MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

2 December 1965

FATAL MYXEDEMA

Case # 1. [redacted] Myxedema Precoma and ASHD.

This 75-year-old man was first seen in the DCHD system in [redacted] of 1965 when he was admitted to [redacted]. His previous history included the following events:

1961 - "light heart attack"
1962 - digitalized for uncertain reasons
[redacted] 1965 - ran out of digitalis
1965 - developed orthopnea, PND, angina, and edema; admitted to a local hospital in congestive heart failure with acute pulmonary edema and hemoptysis. The diagnosis was CHF and pneumonia. Discharged on a low salt diet, nitroglycerine, and digitalis.

Following this admission he did not adhere to the low salt diet. The shortness of breath and epigastric pressure returned, followed by the reappearance of edema and weight gain. At the time of admission ([redacted], 1965) he had a BP of 130/90, distended neck veins, bilateral rales, a gallop rhythm, and 1+ edema; EKG revealed a LBBB; VP was 10 cm; CBC and urinalysis were normal; the chemistries were normal except for a CO_2 of 32. X-ray revealed old fibrosis of the right lung and a slight degree of cardiomegaly.

The diagnoses were: 1) ASHD with an old MI, CHF, and LBBB, 2) old pulmonary fibrosis.

Although the dyspnea responded to IPPB and digitalis therapy, he did not lose weight, despite aggressive diuretic therapy. Gall bladder and upper and lower GI series were all normal. He was discharged on digitoxin, NTG, NH_4Cl, and tincture of belladonna to be followed in the OPD. It is interesting in retrospect that his temperatures varied from 96° to 99° (oral) during this hospitalization.

During his first clinic visit it was noted that the relaxation time of his DTR's was suggestively slow. He was still edematous, dyspneic, and had bilateral rales. T_4 by column was 1.2 µg%. The reason for his failure to respond was thought to be the combination of myxedema and ASHD. Because he gave a history of an increase in the frequency and intensity of anginal attacks (which were characteristic and which were promptly relieved by NTG) it was decided to readmit him to the hospital on [redacted] 1965.

[redacted]: At the time of admission he was noted to be a lethargic man with a temperature of 98°, lateral thinning of the eyebrows, lemon yellow coloring of the skin, a hoarse voice, bilateral moist rales, peripheral edema with only faint pitting, and very slow relaxation times. CBC was normal; urinalysis normal except for a trace (30 mgm%) of protein. BUN 32; CO_2 33; Cl 95; Na 139; K 4.2; chol. 308; liver battery normal; VP 13; FSH 16-50 mµ (normal); 17 OH = 8.0 mg; 17 KS 10.2 mg; I^{131} uptake 2.4%, rising to 4.4% after 3 days of TSH. EKG demonstrated LAD, LBBB, and PVC's.

Initial therapy consisted of digitoxin, peritrate, metahydrin, and KCl. He was noted in the hospital to have anginal attacks daily on exercise. His course can be schematically summarized as follows:

Date	Thyroid Therapy	Minimal Temperature (oral)	Clinical Course
[redacted]	0.0125 mg l-thyroxine	97^6	
[redacted]	0.025 mg l-thyroxine	96^4	No ↑ in chest pain
[redacted]	0.05 mg l-thyroxine	95^0	
[redacted]	0.05 mg l-thyroxine	96^8	Severe, 15 min chest pain
[redacted]	thyroxine decreased to 0.025 mg/day	97^0	Severe 60 min chest pain, requiring MS for relief
[redacted]	0.025 mg l-thyroxine	95^0	Although no unequivoca evidence evolved for a acute MI, he developed increasing pulmonary congestion (VP 21 cm; CT 60 sec) and confusion.
[redacted]	0.025 mg l-thyroxine	98^6(R)	Obtunded; given mercuhydrin which was followed by a diuresis and decrease in his venous pressure (15 cm Mentation improved. Bilateral rales presen
[redacted]	0.025 mg l-thyroxine	101^0(R)	Increasing confusion and somnolence; temp. elevation attributed to urinary tract infection. Marked anoxi (80% saturated; pH 7.33) and difficulty i handling secretions. Tracheostomy was performed, and on IPPB half-time he was fully saturated and had a pH of 7.48 and a CO_2 of 34 mEq.
[redacted]	Therapy changed to TIT (10 µg for one dose and 5 µg q 6 h thereafter). Penicillin and ampicillin therapy began.	97^8	Chest thought to be clearer, still somnole no change in EKG.
[redacted]	TIT 5 µg q 6 h	99^8	More alert; able to si up in bed and eat; no edema. Neck veins les distended. Denied che pain. 8 p.m. found dead in b no autopsy.

Case # 2. [redacted] Heart Failure Due to Myxedema?

This 32-year-old woman was first seen in the hospital in [redacted] of 1961 with typical findings of hyperthyroidism. The PBI was 10.9 and the RAI uptake was 59%. She underwent thyroidectomy and subsequently developed muscle irritability which was controlled with calcium lactate. She was seen in the surgery follow-up clinic still symptomatic and was to be continued on calcium and vitamin D. She was subsequently lost to follow-up.

In [redacted] 1961 and again in [redacted] 1963 she was hospitalized for incomplete abortions. During the 1963 admission she was noted to have a PBI of 1.0 and a cholesterol of 365 mgm%, but she was again lost to follow-up.

In 1964 she again became pregnant and was followed by a local physician who gave her thyroid replacement therapy, which she discontinued following the birth of her child in Nov. She was able to breast feed the baby successfully. During the succeeding 3 months she developed progressive lassitude, dyspnea on exertion and orthopnea, and a coarseness and dryness of the skin. She came to the EOR where she was found to have ascites, pleural effusion and peripheral edema. PBI 1.4; Ca 5.8, P 7.3, I^{131} uptake 2.2%, BUN 17, EKG low voltage with nonspecific ST and T wave changes. She refused admission. L-thyroixine (0.1 mg), vitamin D, and Ca lactate were prescribed, but during the ensuing 2 weeks the signs and symptoms of CHF worsened, and she was admitted from the EOR on [redacted]-65.

P.E. on admission revealed a BP of 100/60, P 100, T 100^6, R 36. She was markedly tachypneic and had bilateral pleural effusion, cardiomegaly with no murmurs, ascites, and gross peripheral edema up to the level of the sacrum. Venous pressure was 42 cm. CBC and urinalysis were normal. Pleural effusion had a SG of 1.012 (1.8 gm% protein), and ascitic fluid had a SG of 1.014 (1.9 gm% protein). BUN 12; CO_2 23; Cl 109; Na 139; K 4.9. Chest X-ray revealed gross cardiomegaly with bilateral pleural effusions and diffuse infiltration suggestive of pulmonary edema.

The initial course was very stormy. Following a thoracentesis (1000 ml) she developed acute pulmonary edema with a frothy pink sputum, a gallop rhythm (130/min), and a decrease in blood pressure. She was given morphine with a temporary symptomatic improvement, and two attempts at pericardiocentesis yielded no effusion but did enter both left and right ventricles. She was thought to be moribund, and the CHF was treated with digoxin, thiomerin, rotating tourniquets, tracheostomy with IPPB, and levophed. Peritoneal dialysis was also begun.

During the next 24 hours she improved markedly. There was a 3 liter diuresis and she had 2 liters of peritoneal and thoracic fluid removed and lost 1 1/2 liters by peritoneal dialysis. The rate was slow, and she had only occasional rales. She continued to do well, despite the temporary reaccumulation of pleural fluid. The heart decreased markedly in size, and she was discharged on 2-28-65 with a VP of 7 cm and clinically asymptomatic. The heart was still enlarged. Her discharge medications included digitalis, thyroixine (0.2 mg), vitamin D, and Ca lactate.

By [redacted], 1965 chest X-ray revealed only mild cardiomegaly and no edema. EKG revealed a 30^o shift of the axis to the right and increased voltage. PBI 5.8, P 5.2. By [redacted]65 the cardiac silhouette was normal in size. She was clinically euthyroid. The last PBI and serum Ca were in the low normal range.

Case # 3. [redacted]. Adrenal Crisis in Secondary Hypothyroidism Precipitated by Thyroid Therapy.

This 68-year-old [redacted] woman had a Cesarean section performed at age 19 for uncertain reasons and had marked post partum bleeding requiring transfusion. There was no subsequent menstruation and no regrowth of the shaved pubic hair. She was admitted to [redacted] during the influenza epidemic of 1958 with post-influenzal pneumonia, coma, and a temp. of 105°. The above history was not obtained. Blood chemistries and blood pressure were normal. No pathogens were cultured, and she was treated empirically with hydrocortisone (200 mg on Day 1, 100 mg on Day 2, and 80 u ACTH/day thereafter) and penicillin. She improved dramatically and was discharged asymptomatic 5 days later.

In a follow-up visit in the OPD in 1960 it was noted that she was clinically myxedematous, (thinning of the lateral eyebrows, slow movements and mentation, and thick, coarse dry skin). I^{131} uptake 3.5% PBI 4 µg%, and serum cholesterol 250. She was consequently readmitted for diagnostic workup:

TSH Stimulation Test # 1	I^{131} uptake 3.5%, rising to 15.7%
# 2	I^{131} uptake 0.2%, rising to 6.2%
EKG RBBB	Chol. 205, 280
CBC and Urinalysis WNL	FBS 46, 95, 110
PBI = 4.0	Electrolytes normal
BEI = 3.0	

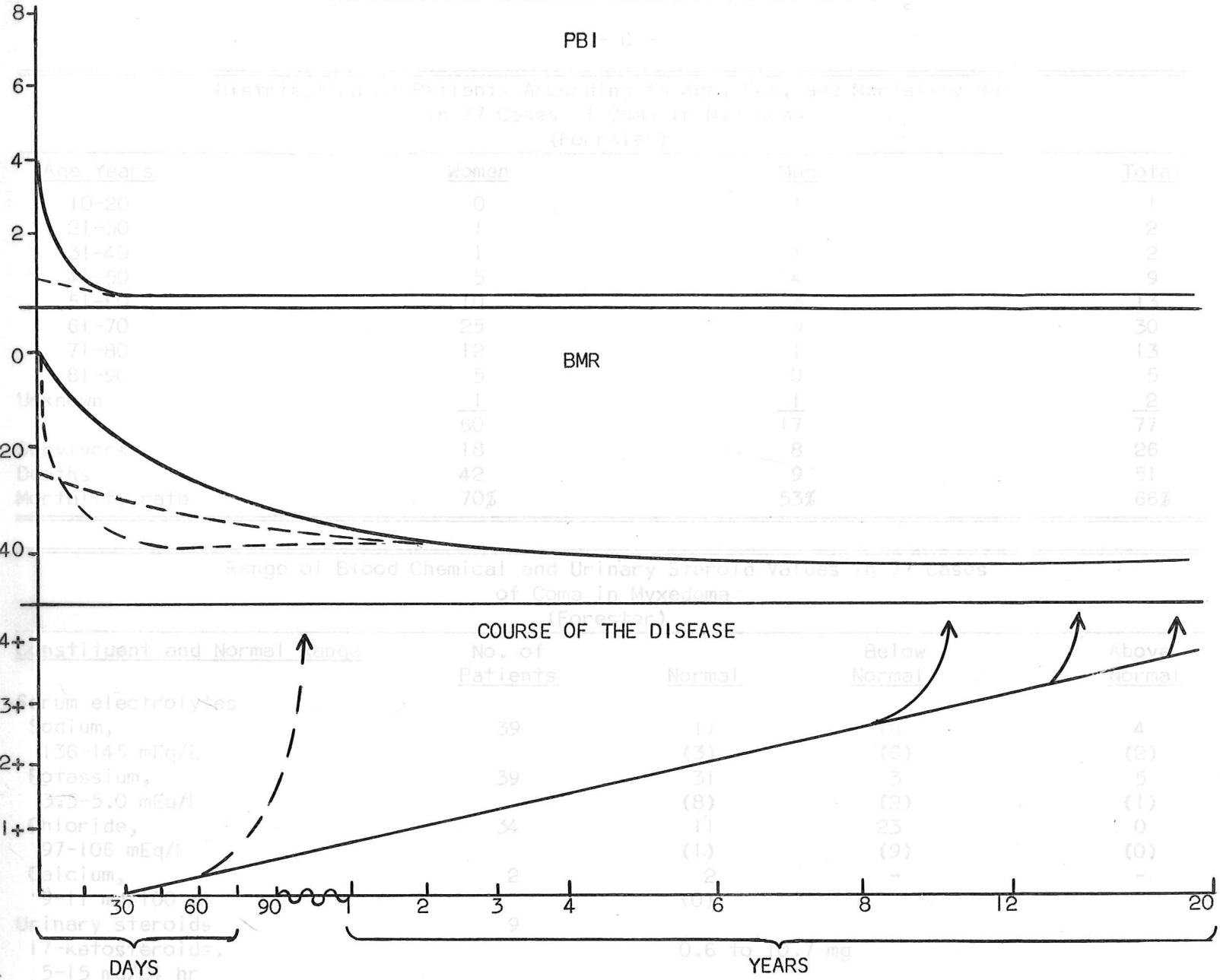
ACTH Stimulation Test	Day 1	2	3
17 Keto	2.1	2.7	3.9
17 OH	1.0	2.8	5.3

The first TSH stimulation test was interpreted as spurious due to previous ingestion of SSKI; the second test was interpreted by the medicine service as negative. It was decided that her history was probably unreliable, and she was started on thyroid extract 0.5 grain per day, increasing to 1.0 grain per day 12 days later.

At first she appeared to do exceedingly well, becoming much more alert. Ten days after the dose of thyroid was increased she was noted to have become much more lethargic to the point that she refused to get out of bed. The electrolytes and BP remained normal. She was given one injection of 25 mg Solu-Cortef IM with no obvious response, and during the next four days she lapsed into coma and died. BP, temperature, and chemistries were normal the day before death.

Autopsy revealed: 1) postnecrotic scarring of the pituitary, severe, 2) atrophy of the thyroid, 3) surgical absence of the uterus, tubes, and ovaries, 4) atrophy of the adrenal cortex, and 5) myocardial fibrosis and pulmonary edema.

HYPOTHETICAL COURSE OF MYXEDEMA (AFTER MEANS)



Relationship of Body Temperature During Coma and Mortality Rate in 66 Cases of Coma in Myxedema (Forester)

Temp., F.	No. Patients	No. Survivors	Mortality Rate, %
< 85	10	0	100
85.1-98.6	44	13	70
98.6+	12	7	42

Relationship of Treatment with Thyroid Hormone and Mortality Rate in 63 Cases of Coma in Myxedema (Forester)

Preparation	No. Patients	No. Survivors	Mortality Rate, %
Thyroid substance	12	2	83
L-Thyroxine	20	4	80
Triiodothyronine	31	14	55

Distribution of Patients According to Age, Sex, and Mortality Rate in 77 Cases of Coma in Myxedema (Forester)

Age, Years	Women	Men	Total
10-20	0	1	1
21-30	1	1	2
31-40	1	1	2
41-50	5	4	9
51-60	10	3	13
61-70	25	5	30
71-80	12	1	13
81-90	5	0	5
Unknown	1	1	2
	60	17	77
Survivors	18	8	26
Deaths	42	9	51
Mortality rate	70%	53%	66%

Range of Blood Chemical and Urinary Steroid Values in 77 Cases of Coma in Myxedema (Forester)

Constituent and Normal Range	No. of Patients	Normal	Below Normal	Above Normal
Serum electrolytes				
Sodium, 136-145 mEq/L	39	17 (3)	18 (6)	4 (2)
Potassium, 3.5-5.0 mEq/L	39	31 (8)	3 (2)	5 (1)
Chloride, 97-106 mEq/L	34	11 (1)	23 (9)	0 (0)
Calcium, 9-11 mg/100 ml	2	2 (0)	-	-
Urinary steroids	9			
17-ketosteroids, 5-15 mg/24 hr		0.6 to 10.7 mg		
11-OH corticoids, 4-9 mg/24 hr		0.2 to 10.3 mg		
Fasting blood sugar 70-126 mg/100 ml	23	18 (3)	4 (1)	1 (0)
Serum carbon dioxide 23-27 mEq/L	28	10 (3)	9 (2)	9 (5)

Comparison of the Characteristics of Congestive Heart Failure and of Typical "Myxedema Heart" (Raab)

	Congestive Heart Failure	Myxedema Heart
Venous pressure	Increased	Normal
Pulmonary congestion	Present	Absent
Hepatic congestion	Present	Absent
Dependent edema	Present	Absent or moderate
Orthopnea	Present	Absent
Tachycardia	Present	Absent
Circulatory volume	Increased	Decreased
Capillary permeability	Normal	Increased
Isolated pericardial effusion	Rare	Common
Protein content of serous effusions	Low	High
Basal metabolism	High	Low
Efficacy of digitalis	Good	Nil
Efficacy of diuretics	Good	Nil
Therapeutic efficacy of thyroid hormone	Nil	Good

REFERENCES

NATURAL HISTORY AND PATHOLOGICAL FINDINGS IN MYXEDEMA

1. Means, J. H., L. J. DeGroot, and J. B. Stanbury. The Thyroid and Its Diseases. New York: McGraw-Hill Co., Inc., 1963. Pp. 287-353.

This textbook probably contains the most thorough coverage of the natural history, clinical features, and therapy of myxedema since the report of the Myxedema Commission.

2. Terman, J. Problems in the diagnosis and management of myxedema. Med. Clin. North America 33:1249, 1949.

3. Bloomer, H. A., and L. H. Kyle. Myxedema, a reevaluation of clinical diagnosis based on eighty cases. Arch. Int. Med. 104:234, 1959.

4. Watanakunakorn, C., R. E. Hodges, and T. C. Evans. Myxedema, a study of 400 cases. Arch. Int. Med. 116:183, 1963.

5. Berris, B., and T. Owen. Unusual manifestations of myxedema. Canad. Med. Assoc. J. 93:21, 1965.

6. Trotter, W. R. Diseases of the Thyroid. Philadelphia: F. A. Davis Co., 1962. Pp. 110-133.

These recent reviews emphasize the nondescript and polymorphic character of the symptoms and the difficulties in diagnosing myxedema. The average patient is not diagnosed until four years after the onset of symptoms, despite the fact that most patients consult a physician within a year.

7. Means, J. H. The Thyroid and Its Diseases. Philadelphia: J. B. Lippincott Co., 1948. P. 205.

8. Douglas, R. C., and S. D. Jacobson. Pathological changes in adult myxedema: survey of 10 necropsies. J. Clin. Endocrinol. 17:1354, 1957.

These two descriptions (a total of 19 cases) of autopsies in patients with myxedema represent the only two large series of autopsies in untreated myxedema since the introduction of thyroid extract into clinical medicine in 1891. (The autopsy data has been left out of the new edition of Means.) Average age of the patients is about 66. Myocardial infarction and/or severe coronary atherosclerosis were present in all the cases in Ref. 7 and was said to be "gross" in the cases in Ref. 6 (no specific protocols given).

9. Gabrilove, J. L., and A. W. Ludwig, M. D. The histogenesis of myxedema. J. Clin. Endocrinol. and Metabolism 17:925, 1957.

This is probably the best histochemical study of the accumulation of "myxedema" in biopsy tissues of patients before and after therapy and after the withdrawal of therapy. Furthermore, it clearly demonstrates that "myxedema" can occur in secondary hypothyroidism.

THE LATE COMPLICATIONS OF MYXEDEMA

MYXEDEMA PRECOMA AND COMA

10. LeMarquand, H. S., W. Hausman, and E. H. Hemsted. Myxoedema as a cause of death. Report of two cases. Brit. Medical Journal 1:704, 1953.

11. Summers, V. K. Myxoedema coma. Brit. Medical Journal 2:366, 1953.

Although hypothermic coma was clearly described as a terminal event in myxedema as early as 1888 by Ord, no further reports were published until 1953 when these two papers redescribed hypothermic coma in seven patients, all of whom died. In view of the fact that the syndrome was previously unknown, these reports are very impressive indeed. The possibility of warming was tried in two patients with no salutary effects. Steroid hormones in moderately large dosage were tried, and finally very large doses of l-thyroxine (4 to 10 mg per day) were tried in all but one patient. (In fact, the patient given 10 mg l-thyroxine I.V. in one dose awoke and improved markedly and died in what sounds like thyroid storm 9 days later.) In these reports the relation between the hypothermia and the environmental temperature was also described. Little has been added to the clinical description since these reports appeared.

Description of the Clinical Syndrome

12. Leon-Sotomayor, L., and C. Y. Bowers. Myxedema Coma. Springfield: Charles C. Thomas, 1964.

This monograph contains the most extensive coverage of this subject. Nevertheless, the recommendations as to therapy are not in agreement with other authors, and most reviewers have objected to these recommendations. Not to be trusted.

13. Nickerson, J. F., S. R. Hill, Jr., J. H. McNeil, and S. B. Barker. Fatal myxedema, with and without coma. Ann. Int. Med. 53:475, 1960.

14. Nielsen, P. E., and P. Ranlou. Myxoedema coma. Acta Endocrinologica 45:353, 1964.

15. Verbou, J. L. Modern treatment of myxoedema coma associated with hypothermia. Lancet 1:194, 1964.

16. Forester, C. F. Coma in myxedema. Arch. Int. Med. 111:100, 1963.

Of the many publications on this subject in the past 12 years these four brief reviews contain the best summaries of the syndrome and its management.

17. Ivy, H. K. Myxedema precoma: complications and therapy. Mayo Clin. Proc. 40:403, 1965.

Myxedema precoma (hypothermia and elevated pCO_2 without loss of consciousness) is pointed out as a potentially ominous event which deserves prompt therapy.

The Central Nervous System Background for Coma in Myxedema

18. Lansing, R. W., and J. B. Trunnell. Electroencephalographic changes accompanying thyroid deficiency in man. J. Clin. Endocrinol. and Metabolism 23:470, 1963.

19. Nickel, S. N., and B. Frame. Nervous and muscular systems in myxedema. J. Chronic Diseases 14:570, 1961.

20. Jellinek, E. H. Cerebellar disorders in myxedema. Lancet 2:1010, 1962.

(Also Ref. 1)

Although myxedema psychosis is a well recognized entity, other C.N.S. lesions are less frequently described. Sensory phenomena including paresthesias, smell, taste, and hearing loss are common. The slowed mentation, sleepiness, and emotional flattening are accompanied by characteristic EEG changes in all patients. Furthermore, the CSF protein, particularly the globulin, is usually elevated, and a variety of discrete, reversible phenomena including cerebellar ataxias and convulsions have been described.

21. Sensenbach, W., L. Madison, S. Eisenberg, and L. Ochs. The cerebral circulation and metabolism in hyperthyroidism and myxedema. J. Clin. Invest. 33:1434, 1954.

The etiology for the CNS abnormalities are poorly understood. Although myxedema is accompanied by increased cerebral vascular resistance and reduced blood flow, the rate of cerebral oxygen and glucose consumption is unaltered. Consequently, it has been concluded that the rate of cerebral metabolism is uninfluenced by thyroid hormone. And, although cerebral O_2 consumption has apparently never been measured in patients with prominent neurological manifestations, it is apparent that there is no over-all correlation between O_2 consumption and the cerebral symptoms. Furthermore, although water content of the brain does increase in experimental athyreosis, no changes different than those which might occur in any cerebral sclerotic subject have been described in the human autopsy studies (Ref. 7 and 8). To date no histochemical or chemical studies as in Ref. 9 have been performed on the brain; however, metachromatic infiltrates do occur in the peripheral nerves (19).

22. Tonks, C. M. Mental illnesses in hypothyroid patients. Brit. J. Psychiat. 110:706, 1964.

Only 6 of 18 hypothyroid patients with mental illness returned to a normal mental state on treatment. No patient with madness of greater than 2 years' duration showed a satisfactory response. This may be due either to: 1.) the coexistence of other mental disease in patients with myxedema or 2.) irreversible CNS changes.

Precipitating Causes for Myxedema Coma

23. Orr, F. R. Haemorrhage in myxoedema coma. Lancet 2:1012, 1962.

24. Catz, B., and S. Russell. Myxedema, shock, and coma. Arch. Int. Med. 108:129, 1961.

25. Wey, J. G., J. R. Calverly, and C. Johnson. Hypothyroidism and alveolar hypoventilation. Arch. Intern. Med. 115:302, 1965.

26. Massumi, R. A., and J. L. Winnacker. Severe depression of the respiratory center in myxedema. Am. J. Med. 36:876, 1963.

27. Levin, M. E., and W. H. Daughaday. Fatal coma due to myxedema. Am. J. Med. 18:1017, 1955.

28. Norregaard, S., and K. Schmith. Coma in myxoedema discussed in the light of two cases. Acta Med. Scand. 165:279, 1959.

29. Brune, D. F., C. vonGastel, P. J. derKinderen, and F. Schwarz. Myxedema coma with extreme hypothermia in patient treated with thyroid preparation of very low biological activity. Acta Endocrinol. 41:154, 1960.

Hemorrhage, infection, CO_2 narcosis due to alveolar hypoventilation, burns, operations, congestive heart failure, and exposure to cold may all be precipitating events in causing coma. Of these, infection is the most common cause and is nearly always present at autopsy. After an extensive review of the coma in this syndrome, Levin and Daughaday concluded that progression from the bare vegetative state of severe myxedema to coma and death is probably not a specific event but is, instead, the result of a variety of precipitating factors superimposed upon the severe CNS involvement of myxedema.

30. Mitchell, J. R. A., D. H. C. Surrige, and R. G. Willison. Hypothermia after chlorpromazine in myxoedematous patients. British Medical Journal 2:932, 1959.

Chlorpromazine deserves special mention as a cause of hypothermia in myxedema. Chlorpromazine lowers the BMR in normal individuals (possibly by blocking thyroxine action at the level of the cells), but it does not cause hypothermia except in myxedema. Other drugs (such as barbiturates and morphine) may cause coma via CO_2 narcosis.

Pathophysiology of the Hypothermia in Myxedema

31. Bodansky, M., J. E. Pilcher, and V. B. Duff. Concerning the relationship to environmental temperature to resistance to thyroid and throxine and creatin content of heart and other tissues in experimental hypothyroidism. J. Exper. Med. 63:523, 1936.

32. Bodansky, M., and V. B. Duff. Nitrogen and creatine metabolism in relation to environmental temperature and thyroid function. Endocrinology 20:822, 1936.

Rats maintained at 3-5°C. can tolerate doses of thyroxine which cause death at room temperature (33-35°C.).

33. Ring, C. C. The importance of thyroid in maintaining an adequate production of heat during exposure to cold. Am. J. Physiol. 137:502, 1942.

An intact thyroid is required for a normal increase in BMR during exposure of rats to the cold.

34. Demsey, E. W., and E. B. Astwood. Determination of the rate of thyroid hormone secretion at various environmental temperatures. Endocrinology 32:509, 1943.

Thyroxine secretion in normal rats rises from 1.7 to 9.5 μg per day as the environmental temperature is lowered from 35° to 1°C.

It is quite clear, however, that myxedema coma is not simply hypothermic coma since rewarming alone has been generally unsuccessful and may even be dangerous.

35. Sheehan, H. L., and V. K. Summers. Treatment of hypopituitary coma. Brit. Med. J. 1: 1214, 1952.

In this single case of hypothermic hypopituitary coma, rewarming produced a dramatic return to consciousness.

36. Marshall, R. J., and W. T. E. McCaughey. Hypothermic coma with muscle damage and acute renal tubular necrosis. Lancet 2:754, 1956.

As in all forms of severe hypothermia, muscle necrosis, myoglobinuria, and acute tubular necrosis may occur in myxedema coma.

37. Fleisher, G. A., W. M. McConahey, and M. Pankow. Serum creatine kinase, lactic dehydrogenase, and glutamic-oxaloacetic transaminase in thyroid disease and pregnancy. Mayo Clinic Proceedings 40:300, 1965.

Patients with myxedema may be uniquely susceptible to muscle necrosis, since elevation of creatine phosphokinase and lactic dehydrogenase is a universal finding in severe myxedema.

38. Astrom, K. E., E. Kugelberg, and R. Muller. Hypothyroid myopathy. Arch. Int. Med. 5: 472, 1961.

Further evidence of the universal myopathy in myxedema is furnished by this report of EMG abnormalities and histological evidence of muscle degeneration in all patients studied. (The myopathy may be a major cause of weakness in this disease.)

The Management of Myxedema Coma

39. Dyson, A., and M. W. W. Wood. Triiodothyronine in myxoedema coma. Lancet 2:757, 1956.

The original suggestion for the use of the short acting TIT in myxedema coma.

40. Angel, J. H., and L. Sash. Hypothermic coma in myxoedema. Brit. Med. J. 2:1855, 1960.

41. Lovel, T. W. I. Myxoedema coma. Lancet 1:822, 1962.

42. Perlmutter, M., and H. Cohn. Myxedema crisis of pituitary or thyroid origin. Am. J. Med. 36:883, 1964.

Although most authors (such as in Ref. 16) argue for the use of moderate doses of triiodothyronine (< 100 μg/24 hours) in myxedema coma these authors take a different view. Half or more of all patients who die from myxedema coma wake up, are thought to be distinctly improved, and then die suddenly. They urge extreme caution in the use of TIT in this condition.

43. Halvey, D. N., C. J. Gardner, J. T. Nicoloff, and J. T. Dowling. Treatment of myxedema coma with intravenous thyroxine. Arch. Int. Med. 113:89, 1964.

Clearly, this is the most impressive report to date on the management of myxedema coma. All 7 patients survived on intravenous l-thyroxine alone. Only the two patients in shock were given steroids. The average dose was 0.500 mg I.V., and distinct improvement was noted in each case in 9-16 hours.

44. Asher, R. The diagnosis and treatment of myxoedema. Postgraduate Medical Journal 36: 471, 1960.

A nihilistic view (quoted approvingly by Trotter): "I have the notion that to leave them severely alone - unheated, unwashed, and undisturbed, but giving thyroxine 0.2 mg daily - gives them as good a chance as any other elaborate regime."

THE HEART IN HYPOTHYROIDISM

45. Raab, W. Hormonal and Neurogenic Cardiovascular Disorders. Baltimore: The Williams and Wilkins Co., 1953. P. 147.

46. Thomas, H. N., Jr. Effect of thyroid hormone on circulation. J.A.M.A. 163:337, 1957.

47. Hamolsky, M. W., G. S. Kurland, and A. S. Freedberg. The heart in hypothyroidism. J. Chronic Diseases 14:558, 1961.

A conspicuous change in the scattered autopsy reports has been fibrous tissue replacement and accumulation of material in large, irregular vacuoles which is brilliantly PAS positive. It is quite clear that these changes (and indeed virtually all the functional abnormalities to be described) did not occur in the therapeutic myxedema studied by the Beth Israel group and given small amounts of thyroid replacement therapy.

PATHOGENIC MECHANISMS AND CIRCULATORY MECHANISMS

48. Ullrick, W. C., and W. V. Whitehorn. Influence of thyroid tissue on respiration of cardiac tissue. Am. J. Physiol. 171:407, 1952.

49. Dock, W., and J. K. Lewis. Effect of thyroid feeding on the O_2 consumption of the heart and other tissues. J. Physiol. 74:401, 1932.

Although thyroid in large doses causes an increase in the O_2 consumption in excised atrium (77%), ventricle (22%), and diaphragm (33%) but not skeletal muscle, dosages compatible with life probably cause increases in O_2 consumption in the intact heart which can be explained in large part by alterations in rate.

50. Ellis, L. B., J. G. Mebane, G. Moresh, H. N. Hultgren, and R. A. Bloomfield. Effect of myxedema on the cardiovascular system. American Heart Journal 43:341, 1952.

51. Brewster, W. R., J. P. Isaacs, P. F. Osgood, and T. L. King. The hemodynamic and metabolic interrelationships in the activity of epinephrine, norepinephrine, and the thyroid hormones. Circulation 13:1, 1956.

52. Groetlingen, J. S., J. J. Muenster, C. S. Checehia, R. L. Grissom, and J. A. Campbell. A correlation of clinical and hemodynamic studies in patients with hypothyroidism. J. Clin. Invest. 37:502, 1958.

The total peripheral blood flow is decreased, and the peripheral resistance is decreased. The cardiac output is significantly decreased, mainly because of a decreased stroke volume (approximately 47% of normal). In general, however, congestive failure in the usual sense is rare:

1.) Pulmonary congestion is unusual.
2.) Resting pulmonary artery pressures are near normal.
3.) Right ventricular pulse and end-diastolic pressure are normal.
4.) Peripheral venous pressures are normal.
5.) Effusions when present have high protein.
6.) Plasma volume is low.
7.) Generally does not respond to digitalis.

53. Scott, J. C., T. A. Balourdas, and M. N. Crull. Effect of experimental hypothyroidism on coronary blood flow and hemodynamic factors. Am. J. Cardiol. 7:690, 1961.

The experimental myxedematous state is characterized by a reduction in coronary sinus blood flow, left ventricular O_2 consumption, and heart rate; atropine causes these to increase to the same total level as is seen with atropine in normals, probably because the capacity of the hypothyroid heart to change its rate appears unimpaired. However, cardiac index in the hypothyroid heart is low and fails to return to normal control levels in response to atropine, probably because of a greater reduction in cardiac output than in total O_2 consumption.

54. Marks, P. A., and B. S. Roof. Pericardial effusion associated with myxedema. Ann. Int. Med. 39:230, 1953.

Although pericardial effusion plays a frequent and important role in the genesis of the myxedema heart, tamponade is very rare.

55. Douglas, A. H., and P. Samuel. Analysis of electrocardiographic patterns in hypothyroid heart disease. New York State Journal of Medicine 60:2227, 1960.

Charges which have been described in myxedema include flattening and inversion of the T wave, low voltage, notched and widened QRS complexes, conduction disturbances, and axis deviation. The T wave abnormality is the most common, probably present in nearly all cases in lead II.

CONGESTIVE HEART FAILURE v.s. "MYXEDEMA HEART"

56. McBrien, D. J., and W. Hindle. Myxedema and heart failure. Lancet I:1066, 1963.

Of 7 patients with myxedema and an enlarged heart, elevated venous pressure, and edema, in only one did the stroke output rise as the filling pressure was reduced. This patient was not able to tolerate thyroid hormone and died shortly thereafter. The six remaining patients all recovered completely on thyroid therapy.

57. Hoffman, F. G. Postoperative myxedema cardiopathy. Am. Heart J. 57:463, 1959.

This patient in course and response more nearly resembles our patient 2 than any other in the literature.

THE PROBLEM OF ATHEROSCLEROSIS

58. Blumgart, H. L., A. S. Freedberg, and G. S. Kurland. Hypercholesterolemia, myxedema, and atherosclerosis. Am. J. Med. 14:665, 1953.

59. Blumgart, H. L., A. S. Freedberg, and G. S. Kurland. Radioactive iodine treatment of angina pectoris and congestive heart failure. Circulation 16:110, 1957.

On the basis of an autopsy study of 8 patients who died an average of 7.4 years after therapeutic myxedema was induced for either RHD or cor pulmonale (only 3 of whom had severe atherosclerosis at the time of death) these authors conclude that the hypothyroid state is not a significant etiologic factor for the development of coronary atherosclerosis. However, all their patients were partially treated to maintain the BMR around -20; consequently, this study cannot be regarded as evidence on either side of the question. While this problem remains entirely unsettled, it is clear from the autopsy studies to date (Ref. 7 & 8) that severe atherosclerosis is so universal in late myxedema that at least its presence does not significantly retard the evolution or site of the plaques.

EFFECT OF THYROID HORMONE ON THE HEART

60. McGavack, T. H., K. Lange, and D. Schwimmer. Management of the myxedematous patient with symptoms of cardiovascular disease. Am. Heart Journal 29:421, 1945.

Dosages of thyroid as low as 1/10 grain (6.5 mg) caused intractable angina in several of 24 hypothyroid patients with ASHD and/or HCVD. Furthermore, this very careful study demonstrates that if patients are started on very low dosages (1/20 grain) and increased very slowly can usually tolerate much larger doses than were previously intolerable. The point is also well documented that less than optimal therapy (in regard to the BMR and symptoms) is necessary in some patients.

61. Starr, P., and R. Liebhold-Schweck. The effect of l-thyroxine, d-thyroxine, and l-triiodothyronine on the electrocardiogram in myxedema. Ann. Intern. Med. 42:595, 1955.

Tri-iodothyronine can produce cardiac effects at low dosage levels before demonstrable effects on the BMR (around 35 µg per day). The argument is advanced that return of the T waves toward normal may be seen before any effects on the BMR or PBI when l-thyroxine is used.

62. Anderson, A., and W. Hausman. Triiodothyronine in myxoedema coma. Lancet ii:999, 1956.

63. Frawley, T. F., J. C. McClintlock, R. T. Beebe, and G. L. Marthy. Metabolic and therapeutic effects of triiodothyronine. J.A.M.A. 160:646, 1956.

The incidence of angina, palpitations, and temporarily increased severity of CHF is much greater on a minimal dose of TIT to maintain the BMR normal than on the minimal dose of l-thyroxine which has the same effect on the BMR. Death has resulted from 50 µg TIT in a single dose.

64. Wallach, E. E., G. D. Lubash, B. D. Cohen, and A. L. Rubin. Cardiac disease and hypothyroidism. J. A. M. A. 167:1921, 1958.

65. Gibson, P. C. Control of treatment in myxoedema by electrocardiography. Lancet 1:128, 1958.

These two articles emphasize the surprising frequency of angina during even the most cautious treatment of myxedema. Of 9 patients with myxedema two died and two developed severe angina on dosages of dessicated thyroid as low as 7.5 mg and TIT as low as 15 µg per day.

66. Ibbertson, K., R. Fraser, and D. Alldis. Rapidly acting thyroid hormones and their cardiac action. Brit. Med. J. ii:52, 1959.

In every myxedematous patient with a previous history of angina very small doses of TRIAC (0.25 mgm versus a normal dose of 18 mgm/day) caused angina or myocardial ischemia.

67. Keating, F. R., Jr., P. W. Parkin, J. B. Selby, and H. S. Dickman. Therapy of heart disease associated with myxedema. Progr. in Cardiovasc. Dis. 3:364, 1961.

This is probably the most important study of the problem of angina in myxedema:

(1.) Although many authors have doubted the entity (notably Friedberg) this study clearly establishes that angina can occasionally improve following thyroid replacement therapy (5 out of 55 cases).

(2.) Far more commonly, however, angina pectoris follows the institution in hypothyroid subjects of thyroid replacement therapy given either too rapidly or in too big a dose. This angina characteristically occurs at rest.

(3.) The occurrence of this phenomenon is unusual in patients started on very low doses and increased slowly.

68. Winson, T., J. Poole, and D. Trotter. Thyroid analogues and coronary insufficiency. Clin. Pharm. Thera. 5:12, 1964.

In euthyroid subjects with angina, all thyroid analogues in dosages which decrease the serum cholesterol aggravate angina pectoris.

ABNORMALITIES IN RHYTHM IN MYXEDEMA

69. Hansen, J. E. Paroxysmal ventricular tachycardia associated with myxedema. A case report. Am. H. Journal 61:692, 1961.

70. Winawer, S. J., S. M. Rosen, and H. Cohn. Myxedema coma with ventricular tachycardia. Arch. Int. Med. 111:647, 1963.

In these two patients treatment of the myxedema caused improvement in the arrhythmia.

71. Lipton, E. L., M. L. Voorhess, A. Steinschneidy, J. Hollowell, P.J.N. Cox, and L. I. Gardner. Cardiovascular effects of therapy in congenital hypothyroidism. J. Pediatrics 66:79, 1965.

Two of three congenitally hypothyroid subjects manifested potentially severe arrhythmias during the first 10 days of therapy. Although no comparable, long term monitoring study has been performed in adults, this possibility should be kept in mind as a theoretical cause of sudden death in patients under treatment.

OTHER POTENTIAL CAUSES OF DEATH

72. Evans, E. C. Neurological complications of myxedema: Convulsions. Ann. Int. Med. 52: 434, 1960.

Also see Ref. 18-20.

73. Haley, H. B., C. Leigh, D. Bronsky, and S. S. Waldstein. Ascites and intestinal obstruction in myxedema. Arch. Surg. 85:328, 1962.

74. Koren, R. S., and M. Atkinson. Ascites in hypothyroidism. Lancet 1:527, 1963.

75. Naeye, R. L. Capillary and venous lesions in myxedema. Lab. Invest. 12:465, 1963.

Ascites and pleural effusion which may occur in the absence of significant cardiac involvement are characterized by high protein content. These effusions are apparently due to a diffuse capillary lesion which contains acid muco-polysaccharides.

76. Goldberg, M., and M. Reivitch. Studies on the mechanism of hyponatremia in myxedema. Ann. Int. Med. 56:120, 1962.

77. Cohen, R. D. Water and electrolyte metabolism during the treatment of myxedema. Clinical Science 25:293, 1963.

78. Pettinger, W. A., L. Tolner, and T. F. Ferris. Inappropriate secretion of ADH due to myxedema. New England Journal Med. 272:362, 1965.

Although other factors may be involved, inappropriate ADH secretion probably can account for the major portion of water retention and decreased osmolarity in myxedema. This is usually asymptomatic but is said to be associated with a "significant mortality".

79. Wilson, W. R., and G. N. Bedell. The pulmonary abnormalities in myxedema. J. Clin. Invest. 39:42, 1960.

Every patient with myxedema has a decreased ventilatory response to carbon dioxide, and CO_2 narcosis is an ever present danger (also Ref. 25 & 26).

80. Asper, S. P. Physiological approach to correction of hypothyroidism. Arch. Int. Med. 107:112, 1961.

Finally, in secondary myxedema the administration of thyroid replacement without steroid therapy may precipitate overt adrenal insufficiency.

81. Bloodworth, J. M. B., W. M. Kirkendall, and T. L. Carr. Addison's disease associated with thyroid insufficiency and atrophy (Schmidt Syndrome). J. Clin. Endocrinol. 14: 540, 1954.

82. Carpenter, C. J. G., N. Solomon, S. G. Silverberg, T. Bledsoe, R. C. Northcutt, J. R. Klinenberg, I. L. Bennett, Jr., and A. M. Harvey. Schmidt's syndrome: A review of the literature and a report of fifteen new cases including ten instances of diabetes mellitus. Medicine 43:153, 1964.

Previously thought to be a rare disease, the recent studies of Schmidt's syndrome suggest that hypothyroidism is very common in idiopathic Addison's disease (probably not in the tuberculous variety), possibly the result of an autoimmune disease.