



*Bulletin* of the

**University of Minnesota Hospitals  
and  
Minnesota Medical Foundation**



**Localized Myxedema**

BULLETIN OF THE  
UNIVERSITY OF MINNESOTA HOSPITALS  
and  
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I. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL  
CALENDAR OF EVENTS

February 20 - 26, 1949

No. 236

Sunday, February 20

9:00 - 11:30 Surgery Grand Rounds; Station 22, U. H.  
 Surgical Topic; Rm. M-109, U. H.

Monday, February 21

- 8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
- 9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.
- 10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.
- 11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans Hospital.
- 11:00 - 11:50 Physical Medicine Seminar; Rehabilitation of the Blind; Mr. Stanley Potter, Society for the Blind; E-101, U. H.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.
- 12:00 - 1:00 Physiology Seminar; 214 M. H.
- 12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
- 12:30 - 1:20 Pathology Seminar; Review of 10,000 appendicectomies; Elmer C. Paulson; 104 I. A.
- 12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.
- 1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.
- 1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
- \*4:00 - 6:00 Kellogg Lecture; Some Present Concepts of Physical Medicine; Miland E. Knapp; Powell Hall Amphitheater.

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\* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.

- 4:00 - Pediatric Seminar; Chemotherapeutic and Antibiotic Treatment of Tuberculosis; William Johnson; 6th Floor, Child Psychiatry, U. H.
- 5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.
- 5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, February 22 - HOLIDAY

Wednesday, February 23

- 8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.
- 8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.
- 8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.
- 8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. F. Faker and Joe R. Brown; Veterans Hospital.
- 11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 12:00 - 12:50 Radio-Isotope Seminar; Geometry of Particle Measurement (with Demonstration); J. C. Wang; Rm. 212 Hospital Court, Temporary Bldg.
- 1:00 - 3:00 Kellogg Lecture; Pathology of Bone Tumors; John R. McDonald, Mayo Clinic.
- 3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.
- 4:00 - 5:00 Infectious Disease Rounds; Medical Conference Room, Veterans Hospital.
- 8:00 p.m. Minnesota Pathological Society Meeting; Cytologic Examination of Body Secretion as an Aid in the Diagnosis of Cancer; John R. McDonald, Mayo Clinic; MeS Amphitheater.

Thursday, February 24

- 8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M. Stauffer; M-109, U. H.
- 8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

- 11:00 - 11:50 Urology Seminar; Surgical Injuries to the Ureter; T. H. Sweetser; E-101, U. H.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.
- 11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.
- 12:00 - 1:00 Physiological Chemistry Seminar; Tissue Proteins and Carcinogenesis; Fred Bock; 214 M. H.
- 1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.
- 2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.
- 4:00 - 5:00 Bacteriology and Immunology Seminar; Enzymatic Activities of Viruses; Ralph Wands; 214 M. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
- 5:00 - 6:00 X-ray Seminar; Duodenal Tumors; James Miree; Todd Amphitheater.

Friday, February 25

- 8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.
- 9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans Hospital.
- 10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.
- 11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.
- 11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Cerebral Arteriography; Powell Hall Amphitheater; L. A. French and P. Blake.
- 12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Large Classroom, Minneapolis General Hospital.
- 1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.
- 1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Electrocardiographic Conference; George N. Aagaard; 106 Temp. Bldg., Hospital Court, U. H.

Saturday, February 26

- 7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 20, U. H.
- 8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.
- 8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.
- 8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.
- 9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 9:00 - 11:30 Surgery-Roentgenology Conference; Experiences with Surgical Treatment of Ulcerative Colitis; Clarence Dennis; Todd Amphitheater, U. H.
- 9:00 - 12:00 Child Psychiatry Conference; Powell Hall Amphitheater.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.
- 11:00 - 12:00 Anatomy Seminar; The Action of Thyrotrophin, Arthur Sethre; Cerebral Control of Motor Activity, Harold Brody; 226 I. A.

## II. LOCALIZED MYXEDEMA

Harold G. Hurst

### Introduction

This condition is of unusual interest because of the seeming paradox of circumscribed myxedema occurring during periods of increased general metabolism. The term Localized Myxedema is acceptable because histologically the lesions are as characteristically myxedematous as in generalized myxedema. Localized myxedema is the name given to lesions of solid, non-pitting edema developing on the lower legs and which are constantly associated with thyroid disease. Although the appearance is characteristic, there is little doubt that some cases of localized myxedema go unrecognized.

### Review of Current Literature

Neither Graves<sup>1</sup> nor Basedow<sup>2</sup> in their original reports of exophthalmic goiter specifically record any lesions corresponding to those of localized myxedema. Sollier<sup>3</sup>, in 1891, was among the first to refer to the possible co-existence of myxedema and Graves' disease. In 1892, von Jaksch<sup>4</sup> reported a patient with typical symptoms of Graves' disease who had a non-inflammatory, non-pitting circumscribed edema of both legs strongly suggestive of myxedema. In 1895, Hektoen<sup>5</sup> in reporting a case of exophthalmic goiter noted "over center of left leg anteriorly an area of doughy swelling in which the pitting caused by pressure soon disappeared." A similar case was described in the same year by Watson-Williams<sup>6</sup> who reported the presence of symmetrical, brawny patches on the lower extremities of a patient with Graves' disease. These appear to be the earliest references to this condition.

Good reviews of localized myxedema have been written by O'Leary<sup>7</sup>, Pillsbury and Stokes<sup>8</sup> and Carol<sup>9</sup>. In 1942, Trotter and Eden<sup>10</sup> summarized the available in-

formation on the subject. They reviewed 73 reported cases and added 4 of their own. Trotter and Eden suggested that hyaluronic acid, an important constituent of many mucins, may be present in the affected skin of patients with this condition, and that the abnormality of the skin may be due to a dysfunction of the normal metabolism of this compound. Prior to this, Chain and Duthie<sup>11</sup>, without presenting any evidence, stated that there seemed to be an accumulation of hyaluronic acid in the skin of myxedematous subjects. Trotter and Eden further suggested that the apparent increase of cutaneous mucin in myxedema might be due to a deficiency of hyaluronidase, the enzyme which hydrolyzes and liquefies hyaluronic acid.

Additional cases of localized myxedema presented at society meetings are recorded by Bamber<sup>12</sup>, Garner<sup>13</sup>, Schmidt<sup>14</sup>, Fraser<sup>15</sup>, Michelson<sup>16</sup>, The Cincinnati Society of Dermat. & Syph.<sup>17</sup>, Freudenthal and Brauhauer<sup>18</sup>, Becker & Rothman<sup>19</sup>, Tillman<sup>20</sup>, Umansky<sup>21</sup>, Nether-ton (2 cases)<sup>22</sup>, Tulipan<sup>23</sup>, Mitchell & Hetreed<sup>24</sup>, Levin & Tolmach<sup>25</sup>, Machacek<sup>26</sup>, and Green & Freudenthal<sup>27</sup>.

Sunseri<sup>28</sup> reported an unusual and extensive case of the nodular variety with myxedematous changes from the waist down in a woman following thyroidectomy. Parekh<sup>29</sup> described a typical case of bilateral plaque type myxedema in an Indian with recurrent thyrotoxicosis. Amersback & Kane<sup>30</sup> and Dedichen<sup>31</sup> reported typical cases. Cohen<sup>32</sup> in reporting a characteristic case in detail discussed nomenclature, etiology, etc.

Watson's<sup>33</sup> paper in 1946, reawakened interest in the subject. His data, although inconclusive, indicated that the content of mucopolysaccharides, including hyaluronic acid and chondroitin-sulphuric acid, was greater than normal in the affected skin of two patients with pretibial myxedema. Watson & Pierce<sup>34</sup> & <sup>35</sup>, investigating the biochemical aspects of the disorder, demonstrated experimentally that affected skin contained an excess of acid mucopolysac-

charides, including a substance exhibiting the characteristics of hyaluronic acid. They expressed the opinion that hyaluronic acid may be involved in the lesions of pretibial myxedema.

Curtis<sup>36</sup> in a recent paper discussed the relationship of localized myxedema to progressive exophthalmos. He thinks or believes that because of the frequent association of the two conditions, the similarity of their development, progress and duration, they may be allied manifestations. He concludes a probable pituitary origin of localized myxedema.

Certain cases<sup>37</sup> as reported, do not seem to meet the essential criteria either clinically or histologically to be included under the term localized myxedema.

#### Classification

Although all cases do not conform, localized myxedema may be divided into two general types. First, the nodular variety<sup>18,27,28</sup>, also called mucoid papular disease and characterized by papular or nodular infiltrations distributed over the face, arms, back, scrotum and other areas. In about one-half of these cases there is a concomitant hyperthyroidism and edema of the legs. Second, a plaque type involving the pretibial regions. The only consistent point of similarity between the two groups are the identical histologic changes. The following remarks will be largely confined to the plaque type.

#### Clinical

Over 75 well documented cases of localized myxedema were reviewed from the literature. Brief mention will be made of the salient symptoms. No case of pretibial myxedema has been described in a patient without past or present thyrotoxicosis. Frequently the hyperthyroidism is of an atypical or recurrent type. The condition may appear at any stage in the course of toxic goiter. It is particularly prone to occur fol-

lowing thyroidectomy, appearing simultaneously with the symptoms of recurrent hyperthyroidism. However, a considerable number of cases have been reported as occurring before operation. The onset of the disorder is usually about 1 year after thyroidectomy. The interval may be as short as 2 weeks or as long as 15 years. Circumscribed myxedema usually affects the anterolateral aspect of the lower half of the legs. Later the lesions may extend to the knee and also to the back of the leg and occasionally to the dorsum of the foot and toes. All cases described have been symmetrical; however, White in discussion on Becker & Rothman<sup>19</sup> mentions a personal case in a young man who clinically and microscopically had localized myxedema of one leg following thyroidectomy. The skin becomes thickened, dimpled at the hair follicles, and symmetrical elevated non-pitting plaques develop. The affected skin may be cooler and drier than the surrounding normal skin. The diagnosis may be established with certainty by biopsy. Usually, the lesions are asymptomatic, although occasionally slight itching or burning is noted. The patients, particularly women, complain chiefly of the cosmetic deformity. With extensive involvement the patient may complain of tiredness and aching of the legs. X-ray studies show no evidence of bony changes. The anemia, albuminuria, hypercholesterolemia, lowered metabolic rate, commonly present in generalized myxedema do not occur in the localized condition. Other blood chemistry examinations are usually within normal limits. The basal metabolic rate while characteristically elevated is occasionally normal and may be subnormal. The serological tests for syphilis are unaltered. Culture of excised tissue has not produced growth of bacteria. As yet similar lesions have not been demonstrated in other than cutaneous tissues.

#### Incidence

The youngest age at which the condition has been reported is 19 years and the oldest, 69 years, with the peak of

frequency being in the third and fourth decades of life. No case of circumscribed myxedema has been reported in childhood. Whereas hypo- and hyperthyroidism are about four times commoner in females than in males, localized myxedema occurs in the ratio of 1.2--1. Patients of the white races predominate but cases have been reported as occurring in the Negro<sup>26</sup>, Indian<sup>29</sup> and Chinese<sup>38</sup> races. There seems to be no particular occupational incidence, nor is there record of any hereditary tendencies. Cases have been described from all parts of the world, most often from the United States, Great Britain and Germany.

In spite of statements to the contrary, I believe that the incidence of the condition is not great. Trotter & Eden in 1942 referred to 77 cases. Since then 22 cases have been reported plus the 7 in this paper, making a total of 99 cases. Records from the University Hospitals of over 100 well documented cases of toxic and recurrent goiter were examined for mention of lesions suggestive of localized myxedema. In two cases, lesions resembling localized myxedema were described. Physical examination and biopsy sections from the pretibial areas of these patients were normal. The condition has been described in association with many other diseases, particularly diabetes and hypertension. The author was fortunate enough to observe a number of cases exhibiting most, if not all, essential diagnostic features of this interesting but not serious disease. These cases are recorded in detail below.

### Report of Cases

#### Case 1

History: , a white single woman, 41 years of age, a patient of Dr. H. E. Michelson, was first observed on May 12, 1948, with pale-red swellings on anterior surfaces of both legs. On admission to the Dermatology Service, University Hospitals, May 13, 1948, she stated that she had been in good health until December 1944, when, three weeks after

giving blood for a transfusion she experienced a severe attack of chills, fever, aching and swelling of both ankles and legs. This illness necessitated bed rest for about two weeks. The muscle and joint aching and pitting edema of legs persisted. At this time she was treated with thyroid extract with no improvement. During the summer of 1945 her weight dropped from 145 to 120 pounds. She also noted the onset of insomnia, weakness, tiredness, nervousness, exertional dyspnea and throbbing of finger tips. Re-examination at this time revealed a basal metabolic rate of plus 85 per cent. Thyroidectomy was performed in September 1945. She was greatly improved during the next two to three months but in December 1945, she noted a gradual onset of protrusion of eyes, excessive tearing, periorbital edema, photophobia, and intolerance of eyes to wind and cold. At this time a recurrence of the symptoms of weakness, tiredness and nervousness were observed. The protrusion of her eyes became progressively worse so that she was unable to close them completely. In January 1947, she sustained an injury to the front of her right leg and shortly thereafter noted the appearance of tender, firm, bluish-purple, blotchy, raised swellings in this area. These lesions gradually coalesced to form a single large swelling, which did not pit on pressure. Three weeks later similar small bluish swellings appeared on left leg. These gradually coalesced and enlarged. It is the patient's belief that the plaques shifted from anterior aspect of the middle third of leg to antero-lateral aspect of lower third. Although she still complained of intolerance of the eyes to light, wind and cold, and difficulty in shutting the eyes, the protrusion seemed less. In 1948, at the time of admission, she complained of intolerance to cold but not to heat, weakness, lassitude and exertional dyspnea.

Examination:- The patient was restless and apprehensive. The eyes had a distinct stare and were unduly prominent. With the exception of the legs, the skin of the body was of normal texture.

The blood pressure was 120 mm. of mercury systolic and 70 mm. diastolic. The pulse rate was 80 beats per minute. The temperature was 98°F. The patient weighed 146 pounds (66.2 Kg.). Examination of the eyes revealed marked exophthalmos, the patient being unable to close the lids completely. The pupils, cornea, media and fundi were normal. The vision was 20/70 in both eyes. There was no gross enlargement of thyroid or regional lymphadenopathy. Both legs between the ankles and the knees were somewhat thicker than normal. Measurements taken at the level of the ankle, of the swelling, and of the calf, are of interest to indicate the physical appearance of the leg. The two legs showed essentially similar measurements.

	<u>right</u>	<u>left</u>
ankle	23.3 cm.	23.2 cm.
swelling	29.8 cm.	29.2 cm.
calf	40.0 cm.	39.2 cm.

There were two strikingly symmetrical plaques over the antero-lateral surface of each leg, that on the right measuring 8.5 cm. in length by 7.5 cm. in width. These lesions were raised, firm, dimpled, non-tender, pinkish in color, with no evidence of ulceration. On the right leg there was a second smaller affected area with flat shiny translucent papules above the large lesion. All lesions were quite markedly colder than the surrounding normal skin. This solid non-pitting edema was well demarcated from the surrounding normal skin. The ankles and feet were normal in size and appearance. There was no tremor of extremities nor excessive moisture of palms or soles. Otherwise her physical examination gave essentially negative results.

Laboratory Findings:- Routine laboratory examination of the blood and urine revealed normal findings. The urine urobilin and coproporphyrin were within normal limits. The serological tests for syphilis were negative. The value for blood cholesterol was 171 mg. per 100 cc. of plasma, repeat examination was

190 mg., for cholesterol esters 128 mg. The galactose tolerance test was reported as 27.2 mg. in one hour (normal 30 to 40 mg. in one hour). Fluoroscopic and roentgenologic examination of the chest revealed no evidence of abnormality. A roentgen of legs showed soft tissue swelling of both legs but no evidence of bone pathology; considerable increase in subcutaneous fat and fluid was noted. Roentgenogram of skull gave negative results. Electrocardiogram was reported as normal. The basal metabolic rate was plus 64 per cent. A radioactive iodine tracer test showed 52 per cent retention at 72 hours (normal 25 per cent, plus or minus 5 per cent) a marked elevation.

Histologic Findings:- The microscopic examination of a biopsy specimen from the lesion on the right leg disclosed the following. There was a relative and absolute hyperkeratosis with some flattening of the rete ridges. Striking changes were noted in the cutis, more particularly in the deeper portion. The connective tissue was largely replaced by mucinous material. With the hematoxylin and eosin stain the collagen fibres appeared edematous and homogeneous with a tendency to take the basophilic stain. A mucicarmine stain revealed mucin deposited throughout the cutis and even in the subcutaneous tissue. The Weigert stain for elastic tissue demonstrated marked fragmentation of the elastic fibres. Similarly the van Gieson stain showed edema and degeneration of the collagen.

Course:- The above noted findings indicated a diagnosis of (a) recurrent hyperthyroidism (mild) with exophthalmos, and (b) localized myxedema.

The patient was treated with propylthiouracil and dessicated thyroid. The biopsy wound drained a reddish glairy material for some time. When last seen, in Dec. 1948, the leg lesions and exophthalmos were essentially unchanged although her general condition was improved

Case 2

History:- , a housewife, 55 years of age, a patient of Dr. E. T. Ceder, was first observed at the University Hospitals, Nov. 4, 1948. At this time she presented reddish non-pitting plaques on anterior surfaces of both legs. Her general health had been good until 1945, when she noted a gradual onset of weakness, tiredness, nervousness, tachycardia and intolerance to heat. There was no history of injury to the legs. During the summer of 1947 her legs became painful and swollen causing marked difficulty in walking. During the fall of 1947 there gradually appeared a painful, tender, reddish swelling first on the right leg and then on the left. These swellings did not pit on pressure and looked like "pig-skin". She remarked that they seemed "to be about to burst open". At this time, there was an exacerbation of the previously noted symptoms as well as some blurring of vision. She was treated with penicillin intramuscularly without relief. In July 1948, the basal metabolic rate was determined to be plus 29 per cent, and a subtotal thyroidectomy was done. Her general condition improved.

Examination:- The patient appeared to be in the best of health and was quite cooperative. With the exception of the affected areas on the legs, the skin of the body was smooth and pliable. The blood pressure was 130 mm. of mercury systolic and 85 mm. diastolic. The pulse rate was 80 beats per minute. The patient weighed 135 lbs. (61.2 Kg.). The thyroid was not enlarged. Measurements taken at the level of the ankle, of the swelling and of the calf are of interest when compared with the first case.

	<u>right</u>	<u>left</u>
ankle	23 cm.	23.5 cm.
swelling	25 cm.	24 cm.
calf	37 cm.	37 cm.

Symmetrical plaques were present over antero-lateral portion of each leg, that on the right measuring 16.5 cm. in length by 7 cm. in width and that on left 15 cm. in length by 7 in width. These pinkish-

red swellings were firm, dimpled and non-tender with well demarcated, raised borders. Many fine hairs were present over the lesions. The plaques were colder than the surrounding normal skin. No tremor of the extremities was noted. The remainder of the physical examination was essentially normal.

Histologic:- The microscopic findings in this case were in every respect similar to those in case 1.

Laboratory Findings:- Routine laboratory examination of the blood and urine revealed normal findings. Results of serologic tests for syphilis were reported as negative. The value for blood cholesterol was 200 mg. per 100 cc. of plasma, for cholesterol esters 150 mg. Roentgenologic examination of chest and legs revealed no evidence of abnormality. Electrocardiogram was reported as normal. Routine bacteriologic examination of the mucoid material which could be expressed from the biopsy wound yielded negative results. Special plasma protein fractionation studies showed no definite abnormalities other than a slight elevation of the gamma globulin.

Course:- There was no change in the appearance of the lesions during the time the patient was under observation.

Case 3

History:- , a farmer, 47 years of age, was first seen at the University Hospitals, Dec. 8, 1948. He gave a history of having had diabetes for 16 years. About a year and one half ago beginning exophthalmos was noted; since then, his diabetes became more difficult to control. In January 1948, he had night fevers, chills, diarrhea and weight loss. His teeth were extracted in May 1948. Shortly afterwards he developed a tender left testicle and a high fever which responded to penicillin treatment. Recently there had been some heat intolerance, nervousness and excessive sweating. For three weeks prior to admission he was troubled with severe generalized throbbing headaches, vomiting and flick-

ering of vision.

Examination:- The blood pressure was 145 mm. of mercury systolic over 70 mm. diastolic. The temperature 98.6°F., pulse 95 beats per minute and respirations 18. Bilateral exophthalmos was present, greater on the left. There was slight sclerosis and narrowing of the retinal vessels with a small pinpoint hemorrhage in the right fundus. The thyroid was not enlarged. The chest was clear. The heart was enlarged to the left in the 5th interspace. A systolic murmur was heard over most of the precordium. The skin was warm and moist. There was a fine tremor of the hands. The neurological examination was negative except for a decreased vibration sense. On the anterior aspect of the lower two thirds of both legs were multiple reddish large and small, papular, raised, firm elastic lesions. No pitting was noted. The eruption did not involve the posterior aspect of the legs.

Laboratory:- The blood serology was negative. Urinalyses showed varying degrees of sugar, acetone and diacetic. Urine and blood cultures were sterile. The hemoglobin was 13 gm., the leucocyte count was 5,800 per cmm. with a normal differential. The sedimentation rate was 55 mm. in 1 hour. The B.U.N. was 14 mg. per cent. Fasting blood sugar determinations were 526 and 600 mg. per cent. Total plasma proteins were 7.6 gm. per cent (albumin 5.3 and globulin 2.3 gm. per cent). Creatinine levels were 8 and 3 mg. per cent. The carbon dioxide combining power and the chlorides were normal. Agglutination tests were negative. Tuberculin test 1:1000 was positive. Chest x-ray showed the heart to be of left ventricular type with minimal cardiac enlargement. The skull x-ray showed no evidence of abnormality. Electrocardiogram was within normal limits. Fresh smears of the glairy mucinous material which oozed from the biopsy wound were stained for bacteria with negative results.

Course:- The exophthalmos, moist skin, tremor and irritability all pointed toward a diagnosis of thyrotoxicosis in ad-

dition to that of diabetes mellitus. The patient could not cooperate for a metabolism test. He was found to have a 65 per cent uptake of radio-active iodine. During the course of his diabetic treatment he received 100,000 units of penicillin every three hours for 4 days. No changes were noted in the leg condition. After a short stay in the hospital, the patient became extremely irritable and was finally discharged against advice.

#### Case 4

History:- ., a laborer, 24 years of age, a patient of Dr. E. M. Rusten, Minneapolis, when first seen in May 1934 complained of weakness, nervousness, exertional dyspnea, cardiac palpitations and prominence of the eyes. These symptoms had been present for about a month and were of sufficient severity that he had had to stop work.

Examination:- His pulse rate was 80 beats per minute. The thyroid gland was slightly enlarged and there was mild exophthalmos. The basal metabolic rate was plus 16 per cent. A diagnosis of toxic goiter was made. Treatment with Lugol's solution was instituted and a subtotal thyroidectomy was performed in July, 1934. His immediate postoperative course was satisfactory.

Course:- In December 1934, he experienced a gradual recurrence of his earlier symptoms. The basal metabolic rate was found to be plus 37 per cent. During the winter of 1935, both eyes became more prominent, he tired easily and had occasional palpitation. In Aug. 1935, he received two series of x-ray treatments to the thyroid gland at the University Hospitals, Minneapolis. In Nov. 1935, he noted the gradual appearance of non-pitting swellings over anterior aspects of both legs. These lesions were oval in shape, about 8 cm. in diameter and caused no discomfort. The basal metabolic rate at this time was plus 20 per cent. No history of injury was elicited. He continued treatment with Lugol's solution and dessicated thyroid. Biopsy of the lesion was performed in Jan. 1936. No change in

the appearance of the lesions was noted during the next 6 to 8 months. However, by July 1936 the swellings on both legs were observed to be smaller, particularly the upper portion. By June 1937, the plaque on the left leg seemed to be subsiding. In Dec. 1937 the lesion on the left leg had completely disappeared, while that on the right had receded so that the biopsy site was now outside the 5 cm. area remaining. By Aug. 1939, the patient was feeling fairly well, the exophthalmos was less and all evidence of the non-pitting edema had disappeared. This patient spent 2½ years in the army, including overseas service. During long marches he complained of cramping and aching of legs. There has been no recurrence of the swellings. There are slight depressions over the previously affected areas, the skin having a somewhat waxy appearance. He states that his legs tire and ache upon long standing. He has continued to take Lugol's solution and desiccated thyroid and feels very well.

Histologic:- Biopsy sections taken in Jan. 1936 were diagnostic.

#### Case 5

History:- , a white female, 57 years of age was first seen at the University Hospitals in May 1940 when she was admitted for investigation and treatment. Her past health had been good, except for a history of phlebitis of the right leg 20 years previously. During the year preceding admission she had noticed increasing insomnia. During the fall of 1939 she noted the gradual onset of nervousness, weakness, shortness of breath and increased sweating. She was intolerant of heat and became irritable easily. During the winter she noted a marked "heaviness" in the legs as well as increasing prominence of the eyes. There had been a 30 lb. weight loss since November 1939.

Examination:- The patient was a well-developed, well-nourished female. Temperature was 99.4°F., pulse 120 beats per minute and respirations 20 per min-

ute. The blood pressure was 200 mm. of mercury systolic and 100 mm. diastolic. The patient was restless, her skin was flushed and warm. There was bilateral exophthalmos more marked on the right. The thyroid gland was symmetrically enlarged. The heart was slightly enlarged to the left. A hard edematous swelling of the legs was noted. The remainder of the physical examination was negative.

Laboratory:- The hemoglobin was 70%. The leucocyte count was 10,700 per cmm. with 66% neutrophils. The electrocardiogram was within normal limits except for sinus tachycardia. The basal metabolic rate on May 24, 1940 was plus 61 per cent. A diagnosis of Graves' disease with mild essential hypertension was made. On June 14, 1940 a subtotal thyroidectomy was performed. Microscopic section of the gland was reported as typical of Graves' disease. She made satisfactory progress postoperatively.

Course:- In August 1940 she complained of weakness and aching of the legs. In Oct. 1940 a leathery, reddened non-pitting, non-tender soft tissue swelling appeared above both ankles. At first the swelling and redness disappeared after elevation of legs or after bed rest, but gradually it became more permanent. Examination in Feb. 1941 showed these brown, indurated lesions to be present still on antero-lateral surfaces of the legs just above the ankles. During the latter part of 1943 a gradual regression of the leg lesions occurred. This continued slowly during the following year. In Jan. 1945 she developed nervousness, tachycardia and palpitation. Her blood pressure was 175 mm. of mercury systolic and 90 mm. diastolic. There was a moderate exophthalmos of the right eye and a fine tremor of the hands. There was no evidence of a recurrence of the previously noted leg lesions. A diagnosis of recurrent hyperthyroidism was made. Her condition improved with treatment. She has continued in fairly good health to the present with no symptoms or recurrence of the leg lesions.

Histological:- Biopsy sections taken in Oct. 1940 showed the characteristic histo-

logical picture of localized myxedema.

### Case 6

History:- , a white married male, 45 years of age, was first seen at the University Hospitals on Dec. 17, 1934. The patient stated that he had not been well since an attack of influenza in 1918. He complained of weakness, shortness of breath, increasing nervousness, palpitation and protrusion of the eyes. A diagnosis of hyperthyroidism was made and thyroidectomy was performed in Jan. 1931. Shortly after this he noted for the first time a peculiar, non-pitting swelling of his feet and legs. In Feb. 1932 a second thyroidectomy was performed; however, the swellings on his legs continued to become larger. At the time of his admission to hospital in Dec. 1934, he complained of insomnia, nervousness, irritation of the eyes and changes in the skin over the lower portions of both legs.

Physical Examination:- The blood pressure was 115 mm. of mercury systolic and 79 mm. diastolic. Bilateral exophthalmos was present. Examination of the media and fundi of the eyes was negative. Examination of the legs showed elevated, discrete and confluent papular lesions varying in size from 1 cm. to 5 cm. These swellings were firm and rubbery. The skin surface was smooth and dry and of a reddish-pink color. The lesions were elevated above the surrounding normal skin but did not pit on pressure. The remainder of the physical examination was essentially negative.

Laboratory:- Urinalysis was negative. The hemoglobin was 85%. The leucocyte count was 7,050 per cubic millimeter of which 69% were neutrophils and 31% lymphocytes. The Wassermann and Kahn tests for syphilis were negative. Blood calcium was 11.3 mg. per cent and phosphorus was 3 mg. Basal metabolic rate determinations were minus 14 per cent and minus 6 per cent respectively. Roentgenologic examination of the chest was within normal limits. Electrocardiogram was normal.

Microscopic:- When the biopsy was performed, a mucoid material could be expressed from the wound. The section was in every way typical of localized myxedema.

Course:- No definite diagnosis of generalized hyperthyroidism or hypothyroidism could be made. During the patient's stay in the hospital some regression of the swellings was noted. By 1936, five years after their initial appearance, the nodular lesions on the front of the legs had almost entirely disappeared with those on the posterior aspect of the legs regressing more slowly. However, when seen again in 1945 and in 1946, little change was noted from the original appearance. Prior to this he had frozen his hands and feet while lying unconscious in the snow. Immediately following this exposure to cold, there was a marked increase in the myxedematous areas.

### Case 7

History:- , a white male, 62 years of age, was first observed on Aug. 10, 1933. He gave a history of a subtotal thyroidectomy in 1917. Following the operation he was in good health until 1923 when he had a recurrence of his earlier symptoms. A second operation was performed in 1923. In 1932, fifteen years after the first operation, he noted the onset of leg swelling and the appearance of multiple nodules over anterior surfaces of the legs. The patient ascribed these lesions to a fall in a street car with injury to his legs. Following the injury he soaked his feet in extremely hot water. It was shortly after this that the swellings first appeared.

Examination:- Multiple, firm, reddish nodules, 1 cm. to 2 cm. in size were present over the tibial crests. On palpation the lesions gave the impression of being filled with fluid. A plaque about 3 cm. by 3 cm. was noted on right great toe with similar brawny indurated lesions on both calves. There was slight exophthalmos and some tremor of hands,

Laboratory:- The basal metabolic rate was found to be plus 65 per cent.

Microscopic:- The sections were characteristic of localized myxedema.

Course:- The patient was seen in Oct. 1937 complaining of dizziness and fainting spells. Examination at that time disclosed exophthalmos and a basal metabolic rate of plus 29 per cent. On the middle and lower thirds of both legs were present translucent, indurated nodules. The skin seemed to be thickened, especially around the ankles. Both great toes presented large non-pitting plaques on their dorsal aspects. This patient died of cancer of the stomach in 1943. The leg swellings persisted essentially unchanged up to the time of his death. He was able to walk easily and at no time complained of pain in legs.

#### Comment

#### Nomenclature

There is no generally accepted name by which this condition is known and which might differentiate it from nodular myxedema. Because of the myxomatous changes in the corium it seems reasonable to use the term localized myxedema. It seems better not to include "pretibial" for in many cases the lesions extend completely around the leg and may involve the dorsum of the foot and toes. The disorder is also known as "Localized Pretibial Myxedema", "Circumscribed Myxedema", "Localized Solid Edema of the Extremities in association with Exophthalmic Goitre" and "Myxoedema Circumscriptum Thyrotoxicum", etc.

#### Etiology

The cause of the disease is unknown, nor is it understood whether the condition is local or systemic in nature. Many theories have been advanced as to its pathogenesis. The condition does not seem to be the direct result of either hypothyroidism or hyperthyroidism. Unfortunately the fundamental nature of

Graves' disease remains unknown, and hyperthyroidism per se is to be regarded as only one part of the syndrome. Not infrequently hyperthyroidism is controlled by subtotal thyroidectomy and yet the other features of the disease do not subside. In most cases of the plaque type of localized myxedema, it is noticeable that the area affected is remarkably constant, namely the lower portion of the legs. This should have some causal significance. Many theories have been advanced to explain this phenomenon. Trauma has been suggested as a possible cause. It is to be noted that in this series only one patient gave a history of trauma prior to the appearance of the lesions. There is no constancy of preceding leg edema either due to central or peripheral causes. The presence of toxins and degeneration of the collagen have also been mentioned as possible causes. None of these hypotheses has much to support them. As further advances in internal medicine are made it seems unlikely that overactivity of the anterior pituitary plays a specific role in the etiology; however, localized myxedema and exophthalmos both develop in connection with thyrotoxicosis and the thyrotropic hormone may have some causal influence.

Thyroid hypofunction produces retention of salt, water and protein in the tissue spaces. The skin becomes dry, rough, swollen and inelastic, not pitting on pressure. Originally it was thought that these changes resulted from the over production of mucin. Recent observations confirm the existence of extracellular increase of mucoprotein in hypothyroidism. In addition to retained protein appreciable quantities of water and sodium chloride are stored. Utilizing a photo-electric skin colorimeter after injection of fluorescein, Lange<sup>39</sup> demonstrated a decided increase in capillary permeability in 5 cases of generalized myxedema. With thyroid therapy the permeability rapidly returned to normal. Michael<sup>40</sup> thought that the myxedematous changes in the skin of Graves' disease patients were caused by chemical transformation of thyroxine within circumscribed areas of the skin.

It has been demonstrated that the affected skin of patients with pretibial myxedema contains an excess of hyaluronic acid<sup>33</sup>, the abnormality thus may be related to a disturbance of the hyaluronic acid--hyaluronidase balance. We know that hyaluronic acid in animal tissues seems to bind water in interstitial spaces. It further holds cells together in a jelly-like matrix. Thus the physiologic aspects of hyaluronic acid seem of considerable importance. Mucoid material obtained from a plaque of localized myxedema was negative when tested for the presence of sugar. After precipitation from an aqueous solution by acidification a faintly positive reaction was obtained. Because of the small amount of material available for examination this could not be confirmed. If positive it would indicate that the mucinous material was of the nature of a glycoprotein. Solution of this problem must await an increase in our meagre knowledge of the physiologic chemistry of normal and myxedematous skin.

### Histology

In reviewing the histologic sections of the reported cases certain findings were observed to be fairly constant. It was felt that the microscopic picture of localized myxedema was diagnostic and characteristic. This is in distinction to the variety of microscopic changes noted in the skin in generalized myxedema<sup>41</sup>. Tissue sections were stained with hematoxylin and eosin, mucicarmine, van Gieson and Weigert stains. Sections revealed a variable degree of hyperkeratosis, plugging of the hair follicles and thinning of the remainder of the epidermis. This thinning or flattening of the epidermis appeared to be secondary to changes in the dermis and was in proportion to the duration of the disease. The papillary layer in the upper cutis was essentially unchanged. This was well illustrated by the delicate elastic fibres running vertically in the papillary bodies and the normal staining collagen. The remainder of the cutis showed extensive changes. There was marked edema with

spreading apart of the connective tissue and elastic fibres. The degree of edema in the cutis varied considerably. In some sections it resulted in almost complete loss of structure. In others, it was less marked. Various sections showed well developed normal appearing hairs, erector pili muscles and sebaceous and sweat glands with normal glandular epithelium. Nor was there evidence of any changes in the deeper vessels. A minimum of true inflammatory changes was noted.

In sections of normal skin, mucinous staining material is constantly present in very small amounts, but much less than in myxedematous skin<sup>9,41</sup>. Excess of mucin is found in the skin of adults in only two conditions; namely, hypothyroidism (generalized myxedema) and localized myxedema. Presently available mucin stains are unsatisfactory because of the tendency of the stain to diffuse giving a false reaction to some of the collagen fibres. However, the stain is of considerable value in differentiating the condition because of the constant presence of this purplish staining substance.

### Diagnosis

In the differential diagnosis the following entities must be considered. Amyloidosis cutis may be localized to small areas, such as the leg. Here the consistency of the lesions is firmer, the color lighter and the lesions are usually smaller. Vital staining of the nodules can be demonstrated by intracutaneous injection of Congo Red. In scleroderma which may occur in association with Graves' disease, the skin is indurated and feels stiff, the color may be yellow or ivory and later the skin and subcutaneous tissues become firmly bound to the underlying structures. Lymphedema is less likely to be circumscribed and verrucous changes may be exhibited. In colloid degeneration of the skin the lemon-yellow colored papules usually occur on the face and the backs of the hands. Erythema nodosum, multiple ganglioneuroma and leprosy must also be considered.

## Treatment

With the discovery of the newer goitrogenic anti-thyroid drugs such as propylthiouracil, thyrotoxicity can be eliminated almost at will although response is relatively slow. A therapeutic trial of dessicated thyroid is indicated, particularly where a hypothyroid state exists. No satisfactory method of treatment has been found for the local condition. Excision of the affected areas has been carried out for cosmetic reasons with fair success<sup>7</sup>.

Sharlit, in discussion on Curtis<sup>36</sup> stated that hyaluronidase was beneficial in the treatment of localized myxedema. Encouraging results were obtained in the first case by the local use of hyaluronidase and will be the subject of another report<sup>42</sup>. In the second case, 150 turbidity reducing units of hyaluronidase dissolved in normal saline were injected subcutaneously into the plaques on both legs. It is still too early to appraise the results in this patient. Caution must be exercised in the use of this material because while hyaluronic acid is not antigenic, hyaluronidase almost certainly is.

Dependent on the demands of the patient and in view of the fact that many of these lesions spontaneously subside, I feel that any type of radical treatment is contraindicated. Frequently the drainage of mucinous material from the biopsy site results in a temporary decrease in the size of the lesion.

## Prognosis

Spontaneous involution over a period of years has been reported by a number of observers including O'Leary<sup>7</sup>, Trotter & Eden<sup>10</sup> and Dunhill<sup>43</sup>. The leg lesions of two cases in the present series completely regressed within 4 years from the time of onset. These cases were observed for 9 and 15 years with no evidence of recurrence. On the other hand the disorder may persist unchanged for many years as in Case #6 where the leg lesions have remained practically unchanged for 15 years. It

may be speculated that the ultimate disappearance of the lesions was due to a resumption of a normal endocrine balance.

## Summary

This report reviews 7 cases of localized myxedema in patients presenting symptoms of thyrotoxicosis. Five patients gave the characteristic history of thyroidectomy with temporary improvement, recurrence of toxic symptoms and concomitant appearance of localized, firm, non-pitting, reddish-pink plaques on the anterior surfaces of the legs. This type of localized myxedema occurs only in association with exophthalmic goiter.

The classification, clinical course, pathological features and recent literature are reviewed.

The diagnostic histologic picture is characterized by a marked edema in the cutis and the presence of mucin in this area.

The cause of these skin lesions is unknown, although there may be some connection with hyaluronic acid metabolism.

Treatment of the hyperthyroidism does not materially influence the plaques on the legs. Use of the enzyme, hyaluronidase offers some promise in the treatment of the local condition.

Spontaneous involution may occur within a period of three to ten years. Once the condition clears, there is no tendency to recurrence.

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### III. MEDICAL SCHOOL NEWS

#### Coming Events

March 2 - Clarence M. Jackson Lecture-ship; Dr. E. T. Bell; "Pathology of Diabetes"; 8:15 p.m.; Museum of Natural History Auditorium.

March 3 - George Chase Christian Lecture; Dr. Ira T. Nathanson; "Hormonal Alteration of Advanced Cancer of the Breast"; 8:00 p.m.; Medical Sciences Amphitheater.

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#### Cancer Course for Physicians

Non-metropolitan physicians from Minnesota and North Dakota will attend a continuation course in cancer on March 3, 4, and 5. The course is sponsored by the Cancer Control Division of the Minnesota Department of Health, the Minnesota Division of the American Cancer Society, and the Minnesota Medical Association. Dr. Ira T. Nathanson of Harvard University will participate as a member of the faculty and will present the George Chase Christian Lecture at 8:00 p.m., Thursday, March 3, on the subject of "Hormonal Alteration of Advanced Cancer of the Breast."

#### Cancer Course for Lay People

The Center for Continuation Study will be presenting a Cancer Course for Lay People on February 17 and 18. This course is sponsored by the Minnesota Division of the American Cancer Society. Lay workers in the Minnesota Division of the American Cancer Society and its various component Societies will come to the Center and hear lectures and view demonstrations especially planned for lay people to inform them regarding modern concepts of neoplasia and methods of diagnosis and management.

Distinguished speakers who will participate in the meetings will include Mr. Mefford R. Runyon, Executive Secretary of the American Cancer Society; Dr. Harold S. Diehl; and Dr. Owen H. Wangensteen. Other members of the full- and part-time faculty of the Medical School will participate in the program. Dr. David P. Anderson will talk on "Cancer from the Standpoint of the General Physician."

#### New Minn. Medical Foundation Members

Dr. J. B. Clement, Lester Prairie  
Dr. E. A. Olson, Pine Island  
Dr. P. L. Halenbeck, St. Cloud

#### Kellogg Foundation Lectures

The following lectures will be given during the week of February 21. All medical students, interns, nurses, technicians, dietitians, and physicians are cordially invited to attend these lectures. A special invitation is extended to University Fellows.

Dr. Miland E. Knapp	"Some Present Concepts of Physical Medicine"	Monday, February 21, 4:00-6:00 p.m. Powell Hall Amph.
Dr. John R. McDonald	"Pathology of Bone Tumors"	Wed., February 23, 1:00-3:00 p.m., Todd Amphitheater