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Respiration in dystrophia myotonica

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Dystrophia myotonica is an uncommon disease characterized by muscular wasting, myotonia, endocrine dysfunction, and cataract. The wasting particularly affects the facial muscles, the sternomastoids, the trapezii, and the limb muscles, but it may be generalized and produce marked loss of weight. The abdominal muscles are often slack; the pharynx, the larynx, and the diaphragm may all be affected. Myotonia often precedes the wasting but may be absent in the muscles that have atrophied. Myotonia is produced chiefly by sudden movements and occurs commonly in the muscles of the limbs and of mastication. It is diminished by repetitive movements. It has however been observed in the diaphragm (Benaim and Worster-Drought, 1954). The heart muscle may also be involved. Conduction defects and disturbances of rhythm are common (Evans, 1944; Spillane, 1951; Fisch, 1951), and sudden death has been reported (Spillane, 1951; Fisch and Evans, 1954).

Patients with dystrophia myotonica are particularly liable to respiratory disease, and bronchopneumonia is the commonest cause of death (Black and Ravin, 1947). Previous studies of lung function (Benaim and Worster-Drought, 1954; Bashour, Winchell, and Reddington, 1955; Kilburn, Eagen, and Heyman, 1959a; Kilburn, Eagan, Sieker, and Heyman, 1959b; Cannon, 1962) have shown that the usual respiratory defect consists of alveolar hypoventilation without evidence of airway obstruction or intrinsic lung disease. The muscular disease weakens the bellows action of the thoracic cage and this produces hypoventilation.

There is also a high incidence of complications when patients suffering from dystrophia myotonica are submitted to anaesthesia. Twenty-five patients were recently studied (Kaufman, 1960): five had profound or prolonged respiratory depression during operation and a further four died in the immediate post-operative period. Dundee (1952) postulated that there might be a specific idiosyncrasy to thiopentone, but in the series of patients investigated by Kaufman (1960) some patients had no abnormal respiratory response to the drug. In other instances profound respiratory depression was noted after ether and morphine.

In the present paper an attempt has been made to study some aspects of respiratory function in patients suffering from dystrophia myotonica and to assess the effects of thiopentone on pulmonary ventilation.

MATERIAL AND METHODS

The following lung fuction tests were carried out on 10 patients:

(1) Spirometry was undertaken with a light-weight spirometer (Bernstein, D'Silva, and Mendel, 1952). Forced vital capacity (F.V.C.) and forced expiratory volume in one second ($F.E.V._{1}$) were measured. The indirect maximum breathing capacity (M.B.C.) was calculated by multiplying the $F.E.V._{1}$ by 35 (Gandevia and Hugh-Jones, 1957).

(2) Mixed venous P_{CO_2} was measured by the rebreathing method (Campbell and Howell, 1960). The gas was analysed in a Scholander dry gas analyser.

(3) Maximum expiratory pressure (M.E.P.) was measured by asking the subject to blow up and maintain a sphygmomanometer mercury column. A small leak was present in the mouth-piece so that pressure could not be maintained by closure of the glottis. In three cases simultaneous intra-oesophageal pressure was measured by means of a water-filled polythene tube connected to a capacitance manometer.

(4) In six cases and 10 normal subjects, the prolonged effect on ventilation of 100 mg. of thiopentone (1·25% solution) was measured using a jerkin plethysmograph (Heaf, Scott, Smith, and Williams, 1961). The subject lay on a bed in a semi-recumbent position. Twenty minutes was allowed for ventilation to reach resting level, and respiration was measured continuously for at least 30 minutes after the injection of thiopentone. This method had the advantage that no mouth-piece was required, which meant that resting levels and patterns of respiration were easily recorded in untrained subjects and that continuous recording during unconsciousness and sleep could be obtained. The advantages of dispensing with a mouthpiece are particularly valuable in patients with this disease.

The jerkin plethysmograph was calibrated at least three times during the course of each experiment, and

an accuracy for minute ventilation of ±10% was obtained. The limitations of this method are described in detail elsewhere (Gillam, 1964, in preparation).

An attempt was made to assess the sensitivity of the respiratory centre in three of the patients and in a series of controls. They were made to re-breathe for five minutes from a 5-litre spirometer filled with oxygen, with continuous monitoring of the end-tidal CO_2 with an infra-red analyser, and the ventilatory response to CO_2 was thus measured. This response was also measured in a similar manner before and after an injection of 50 mg. of thiopentone.

LIMITATIONS OF METHODS Tests have been limited by the fact that these were all patients with an incurable and distressing disease. We have tried to use only methods with which they could easily co-operate and to avoid those which might add to their discomfort. Arterial punctures have not been performed. As nearly all the subjects were out-patients we have not felt justified in giving more than small doses of thiopentone.

RESULTS

Clinical information about the 10 patients is summarized in Table I. The severity of the muscular disease has been classified into four grades, as follows: grade I, disease mild; grade II, disease moderately severe, but patient still able to do a light job or housework; grade III, patient severely incapacitated; grade IV, patient bedridden. Three of the patients had past histories of pneumonia. Two patients suffered from excessive somnolence. Six patients had undergone general anaesthesia in the past without undue effects. There was no evidence of polycythaemia in the group. Three patients had abnormal E.C.G.s: one had left axis deviation; one had a bundle branch block; and one (case 3) had a wide QRS complex and right ventricular hypertrophy. Chest radiographs which were performed in seven patients were normal. Screening of the chest in four of the patients did not reveal any myotonia of the diaphragm.

Table I also contains the results of lung function tests. There was no evidence of airway obstruction. Although the vital capacity was more than 10% below the predicted normal (Needham, Rogan, and McDonald, 1954) in half of the cases, it was outside the normal range in only three. The mixed venous P_{CO_2} was minimally raised to 52·5 mm. Hg in one case only (case 3). In the other six in whom it was measured there was no evidence of hypoventilation under normal ambulant conditions.

The most striking abnormality was in the maximum expiratory pressure, which was considerably reduced in all the subjects suffering from dystrophia myotonica. There was a highly significant difference between the means of the cases of dystrophia myotonica and a series of 22 controls. The mean of the former was 22·5 mm. Hg (standard deviation ±8·7) whereas in the latter the mean was 81·3 mm. Hg (standard deviation ±25·7).

In the experiments using the jerkin plethysmograph, ventilation was measured before and after the injection of 100 mg. of thiopentone in six patients and in 10 normal subjects. The average resting ventilation was not greatly different in the two groups, being 5·1 litres per minute for the normals and 4·5 litres per minute for the patients. (The average resting minute ventilation was calculated from the mean of the five minutes preceding the injection of thiopentone.)

TABLE I

CLINICAL DATA

No.	Sex	Age	Wt. (lb.)	Duration of History (years)	Functional Grade	F.E.V.$_1$ (ml.)	F.V.C. (ml.)	F.E.V.$_1$/F.V.C. %	Normal Range of F.V.C. (ml.)	Indirect M.B.C. (l./min.)	M.E.P. (mm. Hg)	Maximum Oesophageal Pressure (cm. H_2O)	Mixed Venous P_{CO_2} (mm. Hg)
1	M	50	140	5	I	2,000	2,630	76	2,000–4,400	70	20	—	44
2	F	49	142	20	III	1,100	1,500	73	2,300–3,600	38·5	25	—	—
3	M	32	114	13	II	3,000	3,600	83	3,600–5,400	105	20	20	52·5
4	F	35	116	10	III	2,800	3,150	90	2,200–4,400	102	10	15	—
5	M	43	172	8	III	2,300	2,500	92	3,300–5,000	80·5	30	—	—
6	M	41	122	8	III	2,550	2,800	92	3,300–5,000	91	20	—	45
7	F	46	144	22	III	2,050	2,600	78	2,300–3,600	71	10	—	44·7
8	F	38	105	13	II	2,700	2,950	92	2,200–4,400	94·5	30	—	42
9	F	42	146	27	II	1,900	2,400	90	2,300–3,600	66·5	40	55	45
10	M	45	138	10	I	3,400	4,900	70	3,300–5,000	119	20	—	47

TABLE II

PERCENTAGE DECREASE IN MINUTE VENTILATION AND DECREASE IN RESPIRATORY RATE AFTER INJECTION OF 100 MG. THIOPENTONE (METHOD 4—BREATHING AIR) IN SIX PATIENTS WITH DYSTROPHIA MYOTONICA AND IN 10 CONTROLS

	Controls										Patients with Dystrophia Myotonica					
Subjects	S.M.	D.P	L.H.	F.E.	W.T.	J.M.	W.I.	W.A.	B.D.	J.T.	R.B. No. 8	W.H. 9	J.S. 10	J.G. 3	O.B. 2	T.B. 1
Average resting ventilation (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
Thiopentone (min. after)	Percentage Decrease in Ventilation after Thiopentone															
1	0	13	4	0	0	41	8	45	7	7	0	22	35	0	0	57
2	0	18	0	60	8	57	0	13	30	30	0	25	6	30	46	61
3	0	0	10	30	11	10	0	7	21	21	0	0	0	74	46	60
4	0	0	0	0	0	0	8	22	23	24	0	0	0	60	34	62
5	0	0	0	0	0	0	8	22	20	20	0	0	0	50	22	62
6	0	0	0	0	0	0	12	0	0	17	0	0	0	19	34	66
7	0	0	0	0	0	0	0	0	0	17	0	0	0	27	0	35
10+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	30
Thiopentone (min. after)	Decrease in Respiratory Rate after Thiopentone															
1	0	0	0	1	0	8	1	4	0	0	0	0	2	0	0	2
2	0	0	0	7	1	8	0	1	1	5	0	0	0	9	0	8
3	0	0	0	7	2	4	0	1	1	2	0	0	0	9	0	7
4	0	0	0	0	2	5	0	0	0	2	0	0	0	11	0	6
5	0	0	0	1	1	0	0	0	0	2	0	0	0	5	0	9

Average resting minute ventilation calculated from that of the mean of the five minutes preceding the injection of thiopentone.

TABLE III

RESPIRATORY RESPONSE TO RISING END-TIDAL CO_2 TENSION IN THREE CASES OF DYSTROPHIA MYOTONICA

Subject	Minutes of CO_2	Tidal Volume (ml.)	Respiratory Rate	Ventilation (l./min.)	End-tidal P_{CO_2} (mm. Hg)
W.H.	1	450	13	5·8	38·4
	2	650	14	9·1	40·4
	3	750	15	12·1*	44·4
	4	800	17	14·4*	49·3
	5	900	18	16·8*	52·2
H.N.	1	700	15	8·5	36
	2	700	17	11·9	38·9
	3	850	18	15·3	42·8
	4	1,100	18	18	47·2
	5	1,100	21	23·1	52·5
R.B.	1	400	18	7·2	34·5
	2	500	17	8·5	38·4
	3	550	16	8·8	40·4
	4	500	20	10	45·5
	5	600	20	12	47·3

* Includes one breath of 1·5 l. The end-tidal P_{CO_2} was measured at the middle of each minute.

There was however greater and more prolonged depression after the injection of thiopentone in the patients (Table II; Fig. 1). This was particularly pronounced in three cases (Nos. 1, 2, and 3) in whom marked periodic respiration also occurred (Figs. 2, 3, and 4).

In this paper the term 'periodic respiration' means periods of irregular respiration occurring at more or less regular intervals and often separated by periods of apnoea. Although such periodic breathing was more marked in the dystrophic cases, it was not specific, being also produced after

TABLE IV

RESPIRATORY RESPONSE TO RISING END-TIDAL CO_2 TENSION IN SEVEN CONTROLS

Subject	Minutes of CO_2	Tidal Volume (ml.)	Respiratory Rate	Ventilation (l./min.)	End-tidal P_{CO_2} (mm. Hg)
R.K.	1	350	16	5·6	43
	2	400	16	6·4	48
	3	550	18	9·9	52
	4	850	18	15·3	53
	5	850	20	17	57
J.N.	1	450	19	8·4	35
	2	650	22	14·3	41
	3	800	21	16·8	43
	4	850	22	18·7	45
	5	900	24	21·6	47
D.SH.	1	400	13	5·2	24
	2	750	12	9	36
	3	800	12	9·6	43
	4	900	13	11·7	47
	5	1,050	13	13·9	52
C.Y.	1	800	15	12	42
	2	1,200	14	16·8	48
	3	1,600	16	25·6	55
	4	2,000	14	28	61
	5	2,500	20	50	63
R.S.	1	600	12	7·2	42
	2	800	14	11·2	46
	3	1,050	15	15·7	49
	4	1,100	16	17·6	53
	5	1,300	17	22·1	57
L.H.	1	450	20	9	37
	2	500	22	11	44
	3	700	23	16·1	50
	4	850	25	21·2	56
	5	1,000	28	28	62
D.S.	1	450	21	9·5	38
	2	550	23	12·6	42
	3	700	22	15·4	48
	4	750	22	16·5	52
	5	Unable to continue with test			

The end-tidal P_{CO_2} was measured at the middle of each minute.

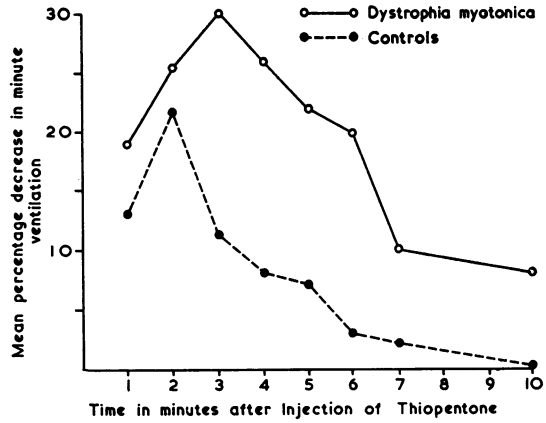

FIG. 1. *Mean percentage decrease in minute ventilation in six patients with dystrophia myotonica and* 10 *controls after the administration of* 100 *mg. thiopentone.*

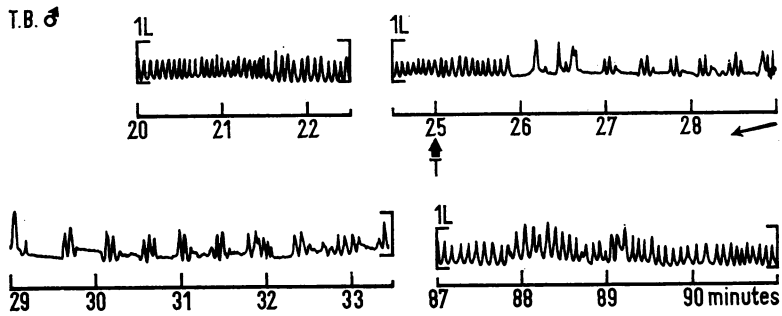

FIG. 2. *Case* 1.

Ventilation

Minutes after Beginning Experiment	*Pulmonary Ventilation (l./min.)*	*Respiratory Rate (per 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	3·0	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	4·0	10
40–41	3·7	13
46–47	4·0	9
47–48	4·0	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

T=injection of 100 *mg. thiopentone*

Minutes after Beginning of Experiment	
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.*

Calibration: 1*L*=1 *litre*

Inspiration : in upward direction

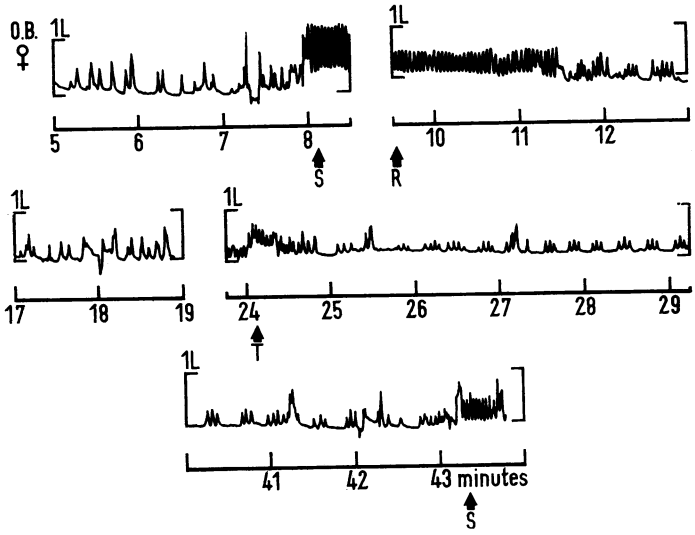

FIG. 3. *Case* 2.

Ventilation

Minutes after Beginning Experiment	*Pulmonary Ventilation (l./min.)*	*Respiratory Rate (per min.)*
5–6	3·1	8
6–7	2·8	7
12–13	4·0	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	2·7	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

Calibration: 1L=1 litre

Inspiration: in upward direction

Explanatory Note

T=injection of 100 mg. thiopentone

Minutes after Beginning of Experiment	
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 while breathing into spirometer (S).*
10–13	*Respiration regular while measuring P_{CO_2} by rebreathing method (R); once the mouth-piece 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.*

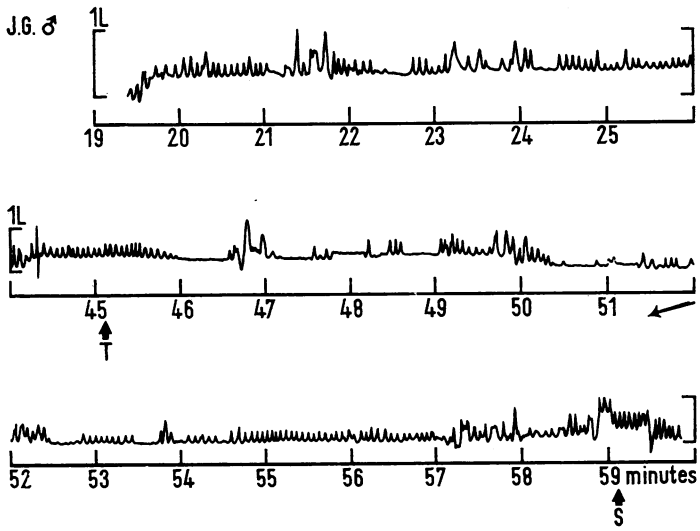

FIG. 4. *Case* 3.

Ventilation

Minutes after Beginning Experiment	*Pulmonary Ventilation (l./min.)*	*Respiratory Rate (per 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

T = injection of 100 *mg. thiopentone*

Minutes after Beginning of Experiment	
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 irregular 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 (*S*).

Calibration: 1*L* = 1 *litre*
Inspiration: in upward direction

the injection of thiopentone in one normal subject (Fig. 5). In two cases irregular breathing was also present before the injection (Figs. 3 and 4).

The ventilatory response in three patients and in seven controls, who were made to re-breathe into a 5-litre spirometer, is shown in Tables III and IV. Figure 6 shows the minute ventilation plotted against the end-tidal P_{CO_2}. There was no apparent difference between the patients and the controls.

The same three patients (Nos. 7, 8, and 9) and one other (No. 6) and three normal subjects were also made to re-breathe into a 5-litre spirometer before and after an injection of 50 mg. of thiopentone. There was no evidence of a fall in

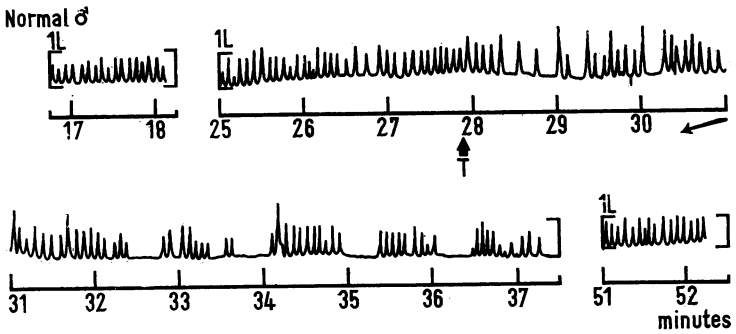

FIG. 5

Ventilation

Minutes after Beginning Experiment	*Pulmonary Ventilation (l./min.)*	*Respiratory Rate (per 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

Explanatory Note

T=injection of 100 mg. thiopentone

Minutes after Beginning of Experiment	
17–18	*Resting respiration fairly regular. Awake.*
25–32	*Short period of apnoea of 12 seconds between 26 and 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 1 minute after the thiopentone.*
51–52	*Patient awakened. Respiration now regular.*

Calibration: 1L=1 litre
Inspiration: in upward direction

ventilatory response to the stimulus after the injection, nor was there any difference between the responses of the patients and of the normal subjects. Furthermore, the stimulus of breathing an increasing concentration of CO_2 failed to evoke myotonia of the respiratory muscles.

DISCUSSION

The purpose of this investigation was to assess the lung function of a group of patients with dystrophia myotonica in an attempt to find an explanation of the liability of these patients to lung infections and anaesthetic morbidity; and to investigate the suggestion that they are specifically sensitive to thiopentone. In the majority of cases previously reported there has been evidence of alveolar hypoventilation (Benaim and Worster-Drought, 1954; Bashour *et al.*, 1955; Kilburn *et al.*, 1959 a and b) without airway obstruction or intrinsic lung disease. It is reasonable to suppose that the muscular disease weakens the bellows action of the thoracic cage and thus produces alveolar hypoventilation. We too have found no evidence of airway obstruction; and in only three patients (two of whom were grossly obese) was the vital capacity reduced. On the other hand, we only found evidence of hypoventilation under normal resting conditions in one patient, who had a raised mixed venous P_{CO_2}. None of our patients was polycythaemic; and only the patient with the raised P_{CO_2} had any evidence on the E.C.G. of right ventricular hypertrophy (which has been reported in other hypoventilation syndromes, presumably caused by pulmonary hypertension resulting from chronic hypoxia). On direct measurement of resting ventilation only one patient had a value more than 10% below the range of our normal subjects, and there was no significant difference between the mean values of the two groups. However, three of our cases showed prolonged and extreme depression of ventilation with periodic respiration after an injection of 100 mg. of thiopentone. Three others

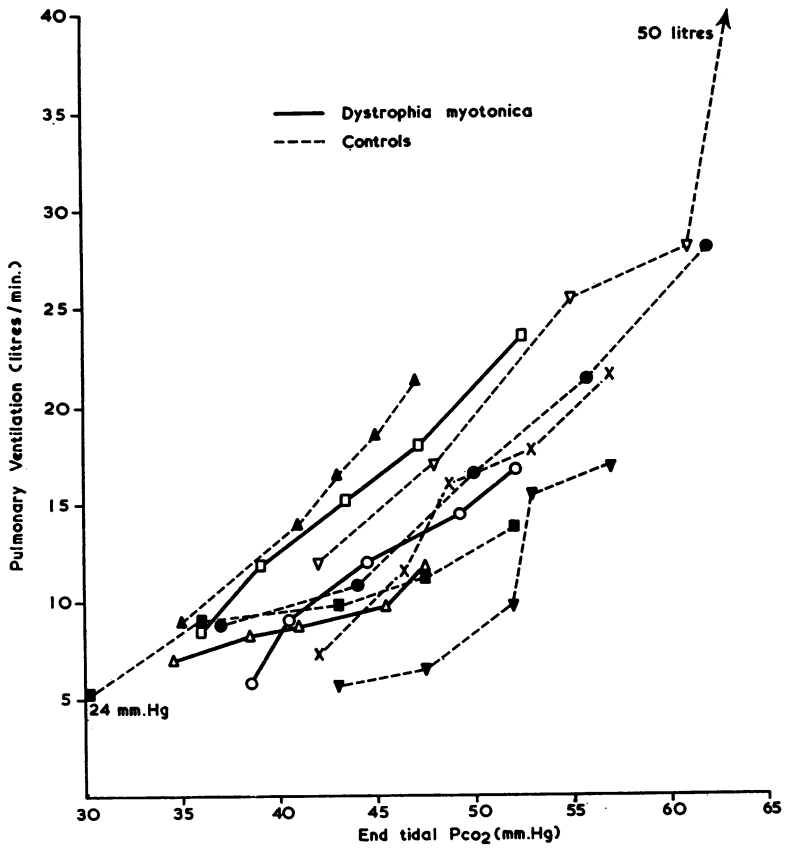

FIG. 6. *Respiratory response to rising end-tidal P_{CO_2} in three patients with dystrophia myotonica and seven controls.*

showed a normal response. In the four patients in whom we tested the sensitivity of the respiratory centre, this too was within the range of our controls.

It is therefore obvious that the lung function of these patients varies greatly, which is what would be expected with a slowly progressive disease such as this. The M.B.C. was almost normal and, although hypoventilation was present in severe cases, it might only occur if a narcotic were given. Dundee (1952) postulated that thiopentone had a specific action on dystrophic muscles, but the evidence for this was based on his finding, in one patient, of respiratory depression beyond the period of unconsciousness produced by thiopentone.

A comparison of our respiratory tracings of dystrophic patients with those of normal subjects given thiopentone, during natural sleep or drowsiness and after other narcotic drugs, showed that there was nothing abnormal about the pattern. Indeed, this pattern of respiration was seen in two of our patients before they received the thiopentone (Figs. 3 and 4). Such patterns have been recorded in states of drowsiness (Magnussen, 1944; Reed and Kleitman, 1925). We do not believe that there is any reason or need to postulate a specific action of thiopentone: this is merely an exaggeration of the normal pattern occurring during somnolence. Figure 7 is the ventilation record of a normal subject showing irregular respiration after the injection of 20 mg. of papaveretum.

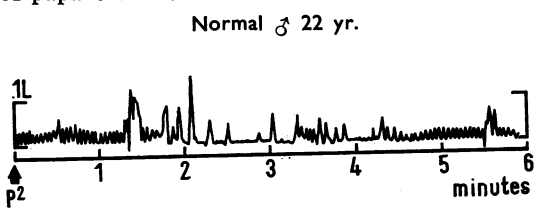

FIG. 7. *P_2 signifies the end of an intravenous injection of 20 mg. papaveretum given over a period of four minutes. Calibration: 1L=1 litre. Inspiration: in upward direction.*

The relation between hypoventilation and somnolence is interesting and obscure. It has been recognized in some obese patients, giving rise to the so-called Pickwickian syndrome (Burwell, Robin, Whaley, and Bickelmann, 1956). Two of our patients (one of whom was grossly obese) suffered from excessive sleepiness, as have several previously reported cases (Benaim and Worster-Drought, 1954; Kilburn *et al.*, 1959 a and b; Phemister and Small, 1961). There is however no direct relation between the degree of hypoventilation and the amount of sleepiness. Many patients with emphysema and a considerably raised P_{CO_2} are not drowsy at all. It is possible that respiratory movement itself is an alerting mechanism (Kilburn *et al.*, 1959a).

Macintosh (1951) noted that if spinal anaesthesia extended above the thoracic region, the patients became drowsy. Diminished stimulation from proprioceptors in the lungs and chest wall may induce the drowsiness which perpetuates the hypoventilation. Even when ventilating normally, patients with dystrophia may have diminished proprioceptive stimulation from their wasted muscles. An injection of thiopentone sets off this self-perpetuating cycle.

The most striking abnormality which we found in all our patients was a gross reduction in the maximum expiratory pressure. We do not think that this was due to weakness of the facial muscles and an inability to close the lips round the mouthpiece: in three cases intra-oesophageal pressures were measured and found to be of the same order. There was a highly significant difference in M.E.P. between the means of the cases and a series of normal controls.

The low M.E.P. is due to weakness of the muscles of expiration and reduces the efficacy of the cough mechanism. Weakness of the laryngeal and pharyngeal muscles would further impair the ability to cough effectively. This may well account for the high incidence of lung infection and post-anaesthetic complications in these patients.

SUMMARY AND CONCLUSIONS

The lung function of patients with dystrophia myotonica varies greatly, depending on the severity of the disease and whether or not respiratory muscles are affected. In our group, unlike those previously reported, there was evidence of hypoventilation in only one case under normal conditions. The ventilatory response to CO_2 was normal, and myotonia of the respiratory muscles was not produced by CO_2. Three cases however showed prolonged depression of respiration after a small dose of thiopentone, and an exaggeration of the normal response to drowsiness or narcosis. Anaesthesia is undoubtedly dangerous in these patients: there is no reason to suppose that this danger is confined to thiopentone. The simple lung function test which reveals most convincingly the disability of these patients is the maximum expiratory pressure: spirometry and mixed venous P_{CO_2} are often normal even in those whose respiratory reserve is greatly diminished.

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