THE PULMONARY ABNORMALITIES IN MYXEDEMA * †

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The purpose of this paper is to report a study of lung function in patients with myxedema. Recently we studied 28 obese persons and found 10 who had alveolar hypoventilation manifested by increased arterial P_{CO_2} (2). They had either lung disease or myxedema in association with their obesity. The nature of pulmonary involvement in patients with myxedema has not been studied. Why did patients with obesity and myxedema develop alveolar hypoventilation? We postulated that patients with myxedema might have one or all of the following: a depression of the respiratory center in the brain, interference with neural conduction or with neuromuscular transmission to the respiratory muscles, disease of the respiratory muscles, or a change in the character of the alveolar capillary membrane.

The existence of central nervous system abnormalities in myxedema is known. In 1904, Gull (3) included myxedema under "Diseases of the Nervous System" in a collection of his writings. Scheinberg, Stead, Brannon and Warren (4) measured cerebral blood flow in eight patients with myxedema by the nitrous oxide technique and found that the average cerebral blood flow was 38 per cent below normal, oxygen and glucose consumption 27 per cent below normal, and cerebral vascular resistance 91 per cent above normal. Browning, Atkins and Weiner (5) found encephalographic changes in seven psychotic adults with myxedema. The electroencephalogram returned toward normal as the patient's myxedema improved. These are a few of the many studies which indicate that central nervous system involvement exists in myxedema. It is reasonable to postulate that the respiratory center could be involved.

The fact that there are lesions in the muscles and perhaps changes in neural conduction or neuromuscular transmission to the muscles is established. Pathologic studies have demonstrated a mucoid substance in skin, subcutaneous tissue, mucous membranes of the upper respiratory tract (6), and skeletal muscles (7–9) in severe myxedema. Lambert, Underdahl, Beckett and Mederos (10) believe the slow ankle jerk in myxedema is caused by an abnormality of the contractile mechanism of the muscle rather than by changes in the neural elements of the reflex or in the mechanism of excitation of the muscle. Waldstein, Bronsky, Schrifter and Oester (11) inserted needle electrodes directly into the muscle of patients with myxedema and found abnormal electromyograms which reverted to normal after treatment of the patients with desiccated thyroid. Ingold (12) abolished the prolonged muscle contraction and relaxation time in myxedematous rats by blocking transmission at the neuromuscular junction with curare. Whether the primary lesion involves the muscle, neural conduction, or neuromuscular transmission is beyond the scope of this paper. "Muscular" involvement might be expected to produce changes in the patient's ability to ventilate his lungs.

Evidence of capillary involvement in myxedema is available. Zondek, Michael and Kaatz (13) studied the ungual limbus capillaries in six patients with myxedema and found them to be reduced in number and size. After thyroid therapy the capillaries were present in normal number and the caliber of the vessels was normal. Lange (14) studied five patients with myxedema and found a large increase in capillary permeability which returned to normal following treatment of the myxedema. In autopsy material, Baker and Ham-

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ilton (15) found thickening of the walls of the capillaries of the heart in myxedema. Foster and Barr (7) found slight but definite fibrous thickening of the alveolar walls of a patient who died with severe myxedema. It is reasonable to postulate similar lesions in the pulmonary capillaries which might cause reduction in the diffusing capacity of the lungs.

This paper reports studies of pulmonary function in 26 patients with myxedema before treatment. Twenty-one were studied again after treatment with desiccated thyroid or triiodothyronine.

METHODS

The patients were selected from the wards and clinics of the University Hospitals and Veterans Administration Hospital, Iowa City. Each patient had a complete history, physical examination, roentgenogram of the chest, thyroid function studies and other indicated laboratory tests. The diagnosis of myxedema was based on characteristic history, physical findings and laboratory findings. We required that the protein-bound iodine determination be below 3.0 μg. per 100 ml. of plasma (the range of normal values in the biochemistry laboratory, University Hospitals, is 3.5 to 8.0 μg. per 100 ml. of plasma); and that the radioactive iodine uptake at 24 hours be less than 10 per cent (the range of normal values in the radiation laboratory, University Hospitals, is 15 to 45 per cent). Pulmonary disease was excluded if the patient had no symptoms of lung disease, no physical findings of lung disease, and a normal roentgenogram of the chest. The basal metabolic rate was measured by standard techniques using the Sanborn basal metabolism apparatus. The protein-bound iodine determinations were performed by a slight modification of Barker, Humphrey and Soley's method (16). The 24 hour uptake of radioactive iodine was measured in the Radiation Research Laboratory by the method of Evans (17). The fasting total serum cholesterol was determined by the method of Pearson, Stern and McGavack (18). Thyroid stimulating hormone (TSH) stimulation tests were done when indicated to help differentiate primary from secondary myxedema. Pulmonary function tests and arterial blood studies were done in the morning after the patient had eaten breakfast, according to methods previously described from this laboratory (2). Predicted normal values for vital capacity were calculated on the basis of the patient's height (19). Predicted normal values for inspiratory capacity are 75 per cent of predicted vital capacity; predicted normal values for expiratory reserve volume are 25 per cent of predicted vital capacity. Predicted normal values for total lung capacity were calculated as follows: for patients 15 to 34 years in age, the predicted vital capacity divided by 0.80 (20); for patients 35 to 50 years in age, the predicted vital capacity divided by 0.766 (20); and for patients over 50 years in age, the predicted vital capacity plus 2,430 ml. (21). The predicted normal values for the maximal breathing capacity (MBC) were the mean values found by Baldwin, Cournand and Richards (22) taking into consideration sex and age of the subject but not body surface area. The predicted normal values for the diffusing capacity of the lung for carbon monoxide (D_{Lco}) were based on the regression equation of Ogilvie, Forster, Blakemore and Morton (23) which is D_{Lco} = height (in inches) × 0.874 − 31.6.

Six of our patients were extremely obese and had myxedema. After the initial studies were completed, these were given an 800 calorie diet and desiccated thyroid or triiodothyronine. When possible, patients were hospitalized until they were nearly euthyroid and had lost 50 to 100 pounds. Sometimes this took six months. Four patients had clinical evidence of lung disease in addition to myxedema.

The remaining 16 patients had myxedema, but no clinical evidence of lung disease. These patients were usually hospitalized for "initial" pulmonary studies and the initiation of thyroid therapy. Then they were seen at three month intervals in the medical out-patient department. At the return visit, each patient had an interval history, physical examination and the necessary thyroid function tests. Most of the patients in this group were judged to be euthyroid or nearly so by the time of the last study.

Statistical analysis of the data was done using the test of significant difference in paired data by the method of Fisher (24). The formula used was:

$$t_{(n-1)} = \frac{\bar{d}}{\sqrt{\frac{\Sigma (d - \bar{d})^2}{n (n - 1)}}}$$

where $\bar{d}$ = the difference between the means, $\Sigma (d - \bar{d})$ = sum of the squares of the individual differences minus the difference between the means and n = number of patients studied.

The patients are divided into two groups. Sixteen patients had myxedema but no evidence of lung disease and are considered in Group I. Patients in Group II had myxedema and either (A) were obese (six patients) or (B) had lung disease (four patients).

RESULTS

A. Patients with myxedema but no clinical lung disease

This group consists of 16 patients whose age range was 26 to 68 years. There were 6 men and 10 women. The average weight of the group was 161 pounds. The results of thyroid function studies in these patients are listed in Table I. The mean basal metabolic rate was minus 27; mean protein-bound iodine was 2.0 μg. per 100 ml. of plasma; mean 24 hour radioactive iodine uptake was 3.3 per cent; mean total cholesterol was 399

mg. per 100 ml. of serum. The type of myxedema, the duration of symptoms and the daily dose of desiccated thyroid or triiodothyronine are shown in Table I. All but one of the patients (M. M.) were studied before thyroid treatment was started. The results of pulmonary function studies in these patients are listed in Tables II and III. The lung volumes were normal. Distribution of inspired air was slightly uneven in six patients as measured by the single breath nitrogen test, but normal as measured by the less sensitive test based on the per cent of nitrogen at the end of seven minutes of oxygen breathing. There were slight abnormalities in the mechanical tests. The mean maximal breathing capacity was 82 per cent of predicted normal. The maximal expiratory flow rate averaged 224 L. per minute while the maximal inspiratory flow rate averaged 154 L. per minute. The mean D_{LCO} was definitely reduced, being 68 per cent of predicted normal.

Thirteen patients in this group were studied after approaching or reaching the euthyroid state. The diuresis produced by therapy caused a significant mean weight loss of 14 pounds ($p < 0.01$). The mean basal metabolic rate increased significantly from -28 to -8 ($p < 0.01$); the mean protein-bound iodine increased significantly from 1.9 to 5.9 μg. per 100 ml. of plasma ($p < 0.01$); while the total cholesterol decreased significantly from 431 to 249 mg. per 100 ml. of serum ($p < 0.001$). Treatment did not alter the lung volumes significantly. Mean alveolar ventilation increased slightly from 4.0 to 4.6 L. ($p > 0.2$). In response to breathing 7.5 per cent CO_2 in air, the mean minute volume of ventilation in these 10 patients increased from 18.7 to 21.6 L. ($p > 0.3$). Alveolar gas distribution as measured by the single breath nitrogen test did not change significantly ($p > 0.9$). The maximal breathing capacity increased significantly from a mean of 78 to 102 per cent of predicted normal ($p = < 0.01$). The mean expiratory flow rate was 213 L. per minute before thyroid replacement and 250 L. per minute afterward ($p > 0.1$). The maximal inspiratory flow rate increased from a mean of 152 to 167 L. per minute ($p > 0.4$). The D_{LCO} in 12 patients increased significantly from a mean of 69 to a mean of 93 per cent of predicted normal ($p < 0.01$).

The results of arterial blood studies in these patients are listed in Table IV. Mean arterial oxygen saturation at rest was 97 per cent, mean pCO_2 was 39 mm. Hg, mean pH was 7.41, and the mean hematocrit was 35 per cent. Thyroid administration to these patients produced no significant changes except that the mean hematocrit increased from 35 to 40 per cent ($p = < 0.05$).

B. Patients with myxedema and obesity

This group is composed of six patients, five women and one man, with myxedema, whose mean weight was 294 pounds. Their ages ranged from 41 to 67 years. The initials, physical characteristics, results of thyroid function tests, type of myxedema, duration of symptoms and daily dose of thyroid in these patients are listed in Table V. The mean basal metabolic rate was minus 17; the mean protein-bound iodine was 1.6 μg. per 100 ml. of serum; the mean 24 hour uptake of radioactive iodine was 2.8 per cent; the mean total cholesterol was 461 mg. per 100 ml. of serum. Five had primary myxedema and one had myxedema following radioactive iodine therapy for thyrotoxicosis. The average duration of symptoms in this group was 8.5 years. Two of the patients (H. K. and E. K.) received small doses of desiccated thyroid before the initial studies were done. Four patients were restudied after treatment with a reducing diet and desiccated thyroid or triiodothyronine. The mean initial weight in these four patients was 292 pounds and at the time of last study it was 223 pounds, a mean loss of 69 pounds.

The results of lung volume studies in these patients are listed in the top half of Table VI. Initially, the lung volumes were reduced. Mean inspiratory capacity was 76 per cent of predicted normal; mean expiratory reserve volume was 64 per cent of predicted normal; mean vital capacity was 71 per cent of predicted normal and mean total lung capacity was 66 per cent of predicted normal. In the four patients studied after therapy, the lung volumes returned to or toward normal.

In the top half of Table VII, the results of ventilatory studies, respiratory mechanics and diffusion are listed. Initially, in these six patients with myxedema and obesity, the mean minute volume of ventilation was 6.4 L. and the mean alveolar ventilation was 2.9 L. The mean maximal breath-

TABLE I

Physical characteristics, thyroid function tests and treatment in patients who have myxedema but no lung disease

Patient	Age	Sex	Ht.	Wt.	Surface area	Date of study	Basal metabolic rate	Protein-bound iodine	Radioactive iodine uptake (24 hr.)	Total cholesterol	Type of myxedema	Duration of symptoms	Daily dose of thyroid
			in.	*lbs.*	*M.²*			*μg./100 ml. plasma*	*%*	*mg./100 ml. serum*		*yrs.*	*mg.*
V. C.	43	F	65	136	1.67	20 June 58	−26	1.6	3	477	Primary	6	None
				115	1.55	15 Sept. 58	− 7	6.4		227			150
L. A.	62	F	63	131	1.62	23 June 58		1.5	3	426	Primary	10	None
				122	1.55	23 Dec. 58	+ 6	5.3		268			60
R. T.	41	M	71	157	1.90	27 June 58	−38	2.2	0	358	Primary	4	None
				148	1.88	8 Oct. 58	−19	1.3		213			100*
M. Mc.	68	F	67	181	1.91	23 Jan. 58	−21	2.7	3	373	Primary	4	None
				165	1.81	7 Oct. 58		3.6		286			60
H. H.	36	F	65	167	1.83	18 Sept. 58	−28	2.7	4	467	I^{131}	1	None
				167	1.83	19 Feb. 59	−12	5.7		295			60
M. M.	68	F	61	167	1.74	10 Dec. 57	−20	1.9	6	507	Primary	8	30
				154	1.72	27 Mar. 58							120
W. P.	26	M	61	203	1.90	16 Dec. 57	−44	0.9	0	347	Primary	11	None
				203	1.90	23 Apr. 58							150*
				178	1.80	1 Oct. 58	−18	1.1		401			None
				151	1.67	10 Dec. 58	+ 2	9.3		157			150
M. R.	54	F	63	119	1.54	27 May 58	−29	1.2	3	400	Primary	5	None
				111	1.50	30 Sept. 58	+ 1	3.7		270			60
A. C.	47	F	60	163	1.71	14 July 58	−25	1.2	4	347	Post thyroidectomy	9	None
				162	1.69	18 Feb. 59	− 8	6.7		238			120
G. D.	47	F	65	142	1.70	17 July 58		1.2	4	407	Post thyroidectomy	4	None
				142	1.70	7 Jan. 59		5.5		250			150
W. R.	59	M	68	176	1.93	14 Mar. 58	−21	2.7	3	405	Post thyroidectomy	13	None
				165	1.87	7 Jan. 59	−10	5.5		207			120
A. F.	57	F	62	157	1.71	8 Oct. 57	−16		2	732	Post thyroidectomy	40	None
				124	1.55	22 Sept. 58	−13			325			90
Cl. P.	35	M	67	138	1.72	4 Dec. 57		3.4	2	260	Post hypophysectomy	1/12	None
				139	1.72	18 Feb. 58		7.5					120
C. P.	50	M	69	156	1.85	3 Mar. 58	−20	2.1	6	257	Pituitary	2	None
L. M.	66	F	66	199	1.98	11 Sept. 58	−26	2.3	5	220	Primary	10	None
E. D.	60	M	70	186	2.00	4 Mar. 59	−39		4	400	Primary	13	None
Mean (initial) 16 patients				161	1.79		−27†	2.0‡	3.3	399		8.8	
Mean (before treatment) 13 patients				157	1.76		−28§	1.9‖		431‖			
Mean (after treatment) 13 patients				143	1.70		− 8§	5.9‖		249‖			

* Triiodothyronine (micrograms).
† Mean value represents only 13 patients.
‡ Mean value represents only 14 patients.
§ Mean value represents only 8 patients.
‖ Mean value represents only 11 patients.

TABLE II

Lung volumes in patients with myxedema but no lung disease

Patient	Date of study	Inspiratory capacity		Expiratory reserve volume		Vital capacity		Residual volume		Total lung capacity		Residual volume/ total lung capacity ratio ×100
		ml.	%*	*ml.*	%*	*ml.*	%†	*ml.*	%*	*ml.*	%*	
V. C.	20 June 58	2,080	84	1,330	160	3,410	103	1,660	164	5,070	118	33
	15 Sept. 58	1,700	69	1,410	170	3,130	95	2,530	250	5,660	131	45
L. A.	23 June 58	1,520	63	700	88	2,220	69	1,920	79	4,140	74	46
	23 Dec. 58	1,390	58	870	109	2,260	71	1,980	81	4,240	75	47
R. T.	27 June 58	2,670	79	2,940	260	5,570	124	2,600	188	8,170	139	32
	8 Oct. 58	3,430	101	2,390	212	5,820	129	2,090	151	7,910	134	26
M. Mc.	23 Jan. 58	2,280	89	870	102	3,210	94	1,110	46	4,320	74	26
	7 Oct. 58	2,460	96	1,140	134	3,600	106	1,710	70	5,310	91	32
H. H.	18 Sept. 58	2,130	86	2,150	262	4,280	130	1,700	168	5,980	139	28
	19 Feb. 59	2,720	110	1,430	174	4,150	126	1,890	187	6,040	140	31
M. M.	10 Dec. 57	2,280	98	660	86	2,860	92	1,700	70	4,560	82	37
	27 Mar. 58	2,150	92	450	58	2,600	84					
W. P.	16 Dec. 57	2,630	91	230	24	2,770	72	990	102	3,760	78	26
	23 Apr. 58	2,740	94	250	26	2,990	77	1,520	157	4,510	93	34
	1 Oct. 58	2,620	90	880	91	3,500	90	1,220	126	4,710	97	26
	10 Dec. 58	2,530	87	1,180	122	3,710	96	1,610	166	5,320	110	30
M. R.	27 May 58	2,100	88	1,420	178	3,520	110	1,770	73	5,290	94	33
	30 Sept. 58	2,330	97	1,220	153	3,550	111	2,270	93	5,820	103	39
A. C.	14 July 58	2,080	91	640	84	2,720	89	1,410	152	4,130	104	34
	18 Feb. 59	2,250	98	410	54	2,660	87	1,150	124	3,810	96	30
G. D.	17 July 58	2,500	101	1,010	123	3,510	106	2,030	201	5,540	129	37
	7 Jan. 59	2,540	102	820	100	3,360	102	1,790	177	5,150	119	35
W. R.	14 Mar. 58	2,360	73	760	70	3,120	72	3,410	140	6,530	97	52
	7 Jan. 59	3,210	99	860	80	4,070	94	2,730	112	6,800	101	40
A. F.	8 Oct. 57	2,240	95	360	46	2,500	79	1,060	44	3,560	64	30
	22 Sept. 58	2,020	86	480	61	3,110	99	1,540	63	4,650	83	33
Cl. P.	4 Dec. 57	2,450	77	1,190	112	3,570	84	1,760	135	5,330	96	33
	18 Feb. 58	2,750	86	1,260	119	4,010	94	1,340	103	5,350	96	25
C. P.	3 Mar. 58	2,000	61	1,860	171	3,860	88	1,770	132	5,630	98	31
L. M.	11 Sept. 58	2,440	97	250	30	2,690	80	1,560	64	4,250	74	37
E. D.	4 Mar. 59	2,800	84	440	40	3,240	73	1,840	76	5,080	74	36
Mean (initial) 16 patients			85		115		92		115		96	34
Mean (before treatment) 13 patients			86		123		94		124‡		101‡	34‡
Mean (after treatment) 13 patients			91		119		99		131‡		107‡	34‡

* Per cent of predicted normal value. † Per cent of predicted value based on height. ‡ Mean value represents only 12 patients.

TABLE III

Studies of ventilation, respiratory mechanics and diffusion in patients with myxedema but no lung disease

Patient	Date of study	Ventilation: Minute volume (Air) Total	Ventilation: Minute volume (Air) Alveolar	Ventilation: Minute volume (7.5% CO_2) Total	Ventilation: Physiologic dead space		Ventilation: Alveolar gas distribution: 7 min. washout	Ventilation: Alveolar gas distribution: Single breath N_2 test	Mechanical tests: Maximal breathing capacity		Mechanical tests: Maximal expiratory flow rate	Mechanical tests: Maximal inspiratory flow rate	Diffusion	
		L.	*L.*	*L.*	*ml.*	%*	% N_2†	% N_2‡	*L./min.*	%§	*L./min.*	*L./min.*	*mm. CO/mm. Hg/min.*	%‖
V. C.	20 June 58	5.5	3.5	9.1	136	37	0.6	1.5	65	73	214	188	24	96
	15 Sept. 58	8.0	4.9	19.7	194	39	2.2	3.8	73	82	177	162	26	104
L. A.	23 June 58	5.1	2.6	15.9	179	48	2.5	1.3	47	64	136	158	14	58
	23 Dec. 58	6.1	3.2	17.4	159	48	2.6	1.1	55	75	100	171	14	58
R. T.	27 June 58	4.3	2.9	14.6	182	33	1.6	1.1	155	142	361	190	18	58
	8 Oct. 58	5.1	3.5	28.0	200	31	0.8	2.0	156	143	408	291	36	116
M. Mc.	23 Jan. 58	6.4	3.5	12.8	282	45	0.5	2.5	31	42	169	91	10	37
	7 Oct. 58	7.6	5.0	22.7	218	35	0.6	2.7	67	91	200	134	19	70
H. H.	18 Sept. 58	5.8	3.4	16.8	114	33	0.8	1.0	109	122	207	162	27	108
	19 Feb. 59						0.9	0.8	112	125	327	220	38	152
M. M.	10 Dec. 57	5.5	3.0		221	45	4.0	1.5	78	106	240	222	24	109
	27 Mar. 58							1.5	77	105	194	171		
W. P.	16 Dec. 57	6.9	4.3	30.0	314	63	0.5	1.0	49	39	182	70	9	41
	23 Apr. 58	13.0	8.6	40.1	200	34	0.7	0.6	52	41	267	92	10	45
	1 Oct. 58	9.3	4.6	11.7	322	50	1.1	0.5	75	60	182	93	20	91
	10 Dec. 58	10.9	4.7	18.7	248	56	0.5	0.5	100	79	215	151	23	105
M. R.	27 May 58	5.7	3.6	6.4	194	37	0.5	0.5	63	86	240	135	17	71
	30 Sept. 58						0.5	0.6	85	116	325	224	16	67
A. C.	14 July 58	7.1	5.2	24.0	124	44	0.5	2.6	39	44	235	130	19	90
	18 Feb. 59	6.9	4.8	35.9	106	30	0.3	0.8	83	93	270	150	22	105
G. D.	17 July 58	6.3	4.8	18.7	205	24	1.2	4.1	80	90	261	174	20	80
	7 Jan. 59	8.7	7.0	17.5	131	20	1.6	1.2	86	96	248	105	20	80
W. R.	14 Mar. 58	11.7	4.8	16.9	222	35	0.2	2.0	62	68	145	125	18	64
	7 Jan. 59	9.5	5.8	13.8	236	39	0.5	2.3	105	116	290	137	26	93
A. F.	8 Oct. 57	6.3	3.4	21.6	230	46	0.5	3.4	43	59	160	128	11	48
	22 Sept. 58	7.2	4.5	29.8	182	38	0.5	1.0	96	131	214	124	21	91
Cl. P.	4 Dec. 57	8.5	5.3	23.1	294	38	0.0	1.3	86	79	218	207	21	78
	18 Feb. 58	4.9	2.5	12.8	212	49	0.3	3.8	85	78	286	125	22	81
C. P.	3 Mar. 58	12.8	6.2	23.0	264	52	0.8	1.9	105	116	295	225	17	59
L. M.	11 Sept. 58	5.1	3.6	16.2	128	29	0.8	1.2	84	114	174	136	17	65
E. D.	4 Mar. 59	3.8	2.2	17.5	208	43	0.8	1.1	68	75	350	130	11	37
Mean (initial) 16 patients		6.7	3.9	17.8**	206	41	1.0	1.8		82	224	154	17	68
Mean (before treatment) 13 patients		6.8¶	4.0¶	18.7¶	217¶	41¶	0.8††	1.8		78	213	152	17††	69††
Mean (after treatment) 13 patients		7.5¶	4.6¶	21.6¶	189¶	39¶	0.9††	1.7		102	250	167	24††	93††

* Per cent of tidal volume.
† Normal values for seven minute nitrogen washout are less than 2.5 per cent N_2.
‡ Normal values for single breath nitrogen test are less than 1.5 per cent N_2.
§ Per cent of predicted value based on age.
‖ Per cent of predicted value based on height.
¶ Mean value represents only 10 patients.
** Mean value represents only 15 patients.
†† Mean value represents only 12 patients.

TABLE IV

Arterial blood studies in patients with myxedema but no lung disease

Patient	Date of study	O_2 content (rest)	O_2 capacity	O_2 saturation		pCO_2 (rest)	pH (rest)	Hematocrit
				Rest	100% O_2*			
		vol. %	*vol. %*	%	%	*mm. Hg*		%
V. C.	20 June 58	13.30	13.61	97.7	100 + 1.71	38	7.43	33
	15 Sept. 58	15.34	15.88	96.6	100 + 1.99	40	7.37	39
L. A.	23 June 58	13.59	13.04	100 + 0.3	100 + 2.69	44	7.38	36
	23 Dec. 58	13.96	15.27	91.4	100 + 1.20	41	7.40	38
R. T.	27 June 58	10.03	10.31	97.3	100 + 1.94	41	7.42	30
	8 Oct. 58	14.78	14.69	100 + 0.1	100 + 1.86	40	7.41	37
M. Mc.	23 Jan. 58	15.35	15.30	100 + 0.1	100 + 2.21	41	7.33	41
	7 Oct. 58	17.45	18.09	96.5	100 + 1.71	36	7.41	45
H. H.	18 Sept. 58	14.95	15.65	95.5	100 + 1.76	40	7.41	37
	19 Feb. 59							44
M. M.	10 Dec. 57	14.94	15.38	97.1	100 + 3.14	46	.7.35	38
W. P.	16 Dec. 57	6.45	6.87	93.9	100 + 1.21	45	7.38	20
	23 Apr. 58	7.39	7.33	100 + 0.1	100 + 1.87	36	7.44	24
	1 Oct. 58	17.64	17.62	100 + 0.02	100 + 1.98	34	7.45	44
	10 Dec. 58	16.46	16.44	100 + 0.02	100 + 2.14	38	7.43	43
M. R.	27 May 58	11.99	12.47	96.2		35	7.50	30
	30 Sept. 58							35
A. C.	14 July 58	16.59	16.19	100 + 0.4	100 + 2.23	32	7.45	40
	18 Feb. 59	16.24	16.06	100 + 0.2	100 + 1.94	33	7.48	40
G. D.	17 July 58	15.83	15.13	100 + 0.7	100 + 2.48	35	7.43	40
	7 Jan. 59	15.70	15.89	98.8	100 + 2.30	36	7.42	43
W. R.	14 Mar. 58	13.76	14.12	97.5	100 + 1.61	36	7.40	33
	7 Jan. 59	17.22	16.39	99.0	100 + 1.98	37	7.41	39
A. F.	8 Oct. 57	13.23	13.65	96.9	100 + 1.58	40	7.38	40
	22 Sept. 58	15.04	14.59	100 + 0.5	100 + 1.87	36	7.39	37
Cl. P.	4 Dec. 57	15.15	15.96	94.9	100 + 1.28	44	7.42	38
	18 Feb. 58	15.75	16.25	96.9	100 + 1.33	37	7.32	38
C. P.	3 Mar. 58	11.02	10.19	100 + 0.8	100 + 2.42	39	7.33	29
L. M.	11 Sept. 58	16.39	17.71	94.1	100 + 1.27	34	7.45	42
E. D.	4 Mar. 59	10.43	11.31	92.2	100 + 1.65	36	7.46	31
Mean (initial) 16 patients				97.1		39	7.41	35
Mean (before treatment) 10 patients				97.8		40	7.40	35†
Mean (after treatment) 10 patients				97.9		37	7.40	40†

* Values following + sign refer to milliliters of O_2 per 100 ml. blood in excess of that required to saturate hemoglobin (*i.e.*, dissolved O_2). Normal value for dissolved O_2 is 2.00 ml.

† Mean value represents 12 patients.

ing capacity was 68 per cent of predicted normal. The maximal expiratory flow rate averaged 135 L. per minute while the mean inspiratory flow rate was 101 L. per minute. The mean D_{LCO} was low, being only 60 per cent of predicted normal. In the four patients studied after therapy, the mean minute volume of ventilation increased from 5.9 to 8.9 L. and the mean alveolar ventilation increased from 2.9 to 5.5 L. The mean maximal breathing capacity increased from 73 to 114 per cent of predicted normal. The mean maximal expiratory flow rate increased from 125 to 275 L. per minute and the mean inspiratory flow rate increased from 90 to 182 L. per minute. The D_{LCO} increased from 14 to 22 ml. CO per mm. Hg per minute (or from 57 to 88 per cent of predicted normal).

The results of arterial blood studies in these patients are shown in the top part of Table VIII. Pulmonary insufficiency for oxygenation and carbon dioxide elimination was present in five of the six patients. The mean arterial oxygen saturation was 84 per cent; the mean pCO_2 was 55 mm. Hg and the mean pH was 7.35. The mean hemato-

TABLE V

Physical characteristics, thyroid function tests, and treatment of: ***A.*** *patients with myxedema and obesity;* ***B.*** *patients with myxedema and lung disease*

Patient	Age	Sex	Ht.	Wt.	Body surface area	Date of study	Basal metabolic rate	Protein-bound iodine	Radio-active iodine uptake (24 hrs.)	Total serum choles-terol	Type of myxedema	Dura-tion of symp-toms	Daily dose of thyroid	Associated disease
			in.	*lbs.*	*M.²*			*μg./100 ml. plasma*	*%*	*mg./100 ml. serum*		*yrs.*	*mg.*	
A. Patients with myxedema and obesity														
L. R.	67	F	64	388	2.62	14 Mar. 57	− 3	0.7	1	247	Primary	10	None	Obesity
				308	2.34	4 June 57				248			120	
				245	2.16	21 Nov. 57		4.3		287			120	
				223	2.04	7 Apr. 58							120	
				221	2.03	9 Oct. 58	+10	2.8		303			120	
H. K.	53	F	63	277	2.20	22 Jan. 58	−17	2.6	2	432	Primary	20	15	Obesity
				254	2.15	14 Feb. 58		4.7		139			120	
				241	2.10	6 Mar. 58							120	
				239	2.09	15 Apr. 58				305			120	
				250	2.14	3 Sept. 58	+ 4	7.2		283			150	
B. B.	54	M	70	261	2.32	17 Sept. 58	−44	0.5	1	659	Primary	12	None	Obesity
				238	2.23	14 Oct. 58				349			10*	
				231	2.21	4 Nov. 58	−28			272			35*	
				200	2.10	25 Feb. 59	−20			174			50*	
E. K.	66	F	61	240	2.09	12 Sept. 58	+10	2.3	8	344	I^{131}	2	60	Obesity
				219	1.95	21 Jan. 59	+30	3.7		277			120	
K. P.	41	F	65	318	2.43	3 Sept. 57	−21	1.4	2	677	Primary	2	None	Obesity
Mar. R.	67	F	67	279	2.31	25 Sept. 58	−29	2.3	3	407	Primary	5	None	Obesity
Mean (initial) 6 patients				294	2.33		−17	1.6	2.8	461		8½		
Mean (before treatment) 4 patients				292	2.31		−14	1.9†		420				
Mean (after treatment) 4 patients				223	2.06		+ 6	4.6†		259				
B. Patients with myxedema and clinical lung disease														
B. W.	59	F	62	120	1.52	20 Nov. 57	−15	2.9	1	308	Post thyroidectomy	5	None	Pneumonia
M. Mar.	73	F	64	117	1.54	9 Apr. 58	− 1	2.1	3	308	Post thyroidectomy	1½	None	Heart failure
A. L.	54	F	64	167	1.79	24 June 58	−19		2	710	Primary	14	None	Heart failure
W. H.	70	M	71	179	2.00	30 June 58	−41	7.2‡	6.9‡	430	Secondary to iodides	⅓	None	Pulmonary emphysema
Mean 4 patients				146	1.71		−19	2.5§	2†	439		5.2		

* Triiodothyronine (micrograms).
† Mean value represents only three patients.
‡ This patient received iodides prior to this test.
§ Mean value represents only two patients.

TABLE VI

Lung volumes in: A. patients with myxedema and obesity; B. patients with myxedema and lung disease

Patient	Date of study	Inspiratory capacity		Expiratory reserve volume		Vital capacity		Residual volume		Total lung capacity		Residual volume/ total lung capacity ratio ×100
		ml.	%*	*ml.*	%*	*ml.*	%†	*ml.*	%*	*ml.*	%*	
A. Patients with myxedema and obesity												
L. R.	14 Mar. 57	1,240	51	410	51	1,550	48	1,390	57	2,940	52	47
	4 June 57	1,330	55	1,120	138	2,380	73	600	25	2,980	52	20
	21 Nov. 57	1,760	72	1,360	168	2,990	92	940	39	3,930	69	24
	7 Apr. 58	2,080	85	1,040	128	3,220	99	1,530	63	4,750	84	32
	9 Oct. 58	2,430	100	880	109	3,310	102	1,310	54	4,620	81	28
H. K.	22 Jan. 58	1,790	75	860	108	2,570	80	740	30	3,310	59	22
	14 Feb. 58	1,760	73	1,080	135	2,830	88	1,090	45	3,920	70	28
	6 Mar. 58	1,850	77	1,110	139	2,950	92	1,230	51	4,180	74	29
	15 Apr. 58	2,210	92	780	98	2,990	93	890	37	3,880	69	23
	3 Sept. 58	2,200	92	800	100	3,000	94	1,010	42	4,010	71	25
B. B.	17 Sept. 58	2,810	84	920	83	3,730	84	1,950	80	5,680	83	34
	14 Oct. 58	2,850	85	1,100	99	3,950	89	1,530	63	5,480	80	28
	4 Nov. 58	3,280	98	1,170	105	4,450	100	1,830	75	6,280	91	29
	25 Feb. 59	3,530	106	1,820	164	5,350	120	2,220	91	7,570	110	29
E. K.	12 Sept. 58	1,600	69	270	35	1,870	60	1,430	59	3,330	60	43
	21 Jan. 59	1,640	71	390	50	2,030	65	1,640	67	3,670	66	45
K. P.	3 Sept. 57	2,340	94	430	52	2,750	83	910	90	3,660	85	25
Mar. R.	25 Sept. 58	2,120	83	480	56	2,450	72	980	40	3,430	59	29
Mean (initial) 6 patients			76		64		71		59		66	33
Mean (before treatment) 4 patients			70		69		68		57		64	37
Mean (after treatment) 4 patients			92		106		96		63		82	32
B. Patients with myxedema and lung disease												
B. W.	20 Nov. 57	1,390	59	720	91	2,030	64	1,250	51	3,280	59	38
M. Mar.	9 Apr. 58	1,120	46	960	119	2,080	64	2,220	91	4,300	76	52
A. L.	24 June 58	1,240	51	160	20	1,400	43					
W. H.	30 June 58	3,040	90	1,150	102	4,190	93	3,860	159	8,050	116	48

* Per cent of predicted normal value.
† Per cent of predicted value based on height.

crit was 43 per cent. Four patients were studied after treatment. The mean arterial oxygen saturation increased from 80 to 93 per cent; the mean pCO_2 decreased from 61 to 40 mm. Hg and the pH increased from 7.32 to 7.40. The mean hematocrit decreased from 44 to 40 per cent.

C. Patients with myxedema and clinical lung disease

This group consists of four patients with myxedema and clinical lung disease. One woman had pneumonia; two women had pulmonary edema secondary to heart disease and one man had pulmonary emphysema. The results of pulmonary function studies and arterial blood studies in these patients are listed in the lower half of Tables VI, VII and VIII.

DISCUSSION

Lung volumes

In contrast to previous investigators (25, 26), we found the vital capacity was essentially normal in 16 patients with uncomplicated myxedema, regardless of the cause. Our results are similar to those obtained by Schnitker, Van Raalte and Cutler (27). In patients with angina pectoris they induced myxedema by total thyroidectomy. Their patients had a normal vital capacity after induction of myxedema. Our patients with myxedema and obesity had moderate reduction in inspiratory capacity, expiratory reserve volume, vital capacity, residual volume and total lung capacity. Obese patients without myxedema or lung disease have reduced lung volumes (2). We think that when the two diseases coexist the reduced lung volumes are secondary to obesity. When the obese patients lost weight, their lung volumes returned to normal (Table VI).

Ventilation

Patients with myxedema alone ventilated adequately as measured by minute volume of ventilation, arterial pCO_2 and arterial O_2 saturation. They had a lower minute volume of ventilation following the stimulus of breathing 7.5 per cent carbon dioxide in air than did a group of normals. In the normals, the mean minute volume during the third minute of carbon dioxide breathing was 31.2 L. as compared to 17.8 L. for the 16 patients with myxedema alone. Whether this diminished response represents primary depression of the respiratory center in the brain or inability of the chest bellows to respond adequately to the stimulus is unknown. Treatment of the myxedema resulted in a small but not significant increase in the minute volume of ventilation of these patients in response to breathing 7.5 per cent carbon dioxide in air.

Four of the six patients with myxedema and obesity had alveolar hypoventilation manifested by increased arterial pCO_2 and low alveolar ventilation. The existence of alveolar hypoventilation in any patient must be caused by lung disease, malfunction of the chest bellows, inadequate neuromuscular coordination, or a central nervous system lesion. The physiologic problem is to identify which of these four causes the derangement of the function. Lung disease and disease of the bony thorax are excluded in these patients. The trouble must be either in the respiratory center in the brain, the muscles of respiration, or neuromuscular coordination singly or in combination. We have no proof of what comes first or of how many mechanisms are involved. We suspect that the muscles of respiration and neuromuscular coordination are impaired. The evidence which favors this is that patients with myxedema alone do have a significantly reduced maximal breathing capacity. The added burden of obesity results in further reduction in maximal breathing capacity and slowing of both expiratory and inspiratory flow rates. The process is reversible because treatment of the patients with myxedema and obesity resulted in restoration of normal alveolar ventilation in most patients. This took place gradually and over a period of several months as illustrated by L. R., H. K. and B. B. (Tables V through VIII).

Mechanics of breathing

The patients with myxedema alone had reduced maximal breathing capacity which increased significantly following therapy. The ability of a patient to perform this test well is dependent on the cooperation of the patient, the force of the respiratory muscles, and the patency of the respiratory airways. We did not measure airway resistance. We believe the patients were cooperative. We

TABLE VII

Studies of ventilation, respiratory mechanics, and diffusion in: A. patients with myxedema and obesity; B. patients with myxedema and lung disease

Patient	Date of study	Ventilation: Minute volume (Air) Total	Ventilation: Minute volume (Air) Alveolar	Ventilation: Minute volume (7.5 CO_2) Total	Ventilation: Physiologic dead space		Ventilation: Alveolar gas distribution: 7 min. washout	Ventilation: Alveolar gas distribution: Single breath N_2 test	Mechanical tests: Maximal breathing capacity		Mechanical tests: Maximal expiratory flow rate	Mechanical tests: Maximal inspiratory flow rate	Diffusion	
		L.	*L.*	*L.**	*ml.*	%†	% N_2‡	% N_2§	*L./min.*	%‖	*L./min.*	*L./min.*	*ml. CO/mm. Hg/min.*	%¶
A. Patients with myxedema and obesity														
L. R.	14 Mar. 57	8.5	2.6		126	70	1.3	1.8	70	95	46	64	7	29
	4 June 57	12.0	6.2	27.4	240	52	0.5	0.5	94	127	214	103	8	33
	21 Nov. 57	10.6	4.4		295	59	0.4	0.2	111	150	286	125	15	62
	7 Apr. 58	10.4	5.5	20.1	231	47	0.5	1.2	103	139	333	136	15	62
	9 Oct. 58	9.6	5.6	20.3	197	42	0.6	1.4	127	172	365	188	24	99
H. K.	22 Jan. 58	5.1	2.6	13.3	175	49	0.8	3.6	63	85	203	64	16	68
	14 Feb. 58	6.0	3.6		145	40	0.6	1.8	79	107	207	77	21	89
	6 Mar. 58	5.9	3.0		183	52	0.7	1.0	81	109	188	105	19	81
	15 Apr. 58	6.2	3.7	14.6	128	39	0.6	0.6	90	122	156	92	16	68
	3 Sept. 58	9.3	6.0	16.8	171	35	1.8	1.9	86	116	343	140	18	77
B. B.	17 Sept. 58	4.0	1.7	3.3	201	57	6.2	5.4	43	47	132	114	19	64
	14 Oct. 58	4.5	1.9	5.0	200	57	2.0	4.7	50	55	164	184	19	64
	4 Nov. 58	3.8	0.8	5.5	455	76			62	58	184	106		
	25 Feb. 59	6.3	4.2	15.5	257	34	2.6	3.1	70	77	258	177	26	88
E. K.	12 Sept. 58	5.8	3.0	12.3	180	48	1.5	3.8	48	65	120	116	15	69
	21 Jan. 59	5.8	3.5	12.6	130	41	0.9	2.7	55	74	186	80	26	120
K. P.	3 Sept. 57	7.7	3.7	11.7	200	42	1.7	1.5	57	64	207	136	20	79
Mar. R.	25 Sept. 58	7.2	3.5	25.2	192	52	3.1	0.4	38	51	100	113	14	52
Mean (initial) 6 patients		6.4	2.9	13.2**	179	53	2.4	2.8		68	135	101	15	60
Mean (before treatment) 4 patients		5.9	2.5	9.6††	171	56	2.5	3.7		73	125	90	14	58
Mean (after treatment)		7.8	4.8	15.0††	189	38	1.5	2.3		110	288	146	24	96
B. Patients with myxedema and lung disease														
B. W.	20 Nov. 57	4.3	2.4		218	44	1.9	4.6	31	42	51	111	9	40
M. Mar.	9 Apr. 58	3.2	1.3	6.0	136	59	1.0	2.5	28	38	94	75	24	99
A. L.	24 June 58	8.8	4.1	16.9	186	53			25	34	98	42		
W. H.	30 June 58	8.8	5.4	15.6	366	39	1.7	8.5	53	58	78	100	10	33

* Minute volume after breathing 7.5 per cent CO_2 in air for two minutes.
† Per cent of tidal volume.
‡ Normal values for seven minute nitrogen washout are less than 2.5 per cent N_2.
§ Normal values for single breath test are less than 1.5 per cent N_2.
‖ Per cent of predicted value based on age and sex.
¶ Per cent of predicted value based on height.
** Mean value represents only five patients.
†† Mean value represents only three patients.

TABLE VIII

Arterial blood studies in: A. patients with myxedema and obesity; B. patients with myxedema and lung disease

Patient	Date of study	O_2 content (rest)	O_2 capacity	O_2 saturation		pCO_2 (rest)	pH (rest)	Hematocrit
				Rest	100% O_2*			
		vol. %	*vol. %*	%	%	*mm. Hg*		%
A. Patients with myxedema and obesity								
L. R.	14 Mar. 57	12.34	15.01	82.2	100 + 1.70	54	7.31	41
	4 June 57	13.35	14.82	90.1	100 + 1.50	42	7.37	38
	21 Nov. 57	13.96	14.64	95.4		42	7.36	37
	7 Apr. 58	14.39	14.94	96.3	100 + 2.09	36	7.42	37
	9 Oct. 58	14.50	15.28	94.9	100 + 1.34	33	7.42	36
H. K.	22 Jan. 58	14.35	18.03	79.6	100 + 0.62	60	7.35	44
	14 Feb. 58	14.67	17.47	84.0	100 + 0.30	48	7.39	43
	6 Mar. 58	14.79	17.35	85.2	100 + 1.09	51	7.37	42
	15 Apr. 58	16.02	18.15	89.9	100 + 0.94	49	7.36	45
	15 Apr. 58†	17.81	18.19	97.9		45	7.37	45
	3 Sept. 58	15.96	16.86	94.7	100 + 1.39	43	7.40	43
B. B.	18 Sept. 58	11.74	15.89	73.9	98.5	82	7.27	44
	14 Oct. 58	12.82	16.88	75.6	94.4	76	7.29	38
	4 Nov. 58	14.22	16.32	87.1	100 + 1.37	63	7.35	43
	25 Feb. 59	14.68	15.71	93.4	100 + 1.23	38	7.46	39
E. K.	12 Sept. 58	16.44	19.58	84.0	100 + 0.42	46	7.37	47
	21 Jan. 59	15.34	17.61	87.1	100 + 1.30	44	7.36	43
K. P.	3 Sept. 57	12.99	14.33	90.6	100 + 0.75	49	7.34	37
Mar. R.	25 Sept. 58	15.99	17.60	90.9	100 + 1.17	38	7.43	42
Mean (initial) 6 patients				83.5		55	7.35	43
Mean (before treatment) 4 patients				79.9		61	7.32	44
Mean (after treatment) 4 patients				92.5		40	7.41	40
B. Patients with myxedema and lung disease								
B. W.	20 Nov. 57	9.48	9.35	100 + 0.1	100 + 3.15	40	7.38	26
M. Mar.	9 Apr. 58	21.83	22.78	95.8	100 + 1.98	36	7.44	57
A. L.	24 June 58	13.30	13.88	95.8	100 + 0.91	36	7.45	36
W. H.	30 June 58	15.82	16.18	97.8	100 + 1.58	30	7.46	40

* Values following + sign refer to milliliters O_2 per 100 ml. blood in excess of that required to saturate hemoglobin (*i.e.*, dissolved O_2). Normal value for dissolved O_2 is 2.00 ml.

† Arterial studies done with patient in sitting position.

suspect that the change in the maximal breathing capacity is caused by changes in the respiratory muscles. We have no evidence to demonstrate whether this is an abnormality in the contractile mechanism of the muscles as postulated by Lambert and co-workers (10) or in the neural conduction or neuromuscular transmission. Treatment of the patients with myxedema alone and those with myxedema and obesity resulted in a return of the mechanical tests to or toward normal, suggesting that the "muscular" lesion is reversible.

Diffusion

Patients with myxedema and no lung disease had a diminished D_{LCO} which improved significantly after thyroid therapy. The D_{LCO} depends on several factors: *1*) the capillary surface available for diffusion, *2*) the thickness of the alveolar capillary membrane and *3*) the total amount of hemoglobin in pulmonary capillary blood and the reaction rate of hemoglobin with carbon monoxide. All three of these factors may be altered in myxedema. The work of Zondek and associates (13), Lange (14), and Baker and Hamilton (15) suggests that the capillaries might be reduced in number and size, and that there might be alterations in the walls of the capillaries. Circulating plasma and total blood volumes are diminished in myxedema (28–30). Therefore it is possible that pulmonary capillary blood volume is reduced. In our 13 patients with myxedema and no lung disease studied before and after therapy, the mean hematocrit increased significantly from 35 to 40 per cent ($p = < 0.05$). The D_{LCO} increased significantly

TABLE IX

D_{LCO}, hemoglobin and hematocrit in Patient E. D. before and after transfusion with washed red blood cells

Date	D_{LCO}	Hemoglobin	Hematocrit	Washed red blood cells
	ml. CO/mm. Hg/min.	*Gm./100 ml.*	%	
11 Mar. 59	10	9.3	31	500 cc.
12 Mar. 59	10	10.7	33	
13 Mar. 59	11	10.8	35	500 cc.
16 Mar. 59	11	11.9	37	500 cc.
17 Mar. 59	10	12.5	39	
18 Mar. 59	11	12.8	40	
19 Mar. 59	9	12.3	41	500 cc.
20 Mar. 59	9	12.4	45	
21 Mar. 59	9	13.2	43	
23 Mar. 59	11	13.2	43	

from 69 to 93 per cent of predicted normal ($p = < 0.01$). Rankin, McNeill, and Forster (31) found D_{LCO} reduced in patients with anemia. In our patients the improvement in the hematocrit parallels the improvement in D_{LCO}, especially in Patients W. P. and W. R. However, D_{LCO} increased with little change in hematocrit in Patients M. Mc. and A. F. Patient E. D., who had myxedema, anemia and a low D_{LCO}, was studied in an effort to clarify this point. His other pulmonary function tests were essentially normal. While still frankly myxedematous his hematocrit was elevated from 30 to 44 per cent by transfusions of washed red blood cells; at the same time D_{LCO} remained essentially unchanged (Table IX). This suggests that there is significant reduction in D_{LCO} which is on the basis of capillary changes in the lungs. This suggestion is supported by the studies of D_{LCO} in patients with myxedema and obesity. Patients with obesity alone have a normal D_{LCO} (2). The four patients with myxedema and obesity had a low D_{LCO} and a normal hematocrit before thyroid therapy and a normal D_{LCO} and slight fall in hematocrit after therapy. We suspect that myxedema produced changes in the capillaries of the lung which result in a lowered D_{LCO}. We do not know if this is a reduction in the total number of capillaries involved in diffusion, a thickening of the alveolar capillary membrane, or both.

SUMMARY AND CONCLUSIONS

We have studied 26 patients with myxedema before treatment and restudied 21 after treatment with desiccated thyroid or triiodothyronine. Sixteen patients had myxedema but no evidence of lung disease, six patients had myxedema and were obese, four patients had myxedema and lung disease.

The lung volumes were normal in the patients with myxedema only. Obese patients with myxedema had moderate reduction in inspiratory capacity, expiratory reserve volume, vital capacity, residual volume and total lung capacity, probably on the basis of obesity. When the obese patients lost weight their lung volumes returned to normal.

Four of six patients with myxedema and obesity had alveolar hypoventilation. The precise mechanism of alveolar hypoventilation is unknown. Lung disease and disease of the bony thorax were absent. This leaves the possibility of malfunction of the respiratory center in the brain, the muscles of respiration or neuromuscular coordination. We suspect that the muscles of respiration or neuromuscular coordination are involved. The maximal breathing capacity was reduced in patients with myxedema and increased significantly after therapy. This suggests that there is a "muscular" lesion which is reversible.

The diffusing capacity of the lungs for carbon monoxide (D_{LCO}) is reduced in patients with myxedema and increases slowly but significantly after therapy. The best explanation for this is pulmonary capillary involvement, either a thickened alveolar capillary membrane or a reduction in the pulmonary capillary bed, or both.

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REFERENCES

1. Wilson, W. R., and Bedell, G. N. The pulmonary abnormalities in myxedema (abstract). Clin. Res. 1958, 6, 420.
2. Bedell, G. N., Wilson, W. R., and Seebohm, P. M. Pulmonary function in obese persons. J. clin. Invest. 1958, 37, 1049.
3. Gull, W. W. A Collection of the Published Writings

of William Wilhey Gull. London, New Sydenham Society, 1894, vol. 1, pp. 315–321.
4. Scheinberg, P., Stead, E. A., Jr., Brannon, E. S., and Warren, J. V. Correlative observations on cerebral metabolism and cardiac output in myxedema. J. clin. Invest. 1950, **29**, 1139.
5. Browning, T. B., Atkins, R. W., and Weiner, H. Cerebral metabolic disturbances in hypothyroidism. Clinical and electroencephalographic studies of the psychosis of myxedema and hypothyroidism. Arch. intern. Med. 1954, **93**, 938.
6. Boyd, William. Pathology for the Physician. Philadelphia, Lea and Febiger, 1958, p. 538.
7. Foster, M., and Barr, D. P. Myxedema: Record of an autopsied case with special emphasis upon lesions of muscles. J. clin. Endocr. 1944, **4**, 417.
8. Means, J. H. The Thyroid and Its Diseases, 2nd ed. Philadelphia, J. B. Lippincott, 1948.
9. Anderson, W. A. D. Pathology. St. Louis, C. V. Mosby Co., 1948, p. 1065.
10. Lambert, E. H., Underdahl, L. O., Beckett, S., and Mederos, L. O. A study of the ankle jerk in myxedema. J. clin. Endocr. 1951, **11**, 1186.
11. Waldstein, S. S., Bronsky, D., Shrifter, H. B., and Oester, Y. T. The electromyogram in myxedema. Arch. intern. Med. 1958, **101**, 97.
12. Ingold, A. H. Tension Output in Hyperthyroid and Hypothyroid Muscles Stimulated Directly and Indirectly (thesis). Chicago, University of Illinois, 1956.
13. Zondek, H., Michael, M., and Kaatz, A. Capillaries in myxedema. Amer. J. med. Sci. 1941, **202**, 435.
14. Lange, K. Capillary permeability in myxedema. Amer. J. med. Sci. 1944, **208**, 5.
15. Baker, S. M., and Hamilton, J. D. Capillary changes in myxedema. Lab. Invest. 1957, **6**, 218.
16. Barker, S. B., Humphrey, M. J., and Soley, M. H. The clinical determination of protein-bound iodine. J. clin. Invest. 1951, **30**, 55.
17. Evans, T. C. Radioactive iodine in the study of thyroid disorders. J. Iowa St. med. Soc. 1955, **45**, 179.
18. Pearson, S., Stern, S., and McGavack, T. H. A rapid accurate method for determination of total cholesterol in serum. Analyt. Chem. 1953, **25**, 813.
19. West, H. F. Clinical studies on the respiration. VI. Comparison of various standards for the normal vital capacity of the lungs. Arch. intern. Med. 1920, **25**, 306.
20. Aslett, E. A., Hart, P. D., and McMichael, J. Lung volume and its subdivisions in normal males. Proc. roy. Soc. B 1939, **126**, 502.
21. Greifenstein, F. E., King, R. M., Latch, S. S., and Comroe, J. H., Jr. Pulmonary function studies in healthy men and women 50 years and older. J. appl. Physiol. 1952, **4**, 641.
22. Baldwin, E. DeF., Cournand, A., and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiologic classification, clinical methods of analysis, standard values in normal subjects. Medicine (Baltimore) 1948, **27**, 243.
23. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J. clin. Invest. 1957, **36**, 1.
24. Fisher, R. A. Statistical Methods for Research Workers, 10th ed. Edinburgh, Oliver and Boyd, Ltd., 1946.
25. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R. Studies on the velocity of blood flow. XIV. The circulation in myxedema with a comparison of the velocity of blood flow in myxedema and thyrotoxicosis. J. clin. Invest. 1930, **9**, 91.
26. Hallock, P. The heart in myxedema, with a report of 2 cases. Amer. Heart J. 1933, **9**, 196.
27. Schnitker, M. T., Van Raalte, L. H., and Cutler, E. C. Effect of total thyroidectomy in man, Laboratory studies and observations of clinical effects in thirty-nine cases. Arch. intern. Med. 1936, **57**, 857.
28. Thompson, W. O. Studies in blood volume. I. The blood volume in myxedema with a comparison of plasma volume changes in myxedema and cardiac edema. J. clin. Invest. 1926, **2**, 477.
29. Gibson, J. G., and Harris, A. W. Clinical studies of the blood volume. V. Hyperthyroidism and myxedema. J. clin. Invest. 1939, **18**, 59.
30. Ellis, L. B., Mebane, J. G., Maresh, G., Hultgren, H. N., and Bloomfield, R. A. The effect of myxedema on the cardiovascular system. Amer. Heart J. 1952, **43**, 341.
31. Rankin, J., McNeill, R. S., and Forster, R. E. Diffusion characteristics of the pulmonary membrane and capillary bed in various diseases of the lungs and cardio-vascular system (abstract). J. clin. Invest. 1957, **36**, 922.