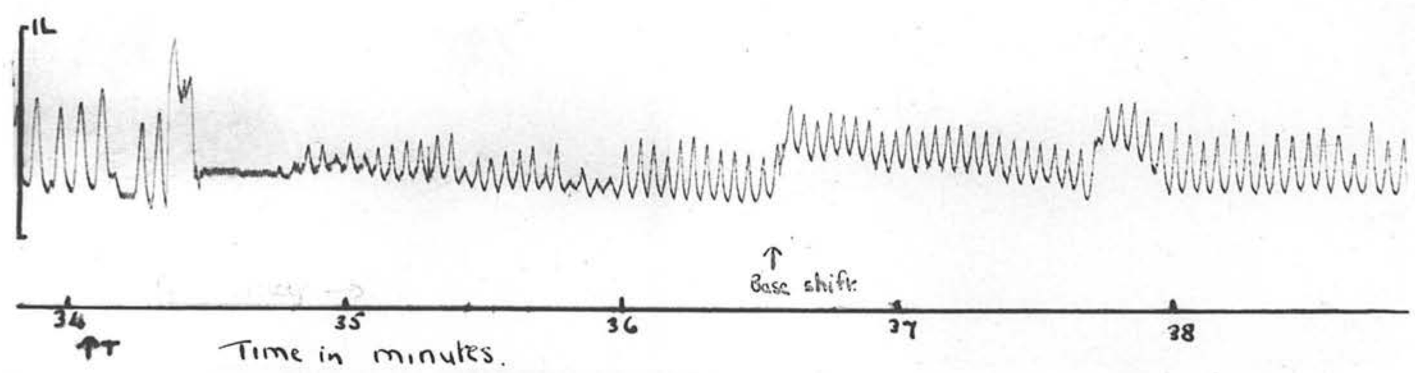
Method III - (breathing air)

WH ♀

Key:- Inspiration in an upward direction. Calibration 1L = 1 Litre.

T = 100mg. Thiopentone with ↑ at end of injection.





LEGEND TO FIG. 6

VENTILATION

Minutes after beg, exp	Pulm Vent L/Min	Resp. Rate /Min
18-19	3.7	16
19-20	4.0	15
20-21	4.4	18
27-28	3.9	10
34	Thiopentone	
34-35	3.1	11
35-36	3.0	20
37-38	4.7	21
38-39	5	18
39-40	3.9	20
40-41	4.3	15
45-46	3.8	13
46-47	3.7	16

EXPLANATORY NOTE

Minutes after begin. of exp.	
20-21	Resting respiration quite regular
27-29	Respiration irregular, with periods of apnoea of 12 seconds
34-38	Apnoea of 20 seconds after thiopentone, but thereafter respiration regular, with little drop in ventilation.

Age 42
Wt. 10st. 6lbs
FEVi 1900 ml
FVC 2400 ml
$\frac{FEVi}{FVC}$ 90%
MBC Direct 84 L/Min
MBC Indirect 66.5 L/Min
MEP 55 mm Hg.
MEP (Oesophageal) 55 cm H_2O

Fig 7

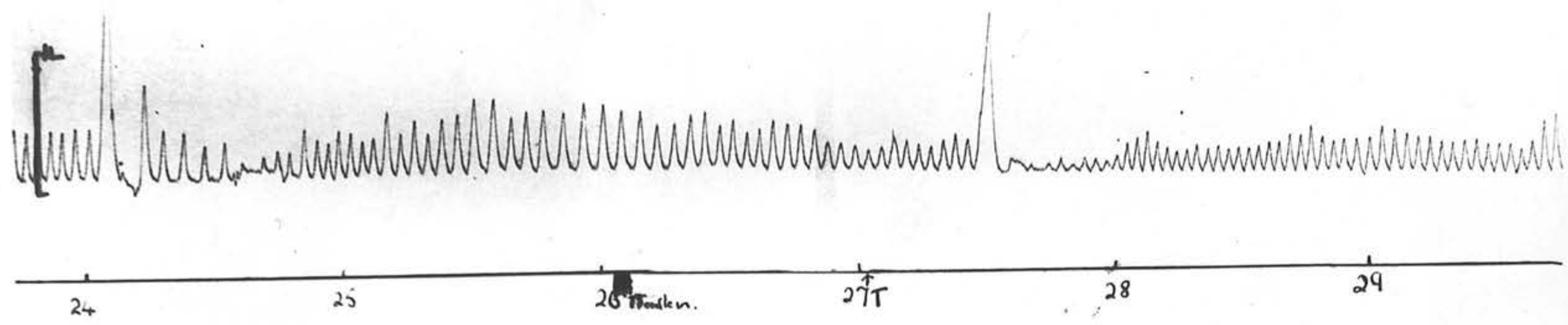
Recording of Pulmonary Ventilation in a case of Dystrophia myotonica

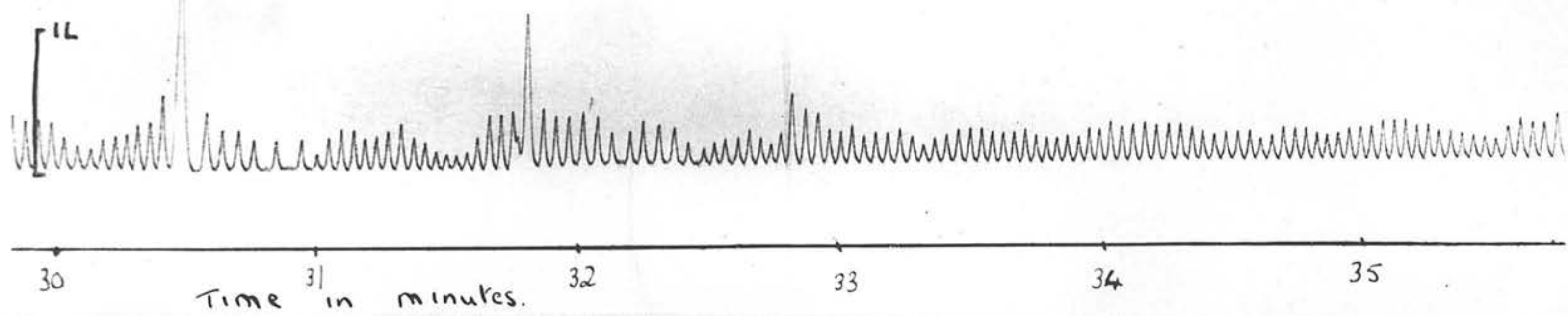
Method III - (breathing air)

JS. ♂

Key :- Inspiration in upward direction. Calibration 1 L = 1 Litre.

T = 100 mg. Thiopentone with ↑ at end of injection.





LEGEND TO FIG. 7

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
20-21	5.7	17
21-22	5.6	17
24-25	5.4	14
25-26	6.1	16
26-27	5.7	18
27	Thiopentone	
27-28	3.3	16
28-29	4.85	24
34-35	4.5	22
38-39	5.2	22
39-40	5.1	22

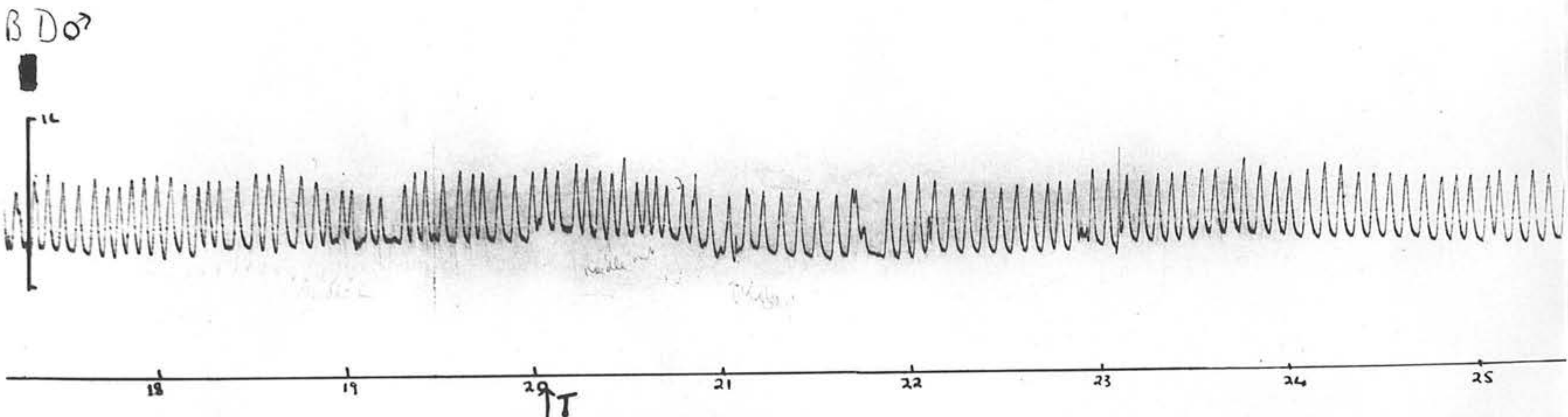
EXPLANATORY NOTE

Minutes after begin. of exp.	
24-29	Resting respiration with no marked irregularity.
	Thiopentone at 27 with marked drop in ventilation for only one minute
30-35	Respiration fairly regular after injection - OCCASIONAL LARGE BREATH IS SEEN.

Age 45
Wt. 10st.
FEVi 3400 ml
FVC 4900 ml
FEVi/FVC 70%
MBC Direct 100 L/Min
MBC Indirect 119 L/Min
MEP 20 mm. Hg.

Fig. 8

Recording of Pulmonary Ventilation in Control Method III - (breathing air)



Key:- Inspiration in upward direction. Calibration on tracing with 1L = 1 Litre.

T = INJECTION of 100mg. Thiopentone WITH ↑ at end of INJECTION.

LEGEND TO FIG. 8

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
15-16	5.4	12
18-19	5.6	12
20	Thiopentone	
20-21	5.1	14
21-22	3.85	11
22-23	4.35	11
23-24	4.8	11
32-33	5.4	12

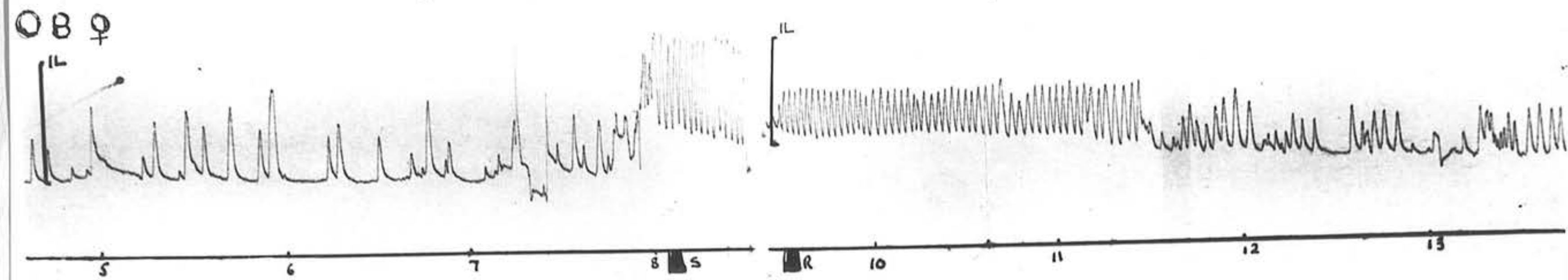
EXPLANATORY NOTE

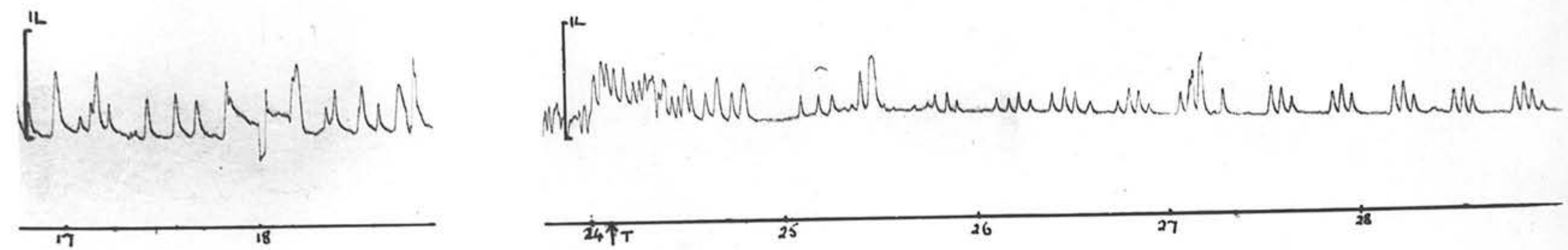
Note Respiration regular.

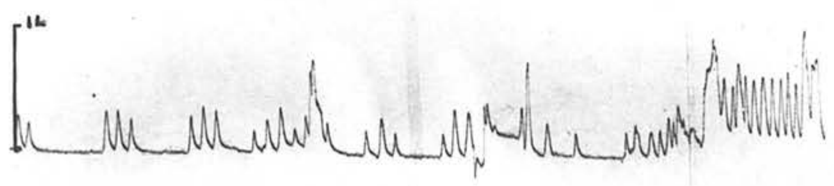
Age 21
Wt. 10st.
FEVi 3000 ml
FVC 4300 ml
$\frac{FEVi}{FVC}$ 70%
MBC Indirect 105 L/Min
MBC Direct -
MEP 110 mm Hg.

Fig 9

Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica. Method III - (breathing air)







Key:- inspiration in upward direction
calibration 1L = 1 Litre
T = 100 mg Thiopentone with ↑ at end of injection.

R = Rebreathing into bag for estimation of mixed venous pCO_2

S = Breathing into Spirometer for calibration.

LEGEND TO FIG. 9

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
5.6	3.1	8
6.7	2.8	7
12-13	4	13
17-18	3.25	10
24	Thiopentone	
24-25	4.6	19
25-26	1.8	11
27-28	1.8	12
28-29	2.2	10
30-31	2.6	14
31-32	2.2	10
34-35	3.3	14
35-36	3.1	10
36-37	3.7	11
37-38	3.1	11
38-39	3.4	11
40-41	2.4	7
41-42	3.9	10
42-43	3.8	10

Age 49
Wt. 10st. 2lbs
FEVi 1100 ml.
FVC 1500 ml

$\frac{FEVi}{FVC}$ 73%
MBC Indirect 38 L/Min
MEP 25 mm Hg.

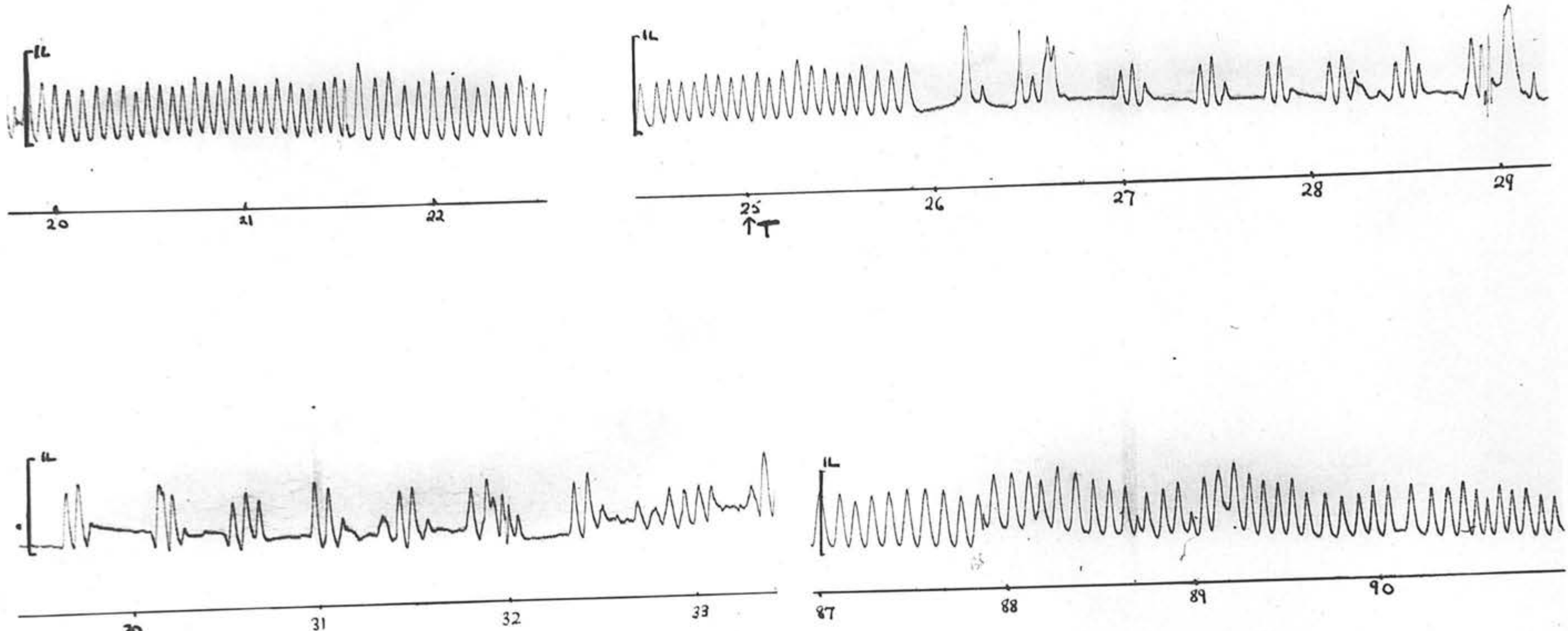
EXPLANATORY NOTE

Minutes after begin. of exp.	
5-8	Resting respiration is seen to be quite irregular, with periods of apnoea of about 12 seconds, followed by 1-2 breaths. Respiration becomes quite regular at S.
10-13	Respiration regular at R, but once the mouthpiece for rebreathing is removed respiration becomes quite irregular again.
17-18	Resting respiration quite irregular
24-28	After thiopentone more marked periodicity of respiration seen, with periods of apnoea of 12 seconds followed by 3-4 breaths, and the cycle repeated. This continued until 37 minutes when the patient was wakened for calibration.
40-44	Resting respiration completely irregular until S at 43 minutes After this respiration was irregular again until the end of the experiment.

Fig. 10

Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica

Method III - (breathing air)



LEGEND TO FIG. 10

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
18-19	6.8	15
19-20	6.6	15
20-21	8.7	16
24-25	7.5	15
25	Thiopentone	
25-26	3.2	13
26-27	2.85	7
27-28	3	8
32-33	2.8	9
34-35	2.8	6
35-36	2.5	8
36-37	4.8	10
37-38	4.8	11
38-39	3.4	6
39-40	4	10
40-41	3.7	13
46-47	4	9
47-48	4	7
49-50	4.3	9
50-51	3.9	10
51-52	3.4	9
75-76	5.5	13
90-91	6.4	12

EXPLANATORY NOTE

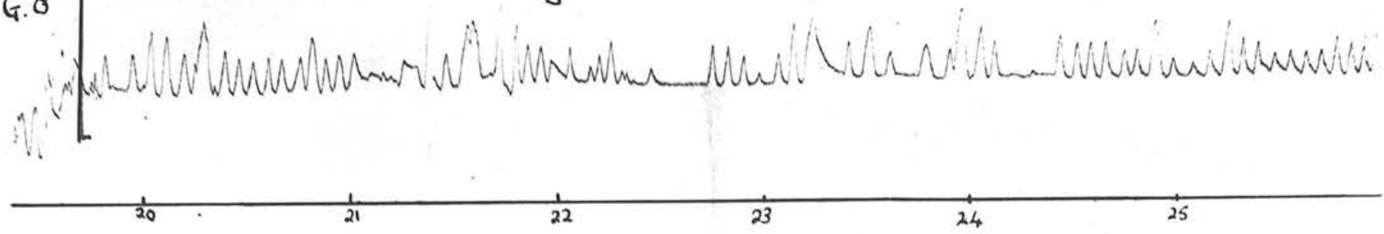
Minutes after begin. of exp.	
20-22	Resting respiration regular
25-29	Thiopentone at 25 after which respiration was periodic in character. Note drop in ventilation and respiratory rate.
30-33	Respiration still irregular, and remained so until 37 (not shown), when awakened for calibration, only to lapse immediately afterwards into irregular respiration again.
87-90	Respiration now regular, but immediately preceding this calibration was performed.

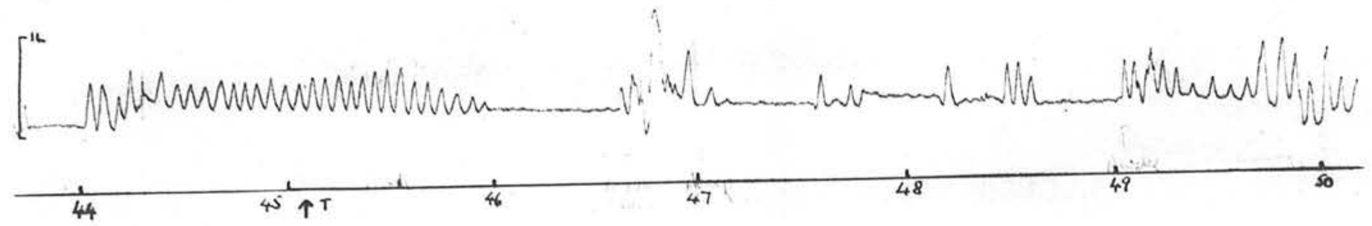
Age 50
Wt. 10st.
FEVi 2000 ml.
FVC 2630 ml.
MEP 20 mm. Hg.

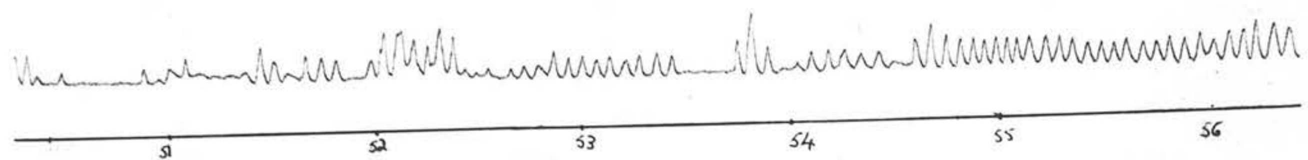
$\frac{FEVi}{FVC}$ 76%
MBC Direct 90 L/Min
MBC Ind. 70 L/Min

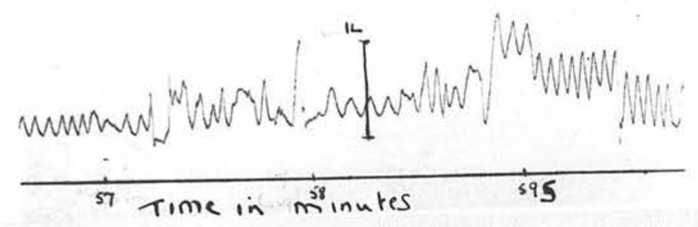
J.G. ♂

Fig. 11.









Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica

Method III - (breathing air)

Key :- inspiration in upward direction

Calibration 1L = 1 Litre

T = 100mg. Thiopentone with ↑ at end of injection.

S = breathing into Spirometer for calibration.

LEGEND TO FIG. 11

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
12-13	3.5	14
13-14	3.5	13
17-18	3.5	13
18-19	3.5	13
20-21	3.5	13
40-41	2.9	10
41-42	4.3	14
44-45	4.5	15
45	Thiopentone	
45-46	4.8	16
46-47	2.6	6
48-49	1 0	6
49-50	1.5	4
51-52	1.9	10
52-53	3.3	14
53-54	2.8	10
54-55	3.9	13
55-56	3.5	14

EXPLANATORY NOTE

Minutes after begin. exp.	
20-25	This patient took 20 minutes to settle down and relax. After this, respiration was still periodic in character with periods of apnoea.
44-50	Thiopentone at 45, followed by 30 seconds of apnoea, five small breaths, then further apnoea. Respiration rate was depressed, with fall in ventilation.
51-56	Respiration still irregular until awake at 55.
57-59	Respiration irregular again until breathing into spirometer for calibration at 59.

Age 32 $\frac{FEVi}{FVC}$ 83%
Wt. 8st. 4
FEVi 3000 ml. MBC Direct 75 L/Min
FVC 3600 ml. MBC Indirect 105 L/Min
MEP 20 mm Hg.
MEP (Oesophageal) 15 mm Hg.

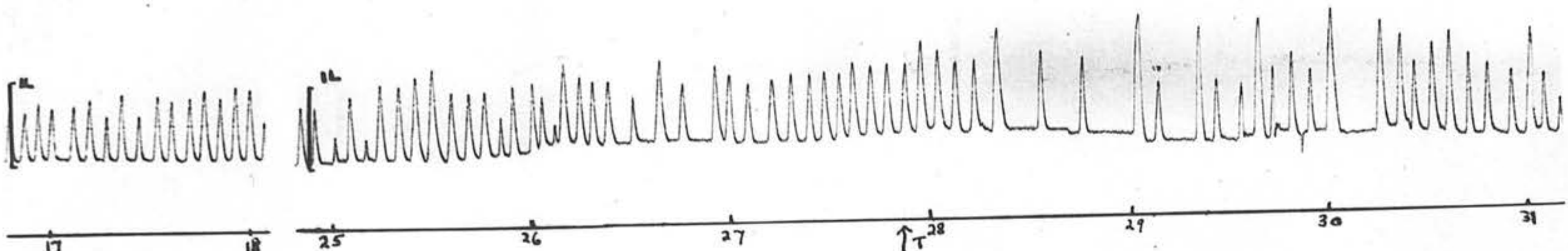
Fig. 12

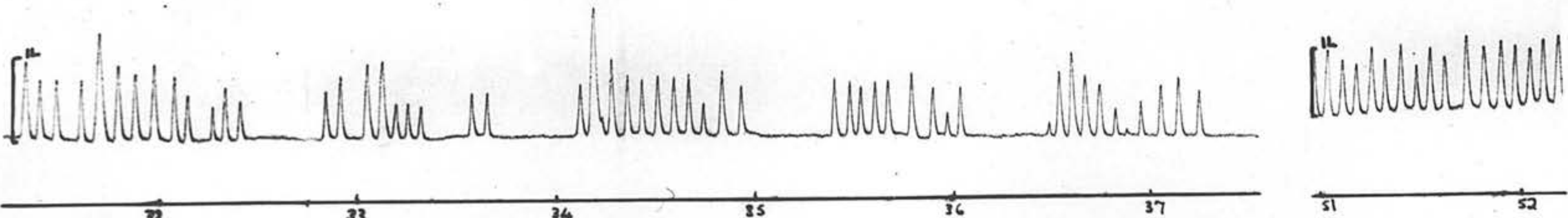
Recording of Pulmonary Ventilation in a Control method III - (breathing air)

WA ♂

Key:- Inspiration in upward direction. Calibration · 1L = 1 Litre

T = 100mg. Thiopentone with ↑ at end of injection.





Time in minutes.

LEGEND TO FIG 12

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
11-12	10.8	13
19-20	9.9	13
22-23	9.5	10
28	Thiopentone	
28-29	5.5	6
29-30	8.7	9
30-31	9.3	9
45-46	7.8	21
49-50	7.8	21
51-52	10.7	13

Age 47 FVC 4200 ml.
Wt. 10st. 3 $\frac{FEVi}{FVC}$ 76%
FEVi 3200 ml.
MBC Indirect 106 L/Min
MEP 100 mm Hg.

EXPLANATORY NOTE

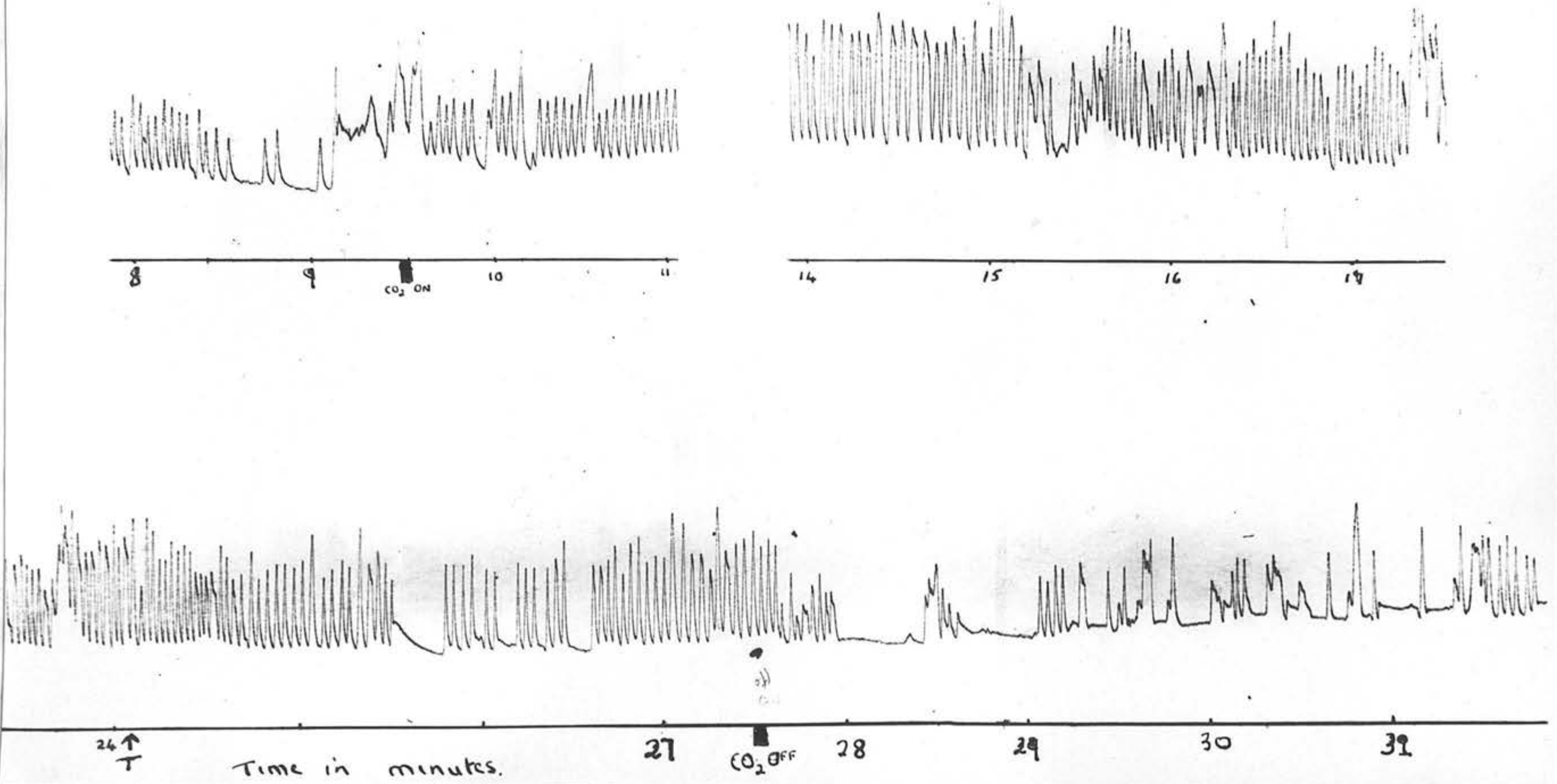
Minutes after begin. of exp.	
17-18	Resting respiration fairly regular. Awake.
25-32	Short period of apnoea of 12 seconds between 26-27 minutes. After the thiopentone, respiration became irregular with periods of apnoea up to 30 seconds. During this time, the patient was asleep. Note that ventilation dropped markedly only for one minute after the thiopentone.
51-52	Patient awakened. Respiration now regular.

Fig 13

Recording of Pulmonary Ventilation in a case of Dystrophia Myotonica

Method III – (breathing CO_2)

Key:- Inspiration in upward direction.



LEGEND TO FIG. 13

No measurement was possible because of a defect in the calibration. Total CO_2 time = 18 minutes, thiopentone being given after 14 minutes of CO_2.

Respiration is irregular before CO_2 commences, becomes quite regular for most of the time the CO_2 is on. After CO_2 removed, respiration becomes irregular again.

Age 46	FVC 2200 ml.
Wt. 10st. 4	$\frac{FEV_1}{FVC}$ 80%
FEVi 1760 ml.	
MBC Indirect 62 L/Min	
MEP 10 mm Hg.	

Fig. 14

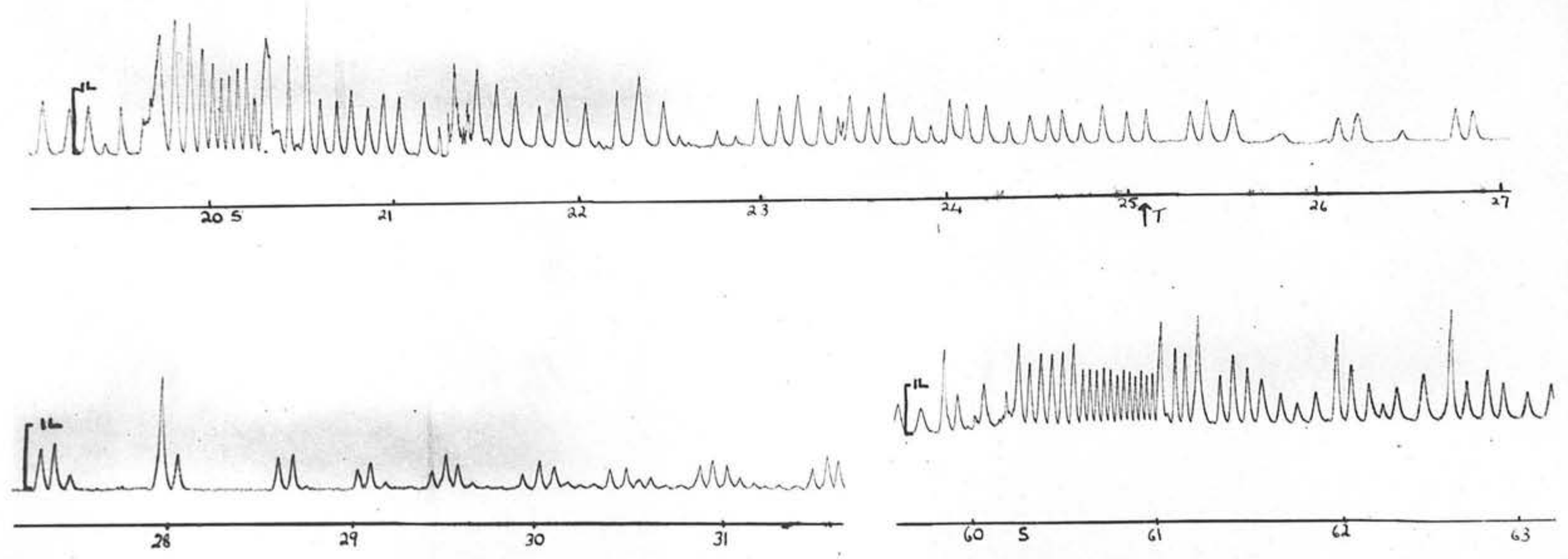
Recording of Pulmonary Ventilation in a case of Motor Neurone Disease

Method III – (breathing air)

Key:- Inspiration in upward direction. Calibration 1L = 1 Litre.

T = 100mg. Thiopentone with ↑ at end of injection.

S = Breathing into Spirometer for calibration.



LEGEND TO FIG. 14

VENTILATION

Minutes after beg.exp	Pulm Vent L/Min	Resp. Rate /Min
11-12	9.2	12
12-13	9	10
21-22	8.2	10
22-23	4.5	9
23-24	5.3	9
24-25	4.5	10
25	Thiopentone	
25-26	2.2	5
26-27	2.1	5
28-29	2	4
30-31	2.6	8
35-36	3.2	8
36-37	4.7	8
42-43	4.6	7
47-48	11.6	13
48-49	6.3	11
55-56	5.3	8
56-57	4.5	7
62-63	8.4	10

EXPLANATORY NOTE

Minutes after begin. of exp.	
5-20	Resting respiration was irregular, but regular when breathing into spirometer at 20.
20-45	After thiopentone at 25 respiration became irregular again, and remained so for another 20 minutes.
45-49	Patient awakened when respiration became regular again. Note increase in ventilation.
60-63	Respiration irregular until breathing into spirometer at S for calibration. Final resting respiration still irregular.

TABLE vii

Ventilation in Control Cases Mèthod 111 (100 mg. Thiopentone: Breathing Air).

Name W.I.	Age 30
Wt. 10st.	MBC indir. 94.5 L/min
FEVi 2700ml	FVC 3500ml
FEVi/FVC 77%	MEP 60 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /Min
11-12	4	16
12-13	4.4	16
25-26	4.1	14
26-27	4	13
27-28	3.7	9
28-29	4.2	13
29-30	4.2	15
30	Thiopentone	
30-31	3.7	14
31-32	4.2	17
32-33	4.0	17
33-34	3.7	14
34-35	3.7	14
35-36	3.5	14
44-45	3.9	12
45-46	3.9	14

Name J.T.	Age 26
Wt. 11st.	MBC indir. 157 L/min
FEVi 4500ml	FVC 5400ml
FEVi/FVC 83%	MEP 90 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /Min
18-19	4.6	11
19-20	4.4	11
32	4.6	11
33	4.3	11
34	3.8	10
35-36	4.7	11
36	Thiopentone	
36-37	4	11
37-38	3	6
38	3.4	8
39	3.3	8
40	3.6	8
41	3.6	8
42	3.6	8
43	3.8	9
44	3.6	8

TABLE viii

Ventilation in Control Cases Method 111 (100 mg. Thiopentone: Breathing Air).

Name J.M.	Age 29
Wt. 10st.9	MBC indir. 105 L/min
FEVi 3000ml	FVC 3700ml
$\frac{FEVi}{FVC}$ 80%	MEP 95 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /Min
17-18	4.4	14
18-19	5.1	17
19-20	5.4	19
20	Thiopentone	
20-21	3	11
21-22	2.2	11
22-23	4.6	15
23-24	4.9	14

Name F.E.	Age 20
Wt. 10st.11	MBC indir 133 L/min
FEVi 3800ml	FVC 5100ml
$\frac{FEVi}{FVC}$ 75%	MEP 95 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /Min
15-16	5.6	20
16-17	5.3	20
30-31	4.7	18
31-32	4.9	20
32	Thiopentone	
32-33	5.2	19
33-34	2	13
34-35	3.6	13
35-36	5.1	20
36-37	5.2	19
37-38	5.2	19
38-39	5.2	19

TABLE ix

Ventilation in Control Cases Method 111 (100 mg. Thiopentone: Breathing Air).

Name W.T.	Age 49
Wt. 9st. 2	MBC indir. 120 L/min
FEVi 3150ml	FVC 3700ml
FEVi/FVC 85%	MEP 70 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /min
11-12	4	20
17	3.8	20
18	3.8	19
19	3.8	18
20	Thiopentone	
20-21	3.8	18
21	3.5	17
22	3.4	16
23	3.8	16
24	4.1	17
25	4.4	22
26	4.4	20
40-41	4.8	18
41-42	4.8	18

Name S.M.	Age 34
Wt. 10st.	MBC indir 138 L/min
FEVi 3950ml	FVC 4900ml
FEVi/FVC 80%	MEP 90 mm Hg

Minutes after beg.exp	Ventil L/Min	Resp.Rate /Min
9-10	5.8	16
10-11	5	16
23-24	5	16
24-25	4.9	16
25-26	5.4	16
26-27	4.9	15
27	Thiopentone	
27-28	5.5	15
28-29	5.1	16
29-30	5.5	16
30-31	6	17
31-32	5.7	16
32-33	5.8	16
40	7.1	16

TABLE x

Ventilation in Control Cases Method 111 (100 mg. Thiopentone: Breathing Air).

Name L.H.	Age 23
Wt. 9st. 3	MBC indir 112 L/min
FEVi 3200ml	FVC 4300ml
FEVi / FVC 74%	MEP 90 mm Hg

Name D.P.	Age 47
Wt. 9st. 7	MBC indir 112 L/min
FEVi 3200ml	FVC 4400ml
FEVi / FVC 73%	

Minutes after beg. exp	Ventil L/Min	Resp. Rate /Min
17	4.1	9
20	5.4	9
21-22	4.7	8
22	Thiopentone	
22-23	4.5	8
23-24	5	10
24-25	4.2	10
25-26	4.7	10
26-27	5.2	10

Minutes after beg. exp	Ventil L/Min	Resp. Rate /min
21	3.4	9
22	4.5	9
23	3.4	9
24-25	4.3	11
25	Thiopentone	
25-26	3.2	11
26-27	3.4	18
27-28	4.5	17
28-29	4.2	14
48-49	5.2	14

TABLE xi

Ages, Weights and Pulmonary Function Tests on Miscellaneous Cases.

Patient	Disease	Age	Weight (st.)	FEVi ml	FVC	FEVi% / FVC	Direct MBC L/Min	Indirect MBC L/Min	MEP mm.Hg.
W.K.	Myopathy	28	17	700	800	86	30	24.5	50
J.C.	Dystro. Myotonica	49	-	1950	2500	78	-	68.25	-
A.B.	Motor Neuro.Dis.	58	-	3450	4400	80	-	120	70
F.R.	Myopathy	50	-	3610	4300	84	158	126	-
R.O.	Peroneal M. Atrophy	13	6	2300	2800	82	77	80.5	100
S.N.	Myopathy		10	2200	2600	84	-	77	20

C A S E   R E P O R T

D. H. (AL 3267) was aged 41 years. He had lost 2 stones in weight over the last few years, and now weighed 8 stones 10 lbs. For the past five years, he had begun to have difficulty in walking because of weakness of his legs, and he also had frequent falls and stumbles. He found it difficult to relax his grip, and this worsened during spells of cold weather. His wife stated that he was very moody, ill-tempered, and became easily tired. There was no radical voice change, but for many years this had been nasal in character. Sometimes he found speaking difficult.

On examination, the patient was bald, very thin, with generalised wasting of most of his muscles, especially the sterno-mastoids, which were completely absent. He had bilateral cataracts; active myotonia of both hands was present; and percussion myotonia could be demonstrated in the thenar eminences.

Investigations: E.C.G. revealed bundle branch block.
Urinary creatine 0.22 G. per 24 hrs.
Urinary creatinine 0.71 G. per 24 hrs.
Haemoglobin 99%
The diaphragm on fluoroscopy had a small excursion, but there was no paradoxical respiration.

Procaine amide 1 G. q.i.d. had been prescribed for treatment of the myotonia, without much success.

CASE REPORT

D. H. (continued):

Ventilation tests were performed on this patient by Method 1 (breathing endogenous CO_2), and two years later by Method 111 (jerkin plethysmograph, breathing CO_2). The dose of thiopentone in each case was 50 mg.

CASE REPORT

J. H. (D 2149) aged 43 years, He had a history of difficulty in relaxing for 8 years and also a feeling that his head required support and was continually falling backwards. He had noticed weakness of his legs, and also coldness of his fingers for one year. Three years ago he had had a severe respiratory infection, for which condition he was admitted to hospital. He was unable to work, and has been too ill to return for re-assessment of his condition. He had gained weight, weighing now 13 stones.

On examination, he was bald; he had early cataracts; and there was weakness and wasting of the trapezii, latissimus dorsi and the forearm muscles. The legs were also wasted. The sterno-mastoids were almost completely absent.

He had active myotonia of the hands, and percussion myotonia of the biceps muscles.

Investigations: E.C.G. the P-R interval was 0.2 sec.
B.M.R. was -4%
Haemoglobin 85%

On screening, the diaphragm was found to move satisfactorily.

Quinine sulphate was of no benefit in the treatment of his myotonia.

The ventilation test performed on this patient was by Method 11 (inhaling 5% CO2, with a dose of 50 mg. thiopentone).

CASE REPORT

W. H. (L 5944) was a married woman, aged 42 years. (She has one child, who is similarly affected). She weighs 10 stones 6 lbs. She has had difficulty in relaxing her grip for more than 20 years; and difficulty in holding her head upright, and in walking for the past 10 years. She has had many operations under general anaesthesia without incident, viz; 1935 appendicectomy 1945 thyroidectomy 1955 myomectomy (anaesthesia:- papaveratum 20 mg.: hyoscine 0.4 mg. as pre-medication. Thiopentone 400 mg., gallamine 120 mg., nitrous oxide and oxygen). Respiration was controlled via endotracheal tube. Anaesthesia was uneventful and papaveratum 20 mg. was prescribed twice in the post-operative period without untoward effect.

She also had both cataracts removed under local anaesthesia in 1955 and 1957.

In 1959 she had difficulty in swallowing, but barium swallow was normal.

On examination, she had bilateral ptosis; absent sterno-mastoids; and wasting of the dorsi-flexors of the feet. The palate was seen to move poorly in the mid-line, and there was an escape from the nose in the test for palatal weakness.

Investigations: E.C.G. revealed left ventricular hypertrophy.

Haemoglobin 97%

W. H. (continued):

Myotonia was present when she tried to relax her grip, (active myotonia).

Quinine sulphate was prescribed without effect on the myotonia.

Ventilation tests consisted of Method 1 (endogenous CO2 and 50 mg. thiopentone), and Method 111 (jerkin plethysmograph and 100 mg. thiopentone). Maximum expiratory pressure by oesophageal tube was 55 cms. H_2O.

CASE REPORT

C. J. (W 6337) was a married woman aged 35. She had been easily fatigued for very many years; all her movements were slow, especially walking; and she had been unable to run for about 10 years. For about one year, she had been unable to walk up and down stairs. She needed to rest her head on a pillow many times during the day, because she felt that it needed supporting. When she was in a recumbent position, she could not raise herself without the support of her hands. She experienced difficulty in relaxing her hands, but this improved with repetitive movement. Her weight was 8 stones 4 lbs., and she had lost a lot of weight recently. She was a very heavy sleeper and difficult to arouse.

In 1952, she had a child delivered by forceps, under general anaesthesia, during which she collapsed - possibly due to post-partum haemorrhage.

On examination, she was very thin, with wasting of the hands and legs. The rhomboids, quadriceps were noted to be wasted, and the sterno-mastoids and trapezii were absent. There was no abvious weakness of the palate. There was active myotonia of the masseters and the hands. Percussion myotonia was present, especially on the thenar eminences. Electromyography (E. M. G.) confirmed the presence of myotonia.

CASE REPORT

C. J. (continued):

Investigations: E.C.G. Sinus Bradycardia

X-ray of skull No abnormality

Screening of the chest revealed the diaphragm to move quite freely.

Haemoglobin 95%

Urinary creatine 0.55 G per 24 hrs.

Urinary creatinine 0.71 G per 24 hrs. (normal 1 - 1.84 G per 24 hrs.).

Maximum expiratory pressure by oesophageal tube 15 cms. H_2O.

Quinine was of no value, but procaine amide 1 G. t.d.s. improved the patient's myotonia, and she was able to walk much better. The procaine amide produced insomnia, and she was sedated with 100 mg. quinalbarbitone, and after one hour her respiration became almost imperceptible. Two hours later the respiration was still very shallow, and the rate was 18 per minute. It was impossible to arouse her for nearly 6 hours.

Ventilation tests consisted of Method 1 (endogenous CO_2 and 50 mg. thiopentone).

CASE REPORT

J. G. (41798) was aged 32. He weighed 8 stones 4 lbs., having lost weight recently. He had weakness of his legs for about 10 years, with recurrent periodic falls from which he found difficulty in arising. He had difficulty in relaxing his grip. In 1959, he was admitted to hospital with left lower lobe pneumonia.

On examination, he had bilateral ptosis; no cataracts; but had wasting of his face, neck, pectorales major, the forearms and the small muscles of his hands. There was some palatal weakness. Myotonia was present in the hands. The sterno-mastoids were absent, and there was a lot of wasting of the extensor muscles of the knees.

Investigations: E.C.G. was normal
Urinary creatine 0.12 G. per 24 hrs.
Urinary creatinine 0.885 G. per 24 hrs.
X-ray of the chest (1959) confirmed the presence of the left lower lobe pneumonia.

He had been treated with quinine with little effect.

Ventilation tests consisted of Method 111 (jerkin plethysmograph, breathing air; the dose of thiopentone was 100 mg.).

Maximum expiratory pressure by oesophageal tube was 20 cms. H_2O.

CASE REPORT

<u>R. B. (AN 2506)</u>: aged 38, was a married woman with one child. She now weighs 7 stones 7 lbs., having lost weight recently. She had complained of weakness of the neck for 10 years, and had to support her head, as she felt it continually falling forward. She had stiffness of her hands and legs, and difficulty in releasing her grip. She found that all her muscular movements were slowing down, and she became breathless on exertion. She had some difficulty in swallowing, and loss of volume of her voice.

On examination, she had wasting of the sterno-mastoids, the trapezii, and the temporals. There was no obvious palatal weakness. She had myotonia of the tongue. She had a myotonic grip, which improved with repetitive movement. She had great difficulty in raising her head, and had weakness of the dorsi-flexors of the ankles. She had no cataracts.

<u>Investigations</u>: E.C.G. P-R interval 0.2 sec.

Urinary creatine 0.8 G. per 24 hrs.

Haemoglobin 92%

X-ray of chest nothing abnormal detected.

Procaine amide appeared to be of some assistance to her.

Ventilation tests were by Method 1 (endogenous CO2 and 50 mg. thiopentone), and Method 111 (jerkin plethysmograph, breathing air, and 100 mg. thiopentone).

CASE REPORT

H. N. (57958) aged 46, was an unmarried woman. She had complained of generalised muscle weakness for 20 years, and had numerous fainting attacks. She had difficulty in swallowing. She needed assistance in climbing stairs, and had difficulty in relaxing her hands. She could not raise her head from a pillow unaided. She weighed 10 stones 4 lbs., and in 1953 her weight was 7 stones. She had had two operations, viz; 1953, excision of papilloma of the breast (pre-medication; quinalbarbitone 100 mg., atropine 0.5 mg.; anaesthesia consisted of 150 mg. thiopentone, nitrous oxide, oxygen and trichlorethylene. During the operation, myotonia of the hands was noticed); 1959, incision of abcess of axilla (pre-medication; atropine 0.5 mg., anaesthesia consisted of thiopentone 250 mg., nitrous oxide, oxygen and trichlorethylene. During the operation, myotonia of the hands developed, taking about 5 minutes to relax. It was noted that during anaesthesia, respiration appeared to be entirely diaphragmatic).

On examination, there was active myotonia of the hands; percussion myotonia of the thenar eminences; as well as myotonia of the tongue. The masseters and the trapezii were wasted, while the sterno-mastoids were completely absent. The dorsi-flexors of the ankles showed wasting. She has put on weight, mostly adipose tissue.

C A S E   R E P O R T

H. N. (continued):

Investigations: E.C.G. P-R interval 0.2 sec.

Haemoglobin   113%

X-ray of chest (1953) no abnormality was detected.

Quinine sulphate was of little help in improving her myotonia.

Ventilation tests were by Method 1 (endogenous CO_2 and 50 mg. thiopentone), and Method 111 (jerkin plethysmograph , breathing air, and 100 mg. thiopentone)

CASE REPORT

O. B. (X 5512) was an unmarried woman, aged 49, who had weakness of her legs for about 20 years; and stiffness of her hands for about 10 years. Her weight was 10 stones 2 lbs. She fell asleep easily, and was difficult to arouse. She had no difficulty in swallowing, but her speech was nasal in character. She has had operations for cataract extraction in 1955 and 1957.

On examination, she was very obese, but there was wasting of the sterno-mastoids and trapezii. All the limb muscles were wasted. She had active myotonia of the hands.

C A S E   R E P O R T

J. S. (F 8603)   was aged 45. He weighed 9 stones 12 lbs. He had difficulty in relaxing his grip for at least 10 years, especially in the morning. He had lost 2 stones in weight over the past 2 years. He had difficulty in swallowing; his speech was nasal in character; and he had difficulty in relaxing his jaw. He has had operations for cataract extraction.

On examination, he had complete absence of the sterno-mastoids, and generalised muscular wasting. Active myotonia of the hands was present, as well as bilateral ptosis. He was bald.

Ventilation tests were by Method 111 (jerkin plethysmograph, breathing air, and 100 mg. thiopentone).

CASE REPORT

J. C. (AH 8628) was a man aged 49. He had noticed wasting of the left leg 2 years ago, and had to lessen his walking ever since. He had pneumonia 6 years ago.

On examination, he had active myotonia of the hands, with wasting of his arms. The sterno-mastoids were completely absent, and he was unable to lift his head from the pillow. He had bilateral ptosis, and a cataract in his left eye, as well as percussion myotonia of the right thenar eminence.

Investigations: E.C.G. P-R interval 0.22 sec.

Urinary creatine 0.66 G. per 24 Hrs.

Urinary creatinine 0.023 G. per 24 hrs.

Haemoglobin 110%

FEVi was 1950 ml. FVC 2500 ml.,

$\frac{FEVi}{FVC} = 78\%$

Quinine sulphate was of little assistance in improving the myotonia.

Two days after he had been discharged from hospital, he complained of pain in his chest, and coughed up blood. He was thought to have had a pulmonary embolus.

X-ray of the chest revealed a right lower lobe collapse. Later, when his health improved, screening revealed an elevated right dome of the diaphragm with diminished movement, but in the normal direction, both on breathing and sniffing.

C A S E R E P O R T

T. B. (O.P.) was a male aged 50. He weighed 10 stones. He had some stiffness of his hands and legs, but despite that remained very active. He had never had any difficulty in swallowing, nor was there any change in the character of his speech. He had one cataract removed. He had an attack of pneumonia two years ago, which kept him away from work for 6 weeks.

On examination, he had wasting of the sterno-mastoids, bilateral ptosis and frontal baldness. There was active myotonia of both hands, but he was able to work this off very quickly. His walking was stiff.

Ventilation tests were by Method 111 (jerkin plethysmograph, breathing air, and 100 mg. thiopentone.

ANÆSTHESIA IN DYSTROPHIA MYOTONICA
[Abridged]

A Review of the Hazards of Anæsthesia

BY

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London

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Anæsthesia in Dystrophia Myotonica [*Abridged*]

A Review of the Hazards of Anæsthesia

REGISTRAR'S PRIZE ESSAY

By Leon Kaufman, M.B., F.F.A. R.C.S.
London

Recent comments on the use of thiopentone in patients suffering from dystrophia myotonica have assessed this drug unfavourably, small doses apparently producing prolonged respiratory depression (Dundee, 1952; Bourke and Zuck, 1957; Lodge, 1958; Pachomov and Caughey, 1958). It has been postulated that as the disease is a myopathy, this singular response must be peripheral and that thiopentone exerts its action on muscle itself (Dundee, 1952).

A series of case reports of patients suffering from dystrophia myotonica has recently been studied, and careful scrutiny has in many instances failed to confirm this respiratory depressant effect of thiopentone. On the other hand, in patients who have died in the immediate post-operative period, ether and morphine have been implicated, and two cases of sudden death in this disease are recorded in which neither anæsthesia nor surgery was involved (Spillane, 1951; Fisch and Evans, 1954).

In view of these diverse findings, it became necessary to reconsider the nature of the disease in detail and to reassess the impact of anæsthesia on it.

Case records of over 100 patients suffering from dystrophia myotonica collected by the late Dr. O. Maas before 1939 were inspected and 10 were found to have had operations. One patient died in the immediate post-operative period but no details were available.

In the present series, 79 cases of myotonia have been collected, 8 of myotonia congenita, and 71 of dystrophia myotonica (Table I). Of the cases

Table I.—"Myotonic Syndrome"

Total No. of cases	79
Myotonia congenita	8
Operations	2
Dystrophia myotonica	71
No operation (admitted with bronchopneumonia 2)	24
Operations (no details)	7
Operations	25
Cataract extractions (local analgesia)	15

of dystrophia myotonica, 30 had been given oral barbiturates and no abnormal response was noted, but neither respiratory depression nor prolonged sleep was specifically observed and may have in fact occurred. 15 had cataract extractions under local analgesia without incident. 24 patients did not undergo surgical treatment, but of these 2 were admitted with bronchopneumonia. 32 were submitted to operation but full details are available only in 25 cases. Of these 25 patients 5 had respiratory depression or prolonged apnœa, and a further 4 died (Table II).

Table II.—25 Operation Cases

I	Uneventful	15
II	Myotonia	1
III	Respiratory complications	5
IV	Mortality	4

Dystrophia myotonica is portrayed as a generalized disease with implications of consequence for the anæsthetist, for insufficiency of many a bodily system may be associated with it. Muscular atrophy of a widespread nature and diffuse weakness are not uncommon, affecting not only the sternomastoids, the most important accessory muscles of inspiration (Campbell, 1958), but also the intercostals, the diaphragm, the abdominal musculature, and the larynx. Sternomastoid wasting resulting in inability to raise the head may lead to respiratory obstruction especially in the post-operative period while, consequent upon atrophy, the larynx may lose its protective function. In addition, ventilation may be impaired by myotonia affecting the muscles of respiration. Unilateral elevation of the diaphragm when present is considered not to be due to atrophy or myotonia but a congenital varient of the disease (Caughey and Gray, 1953; Caughey, 1954). The heart is often affected, and defects of conduction and rhythm are frequently present. Adrenocortical function appears impaired to some extent; metabolic rate is depressed; and patients treated with cortisone for myotonia may, unless the dose is adjusted for the stress of operation, become exposed to yet a further hazard. A further complication of steroid therapy especially with triamcinolone and pred-

nisone is that, though they may be of value in the treatment of the myotonia, they themselves can cause muscle wasting: EMG changes are characteristic of a myopathy.

The earliest description of risk associated with anæsthesia is that of a case of myotonia congenita (Johnson and Marshall, 1915). Dyspnœa was present pre-operatively, and at the operation for muscle biopsy, when open ether was administered, respiration was irregular, cyanosis was persistent, and general muscular spasm troublesome. The patient remained semi-stuporous for twenty-four hours.

No more mention was made of the disease in anæsthesia until Dundee (1952), Hewer (1957) and Lodge (1958) recorded cases of apnœa lasting up to 20 minutes and respiratory depression for up to 40 minutes, after only 100 mg thiopentone. However, the import of these observations is lessened by the fact that premedication in the form of pethidine and morphine may have contributed to the respiratory depression. Similarly, the multiplicity of drugs administered in the cases reported by Bourke and Zuck (1957) and Pachomov and Caughey (1958) detracts from the suspicion that thiopentone was the miscreant. In the former, papaveretum, scopolamine, thiopentone, succinylcholine, pethidine, and lignocaine (in spray form) were employed, producing prolonged apnœa. In the latter, quinalbarbitone, thiopentone, ethyl chloride and ether were administered; death occurred half an hour after cessation of the operation, respiration apparently "becoming arrested", and might well have been attended by respiratory obstruction.

Some of the patients so described resemble those suffering from a relative overdose of central respiratory depressant drugs. To produce central depression may require large doses of drugs in the fit patient, but very much less is necessary in the dystrophic one, with wasted muscles of respiration. The dystrophic process may affect the larynx, facilitating intubation, while the low metabolic rate may prolong the action of the drugs as the rate of detoxication is reduced.

Failure of inhalation of carbon dioxide to stimulate respiration during apnœa has suggested to Dundee (1952) that the action of thiopentone was not central; however, the carbon dioxide tension in the blood may already have been elevated. His experiment of giving 50 mg of thiopentone to a single volunteer, which produced respiratory depression without loss of consciousness, is not absolute evidence of a peripheral effect of the drug; it is beset by difficulty in interpretation in the face of the complicated chemical and nervous mechanisms of breathing. That thiopentone has an action on peripheral nerve and the neuromuscular junction in the experimental animal (Secher, 1951; Kraatz and Gluckman, 1954; Sirnes, 1954; Quilliam, 1955) has been shown, but in high concentrations, while lower doses are more effective centrally (Goodman and Gilman, 1955).

Thus an assessment of the cases recorded in the literature of the last decade does not endorse the suggestion that the action of thiopentone is upon abnormally sensitive muscle, but suggests that muscle wasting with reduced pulmonary ventilation leads to increased arterial pCO_2 and is further accentuated by respiratory depressants such as morphine, pethidine and thiopentone.

In the present study in patients suffering from dystrophia myotonica, response to general anæsthesia has been quite uneventful in many cases (Table III), one patient having 500 mg of thiopentone on three occasions within one week without apparent ill-effect. The presumption is thus fostered that it is not the thiopentone *per se* which produces a specific idiosyncrasy in this disease as it does in acute intermittent porphyria. It may well be that the state of disease was not extensive in Group I (Table III), or that the doses of drugs administered were commensurate with the general physical health of the patients.

TABLE III

GROUP I.—Anæsthesia uneventful—15 cases

A. Local and spinal analgesia
- (*a*) Submucous resection 1
- (*b*) Thoracoplasty 2
- (*c*) Hæmorrhoidectomy 1

B. General anæsthesia
- (*a*) Biopsy .. .. 4 (no thiopentone in 3 cases)
- (*b*) Myomectomy (thiopentone, gallamine)
- (*c*) Cholecystectomy (succinylcholine, tubarine, neostigmine)
- (*d*) Inguinal hernia (thiopentone, gallamine)
- (*e*) Thyroidectomy (N_2O-O_2 ether)
  Termination of pregnancy (thiopentone 500 mg, N_2O-O_2, ether—on three occasions)
- (*f*) Dental extraction (N_2O-O_2)
- (*g*) Mastoidectomy (thiopentone, gallamine, N_2O-O_2, ether)
- (*h*) Examination under anæsthesia, dilatation and curettage (thiopentone, N_2O-O_2, trichlorethylene)

One patient (Group II) developed myotonia of the hands in response to incision on both the occasions she was anæsthetized (Table IV). This resolved as the operations progressed: myotonia of the respiratory muscles was not observed.

TABLE IV

GROUP II.—*Myotonia*—1 case

Papilloma of breast (thiopentone 150 mg, N_2O-O_2)
Axillary abscess (thiopentone 250 mg, N_2O-O_2)

GROUP III.—*Respiratory Complications*—5 cases
- (*a*) Cataract (thiopentone, gallamine, N_2O-O_2)
- (*b*) Hernia (thiopentone, pethidine, N_2O-O_2)
- (*c*) Gastro-enterostomy (thiopentone, tubarine, C_3H_6. O_2)
- (*d*) Resection of urethral bar (thiopentone 200 mg, N_2O-O_2, trichlorethylene)
- (*e*) Dental extractions (thiopentone, succinylcholine, N_2O-O_2)

GROUP IV.—*Mortality*—4 cases
- (*a*) Polycystic kidneys; blood urea 300 mg (thiopentone 500 mg, hypothermia)
- (*b*) Cæsarean section (butbalitone, intermittent succinylcholine)
- (*c*) Gastrectomy (thiopentone, succinylcholine, tubarine)
- (*d*) Cholecystectomy (N_2O-O_2, ether)

Laryngoscopy was performed with ease at the end of the operation. This patient had absent sternomastoids, was unable to raise her head, and had diaphragmatic respiration prior to anæsthesia. Subsequent lung function tests confirmed her respiratory inadequacy, with a maximum breathing capacity of 56 litres/minute, and maximum expiratory pressure of 10 mm Hg (H. N. in Table V).

The patients in Group III (Table IV) represent instances where in the presence of poor physical condition and diminished respiratory reserve the action of respiratory depressant drugs was enhanced. All the patients had morphine premedication followed by 250–500 mg thiopentone, and one also had 25 mg pethidine during anæsthesia. Respiratory depression lasting 30 minutes ensued in one instance (hernia repair), while apnœa lasting 30 minutes (cataract extraction) and four hours (gastro-enterostomy) occurred in 2 other cases: all responded to nikethamide.

The patient undergoing resection of urethral bar had marked wasting of all his muscles (he weighed 8 st. 7 lb), diminished vital capacity and auricular flutter. It is hardly surprising that after papaveretum 20 mg and scopolamine 0·4 mg only 200 mg thiopentone and nitrous oxide, oxygen and trichlorethylene were necessary to maintain adequate anæsthesia. Laryngoscopy was performed with ease at the end of the operation. The patient was returned to the ward conscious but had a short period of cyanosis while lying on his back, presumably due to respiratory obstruction.

The child having dental treatment had absence of sternomastoids and wasting of the abdominal muscles. His weight was 3 st. 11 lb. Premedication consisted of papaveretum 16 mg, scopolamine 0·3 mg. After 125 mg thiopentone apnœa ensued lasting for 2 minutes and was terminated by gentle stimulation. Succinylcholine (30 mg) produced myotonia of the hands for one minute. At no time was there any suggestion of myotonia of the respiratory muscles. Spontaneous respiration did not recommence until the end of operation, the patient being manually ventilated with nitrous oxide and oxygen via a nasotracheal tube. Breathing began with movement of the tube *in situ*, respiration being slow and deep.

The patients who died under anæsthesia (Group IV) were all markedly debilitated. A patient undergoing gastrectomy recovered satisfactorily from anæsthesia, only to succumb in the post-operative period after the administration of 20 mg of papaveretum, while another having a cholecystectomy under nitrous oxide, oxygen and ether anæsthesia died suddenly five hours post-operatively, no specific cause being found at post-mortem.

The patient with polycystic kidneys and progressive renal failure (blood urea 300 mg) had multiple punctures performed of the renal cysts under hypothermia, which did not appear to have induced an attack of myotonia. The patient died shortly after return to the ward being unable to cough up secretions.

The patient undergoing Cæsarean section had a severe degree of muscle wasting, crepitations at the lung bases and right bundle branch block, all of which increased the risk of operation. Immediate recovery from anæsthesia was satisfactory but shortly afterwards she became cyanosed and had to have artificial respiration. Bronchial secretions became exceedingly profuse and death occurred eight hours post-operatively.

All the patients in the last group had marked lack of respiratory reserve power and succumbed in the immediate post-operative period presumably as a result of under-ventilation, possible respiratory obstruction and the inability to expectorate secretions. There are also to be noted the effects of anoxia, and the depressant action of thiopentone (Prime and Gray, 1952) on the already damaged heart, while ventilation might be further impaired as a result of abdominal operation (Anscombe, 1957).

Respiratory Function in Neurological Disease

Many of the problems created by respiratory weakness and bulbar palsy in poliomyelitis have been largely solved but it is of great interest that of the 39 cases of myasthenia gravis collected by Rowland *et al.* (1956) 14 died within an hour of being sedated.

In a patient aged 34 suffering from amyotrophic lateral sclerosis (Feltman *et al.*, 1952) diaphragmatic excursion was limited, resulting in a decreased vital capacity of 2,285 ml, maximum breathing capacity of 38 litres/minute, increased arterial pCO_2, oxygen unsaturation (73·3% oxygen saturation), and polycythæmia. The patient developed congestive cardiac failure, presumably from the effect of anoxia on the myocardium, and the effect of anoxia and polycythæmia on the pulmonary vascular bed leading to increased resistance. Miller (1957) found the maximum breathing capacity (M.B.C.) of 2 cases of progressive muscular atrophy and one of amyotrophic lateral sclerosis to be reduced to 32, 42 and 57 litres/minute respectively.

Kilburn *et al.* (1959) and Bashour *et al.* (1955) both reported one case each of dystrophia myotonica with reduced vital capacity (V.C.) and M.B.C. Benaim and Worster-Drought (1954) described one case with myotonia of the diaphragm with a vital capacity of 1,130 ml,

M.B.C. of only 45 litres/minute and arterial pCO_2 of 67·4–72·1 mm Hg. In the present investigation of respiratory function in dystrophia myotonica, V.C., forced expiratory volume over 1 second (F.E.V.$_1$), M.B.C. and maximum expiratory pressures were all measured. Indirect M.B.C. was calculated from the F.E.V.$_1$ by multiplying the result by 35 (Table V). Reduction of the maximum expiratory pressure to 20 mm Hg or less from the normal of 100 revealed marked weakness of the muscles of expiration. The indirect M.B.C., within the normal range in three instances, was markedly reduced on direct measurement, indicating that sustained voluntary effort was more difficult than a single rapid expiration. Thus if these patients are exposed to the stress of depressant drugs or respiratory infection respiratory failure may easily ensue.

TABLE V.—RESPIRATORY STUDIES IN DYSTROPHIA MYOTONICA

	Age	V.C. ml	F.E.V.$_1$ ml	F.E.V.$_1$/V.C.	Indirect M.B.C. l./min	Direct M.B.C. l./min	Max. exp. pressure mm Hg
J. G.	23	3,700	2,900	83%	105–100	75–80	20
D. H.	39	2,800	2,580	92%	91	72–75	20
H. N.	44	2,200	1,700	82%	65	56	10
G. C.	49	2,500	1,950	78%	68		
C. J.	34	2,900	2,500	80%	95	65	12

Myotonia

The phenomenon of myotonia has been investigated by Brown and Harvey (1939) who demonstrated, in congenital myotonia of the goat, where the muscles on electromyography are similar to those of human myotonia congenita, that the abnormality is in the muscle fibre itself, and that contraction is due to a long-lasting irregular tetanus. The prolonged discharge of action potentials on direct stimulation of the muscle is unaltered by nerve section or curarization, and hence the neuromuscular junction is not involved. The repetitive response is increased by acetylcholine and potassium ions, but only in concentrations which normally cause some contraction (Denny-Brown and Foley, 1949). Quinine has a depressant action on the excitability of the myoneural junction and also an effect on the muscle fibre itself where it prolongs the refractory period (Harvey, 1939), and it is this latter action that is so beneficial in the treatment of myotonia. The repetitive discharge of impulses can be induced in normal skeletal muscle by veratrine and abolished by quinine. This action appears to be associated with increased potassium leakage from the cells (Krayer and Acheson, 1946). The resting muscle membrane potential is believed to be proportional to the logarithm of the ratio of the potassium within the cells to that outside the cells. Thus an increase of the extracellular potassium will lead to an unstable membrane and depolarization (Grob *et al.*, 1957).

That the defect of myotonia is within muscle and not at the myoneural junction has been confirmed in man using intra-arterial curare (Lanari, 1946; Landau, 1952), while more recently it was noted by Geschwind and Simpson (1955) that 10 mg of *d*-tubocurarine or 15 mg of decamethonium could not abolish myotonia. The defect may well be an inherent intracellular metabolic disorder allowing potassium to escape more easily from the cells.

Anæsthetic Management

Guidance for the anæsthetic management of patients with dystrophia myotonica should be based on prime principles; critical assessment of the severity of the disease, the extent of the dystrophy and the disability arising from the myotonia is imperative. Lung function should be evaluated, with measurements of vital capacity, forced expiratory volume (1 second) and maximum breathing capacity, while fluoroscopy of the chest should be done to see whether myotonia of the diaphragm can be detected. Cardiovascular involvement may be present, and the possibility of endocrine dysfunction, especially adrenocortical, must be considered. Techniques of anæsthesia and the drugs administered are influenced by due consideration of all these factors. Thus, if respiratory reserve power is diminished, respiratory depressants should be avoided, though emotional upset and fright, such as coming to the operating theatre without sedation, may induce an attack of myotonia as indeed does decrease in temperature. If any respiratory infection is present, mortality increases even without anæsthesia, and non-urgent operations are best avoided. Ventilation should at all times be adequate, but if it should prove otherwise, controlled respiration should be resorted to without delay. The patient may require assistance to respiration also in the post-operative period, when secretions cannot be coughed up, and when ventilation as seen by studies of vital capacity, maximum inspiratory and expiratory flow rates is diminished after operation (Anscombe, 1957). Tracheostomy and artificial ventilation may be required. Myotonia of the respiratory muscles may make ventilation extremely difficult if not impossible, and though curare will not be effective, intravenous quinine has been recommended as the drug of choice to relieve the attack, in the dosage of 300–600 mg of the hydrochloride. Spinal analgesia does not abolish myotonia, which is induced by percussion of muscle. Grund (1919) and Kennedy and Wolf (1937) both report one instance each of persistent myotonia after spinal anæsthesia, which may make operating conditions difficult. Likewise, brachial plexus nerve block, which

produced both motor and sensory paralysis, also could not abolish myotonia produced by mechanical stimulation of muscle (Buchtal and Clemmensen, 1941).

Myotonia, being a disorder of muscle, is abolished by infiltration of the muscle with local anæsthesia (Buchtal and Clemmensen, 1941; Landau, 1952) and this appears to be the anæsthetic of choice if myotonia is troublesome, and the technique is suitable for the nature of the operation.

Relaxants of the competitive type are not contra-indicated, but they do not abolish myotonia; dosage would have to be reduced if the patient is taking quinine, which also has a depressant effect at the end plate (Harvey, 1939). Depolarizing relaxant drugs are at present best avoided if myotonia is marked, since a patient receiving decamethonium had an attack of myotonia with respiratory distress (Richardson, 1959) and it is known that, in the experimental animal, succinylcholine can elevate the serum potassium (Paton, 1956) which can aggravate myotonia. Neostigmine was considered to increase myotonia (Kennedy and Wolf, 1937) but in a more recent study (Landau, 1952) no significant change was detected.

This appraisal of anæsthesia and dystrophia myotonica was initiated with the intention of confirming that the action of thiopentone in this disease was a peripheral one on muscle: this view has been dispelled. It has been shown that patients have undergone thiopentone anæsthesia without incident, though the administration of anæsthesia is still fraught with danger, depending on the severity of the disease. It has also been revealed that there is possible cardiac impairment and endocrine dysfunction, while the respiratory insufficiency resulting from dystrophy or myotonia of the respiratory muscles may be accentuated by the presence of respiratory depressant drugs. The suggestions for anæsthetic management are intended as interim recommendations until results correlating electromyographic studies with pulmonary function are completed.[1]

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