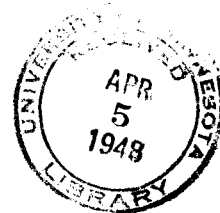


Bulletin of the



University of Minnesota Hospitals
and
Minnesota Medical Foundation



Therapy of
Hyperthyroidism

STAFF MEETING BULLETIN
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Volume XIX

Friday, April 2, 1948

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

April 5 - April 10, 1948

No. 197

Monday, April 5

- 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; Interns' Quarters, U. H.
- 9:15 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
- 10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.
- 11:00 - 11:50 Physical Medicine Conference; Arthritis; Myron Lecklitner; E-101, U.H.
- 11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans' Hospital.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.
- 12:15 - 1:20 Obstetrics and Gynecology Journal Club; M-435, U. H.
- 12:50 - 1:20 Pathology Seminar; Ewing Bone Sarcoma; David Nelson; 104 I. A.
- 12:30 - 1:30 Physiology Seminar; Some Aspects of Estrogen Androgen Mechanisms; Robert Huseby; 214 M.H.
- 12:30 - 1:50 Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis General Hospital.
- 1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
- 4:00 - 5:00 Pediatric Seminar; The Value of Routine Wrist X-rays in Pediatric Practice; William Frey; 6th Floor Seminar Room, U. H.
- 5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-515, U. H.

Tuesday, April 6

- 8:30 - 10:20 Surgery Reading Conference; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.
- 9:00 - 9:50 Roentgenology Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.
- 12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

- 2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.
- 3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.
- 3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.
- 4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. L. Visscher; Eustis Amphitheater, U. H.
- 4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.
- 5:00 - 5:50 Roentgenology Diagnosis Conference; D. L. Fink and Staff of Veterans' Hospital; M-515, U. H.

Wednesday, April 7

- 8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.
- 8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.
- 11:00 - 11:50 Pathology-Medicine-Surgery Conference; Subject to be announced; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, General Hospital, Veterans' Hospital.

Thursday, April 8

- 8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-515, 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; Todd Amphitheater, 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 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.
- 12:00 - 12:50 Physiological Chemistry Seminar; The Mechanism of Phloridzin Glucosuria; Irving Oneson; 214 M. H.
- 1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.
- 4:00 - 4:50 Bacteriology Seminar; Subject to be announced; 214 M. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
- 5:00 - 5:50 Roentgenology Seminar; Observations at the Mayo Clinic; H. M. Stauffer; M-515, U. H.

Friday, April 9

- 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, A. V. Stoesser and Staffs; Minneapolis General Hospital.
- 11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; The Retina in Systemic Hypertension; John Wendland; New Powell Hall Amphitheater.
- 12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Class Room.
- 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 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, April 10

- 7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.
- 8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.
- 8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; Veterans' Hospital.
- 9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; M-515, U. H.
- 10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.
- 11:00 - 12:20 Anatomy Seminar; Right diaphragmatic hernia, L. J. Wells; Experimental studies of prenatal digestive processes in rats, J. F. Hartmann and L. J. Wells; 226 I. A.

II. THERAPY OF HYPERTHYROIDISM

George Cullen
Edmund B. Flink

A survey of the results of the therapy of hyperthyroidism during the past ten years has been undertaken. We have not been able to summarize all of the charts for this period of time because of factors beyond our control. All charts of patients treated with thiouracil have been summarized. The remainder of the charts have been obtained without special selection from the record room. The

study was undertaken with two major objectives in mind. The first was the comparison of the results of therapy in the pre-thiouracil era with those of the thiouracil era. The second objective was to learn our deficiencies in diagnosis and therapy. Incidentally it has been possible to review the incidence of the major manifestations of toxic diffuse and toxic nodular goiter. As the discussion progresses it will be evident that both the medical and surgical services share in the deficiencies as well as the good results. We shall attempt to make a fair appraisal of the facts.

Table 1

	Toxic Diffuse Goiter Female	Toxic Diffuse Goiter Male	Toxic Nodular Goiter Male & Female	Toxic Diffuse Thio. & Surgery	Toxic Nodular Thio. & Surgery	Thio. Maint. Therapy	X-ray Therapy
No. of Patients Total 244	78	22	74	19	26	10	15
Average Age	36.8	41	50	37	57	44	39.2

The cases comprising this study will be discussed in some detail. Table 1 indicates the distribution of the patients according to type of illness and therapy. The predominance of females is evident, 78% of the toxic diffuse goiters occurred in females. The average age of these females was lower than the males and there was a significantly larger number of females in the adolescent period. There were only 7 males out of 100 patients with toxic nodular goiter. As expected the average age of the nodular goiter patients is significantly higher than the average age of the toxic diffuse goiter patients. In addition to the patients listed, there were 14 others. Three of these patients had severe hyperthyroidism but signed out against advice before definitive therapy could be given. Six patients received thiouracil for too short a period to warrant inclusion in the study. Four patients had complications from thyroidectomies carried out elsewhere (one with bilateral vocal cord paralysis, progressive exophthalmos

and hypothyroidism). One patient had a very satisfactory result from surgery here but the chart with details of treatment was lost and hence not included in this series. Therefore, the total number of patients studied actually is 258.

The incidence of the various symptoms recorded before any definite therapy, is found in Table 2. Your attention is directed to the uniform occurrence of nervousness in all groups and the greater incidence of all other symptoms, except choking and dysphagia, in toxic diffuse goiter than in toxic nodular goiter. The incidence of nervous and motor symptoms are uniformly greater in females than males. In general the symptoms corresponded well with those recorded by Williams.¹

Many of our charts are inadequate in that a complete history is not recorded by anyone from the staff members to the clerks. Specific details of symptoms

Table 2

Symptoms	Toxic Diffuse Goiter Female (78)	Toxic Diffuse Goiter Male (22)	Toxic Nodular Goiter Male & Female (74)	Series of Robert H. Williams
Nervousness	100%	96%	97%	99%
Heat Intolerance	92%	87%	63%	85%
Sweating	94%	87%	67%	91%
Incr. Appetite	78%	87%	48%	
Weight Loss	85.6%	100%	70.3%	85%
	23# av.	21# av.	14# av.	
Weakness	96%	87%	77%	70%
Tremor	93%	73%	61%	
Palpitation	94%	82%	85%	89%
Exophthalmos	42%	54%	7%	
Dysphagia	15%	0%	20%	
Choking	24%	27%	67%	
Evident Goiter	69%	54%	93.2%	
Dyspnea	73%	77%	68%	75%
Edema	12%	9%	16%	35%

and particularly those regarding muscle strength, tremor and cardio-vascular symptoms, were often lacking. All too often a statement like this - "typical

symptoms and signs of hyperthyroidism" - were made without any specific details.

Table 3

Signs	Toxic Diffuse Goiter Female (78)	Toxic Diffuse Goiter Male (22)	Toxic Nodular Goiter Male & Female (74)	Series of Robert H. Williams
Exophthalmos	58%	60%	12%	71%
Lid Lag	58%	55%	24%	
Palpable Thyroid	96%	91%	97%	100%
Bruit	62%	45%	12%	77%
Weakness	65%	33%	44%	-
Tremor	90%	96%	70%	97%
Skin (Warm and Moist)	86%	90%	77%	97%
Skin (Pigmentation)	9%	5%	2%	
Nail Changes	9%	43%	20%	-
Palpable Spleen	5%	9%	1.5%	10%
Pulse - Average Rate	110	117	99	-
Pulse - % over 80	100%	100%	89%	100%
Average Systolic B.P.	140	142	142	-
Average Diastolic B.P.	74	73	90	-
Systolic Murmur	70%	78%	45%	-
Edema	8%	9%	1.5%	-
E.C.G. - Auricular Fibrillation	5%	27%	8%	10%
E.C.G. - Significant Changes	16%	40%	12%	-

The incidence of signs is recorded in Table 3. The percentage of patients with objective evidence of muscular weakness may be misleading. The details of tests carried out were scanty and only those with a specific statement regarding the testing for weakness were included. The importance of myasthenia cannot be overemphasized and should be looked for more diligently.² The myasthenia may be so marked that it may be confused with other myopathies. Chronic thyrotoxic myopathy is an entity worthy of recognition, for the condition can be cured completely by proper therapy for the hyperthyroidism.^{3,4} There are some signs whose incidence is undoubtedly too low, such as pigmentation of the skin and nail changes. There are probably too few patients with specific statements regarding the presence of edema of the legs. It is entirely possible that the spleen was not searched for as diligently as might be possible. Often the only statement about the absence of splenomegaly was found in the clerk's record.

It was surprising to find that the average systolic blood pressures of all three groups of patients were practically the same. The average pulse pressure was greater in the toxic diffuse goiters than in the toxic nodular goiters. A few pa-

tients with toxic nodular goiter had a normal pulse rate in spite of distinct evidences of toxicity otherwise. However, 100% of the patients with toxic diffuse goiter had a rapid pulse. The incidence of systolic murmurs over the apex of the heart should be noted. There were many notes in the charts indicating that various persons were unduly concerned about the systolic murmurs in these patients. We believe that the actual incidence is greater even than 70 to 78% as recorded in Table 3. Even so, an incidence of 70% is enough to consider a systolic murmur as one of the usual manifestations of hyperthyroidism. In the instances where edema was noted, there usually was other evidence of cardiac failure too. There was a higher incidence of auricular fibrillation and a higher average pulse and pulse pressure in males with toxic diffuse goiter than in females. This probably is indicative of the greater severity of hyperthyroidism in the males, which is evident again in the higher average basal metabolic rates in males than in females. (Table 4) The incidence of auricular fibrillation in all patients with toxic diffuse goiter is 10%, the same as in Williams series.¹ A word of explanation is necessary for the significant changes in the electro-

Table 4

	Toxic Diffuse Goiter Female (78)	Toxic Diffuse Goiter Male (22)	Toxic Nodular Goiter Male & Female (74)	Toxic Diffuse Thio.& Surgery (19)	Toxic Nodular Thio. & Surgery (26)	Thio. Maint. Therapy (10)
Initial B.M.R.	47.5%	55%	33%	54%	58%	44%
Pre-op. B.M.R.	24.4%	31.5%	20.5%	24%	38%	19%
No. of Days	23.5 d	24 d	30 d	26.5 d	37 d	42 d
Pre-op. Hospital Days	13.3 d	14 d	8.3 d	44 d	48 d	
Post-op. Hospital Days	7 d	10.5 d	7.7 d	6.1 d	7.2 d	
Post-op. Reactions*						
Per Patient	20.5%	59%	26%	30%	25%	
Per Operation	15%	32%	-	30%	25%	
Average Pre-op. B.M.R. (Patient with Reactions)	28.5%	39.9%	24.6%	11.3%	35.5%	

*Temperature over 102 post-operatively.

cardiogram. Auricular fibrillation, changes in atrio-ventricular conduction, ST and % wave changes, evidences of heart strain, etc., are all included. Tachycardia per se is excluded from the category of abnormal electrocardiograms. Incidentally, there were 14 diabetics or 6.0% of the patients studied.

Average basal metabolic rates are recorded in Table 4. Often only one test was obtained before therapy, so the first was used. Of course, the first test is subject to errors, but usually insufficient information was recorded to justify choosing any other. However, occasionally when a series of tests were recorded before therapy and the first was obviously erroneously high, a subsequent result was used. The range of initial basal rates for the toxic diffuse goiter group is +14 to +111% and the range of preoperative basal rates is +6 to +69%. Note the group of toxic nodular goiters treated with thiouracil. These patients had more severe hyperthyroidism than the average in the rest of the groups. The patients who were maintained on thiouracil for three months or more, often had infrequent basal metabolic rates after the first six weeks, so we chose the shortest interval in which a distinct reduction in

the basal metabolic rates occurred, to indicate the rate of response.

The average basal metabolic rates of patients with postoperative febrile reactions are only slightly higher than the average of all cases in the iodine treated patients and actually, less than the average in the thiouracil groups. The hospital stay will be discussed later. An arbitrary limit for postoperative reactions was chosen. Any patients with a temperature elevation to 102° or more is included, even if for only one reading. None of the patients treated preoperatively with thiouracil had a real crisis postoperatively. The incidence of reactions in the iodine treated males with toxic diffuse goiter is striking. Some of the patients had true postoperative thyroid crisis and the records indicate concern for the immediate prognosis of these individuals. Some of the women also had severe reactions which could be classed as postoperative thyroid crisis.

Other laboratory tests were carried out sporadically. Total cholesterol concentrations in mg. per 100 cc. of plasma or serum (not stated in the laboratory reports) were recorded in 110

Table 5

	Details of Operations				
	Toxic Diffuse Goiter (78) Females	Toxic Diffuse Goiter 22 Males	Toxic Nodular Goiter (74) M&F	Toxic Diffuse Goiter Thiouracil (19) M & F	Toxic Nodular Goiter Thiouracil (26) M & F
Bilateral Thyroidectomies	55%	50%	55.5%	95%	100%
Unilateral or Multiple Stage Thyroidectomies	45%	50%	44.5%	5%	
No. of Patients	78	22	74	19	26
No. of Operations	109	39	83	19	26
No. of Surgeons	19	12	19	6	8
Average Weight of Gland Removed in Grams					
Bilateral	41.6	54.9	83.2	39	140
Unilateral	24.9	29	72.6	11 (1)	

instances. 23.6% were below 150 mg., 73.6% were less than 200 mg., but 26.4% were greater than 200 mg. per 100 cc. The oral-venous galactose tolerance test was positive in 23 out of 24 (96%) instances in which it was performed. Hammersten⁷ found the test positive in 59 out of 69 cases (85%) at this hospital. Creatinuria was looked for infrequently but when recorded there was a significant amount of creatine in the urine.

Table 5 is one of the most interesting of the group. Attention is directed to the high percentage of stage operations in the toxic diffuse goiter patients -- 148 operations in 100 patients. In the toxic nodular group there is an apparent discrepancy between the number of operations and the percentage of unilateral operations, but in many instances only one lobe was involved and a lobectomy was all that was considered to be necessary. Most of the operations were performed by the senior surgical residents or junior staff members. Larger amounts of thyroid were removed from males. Approximately the same average weight of gland was removed from patients who received thiouracil as those treated with iodine. The average weight of the thyroid glands removed in the thiouracil-treated toxic nodular goiters was 140 grams compared with 83 grams for the iodine treated group. This is another evidence of the severity of the

disease in this group.

The number of preoperative hospital days in the thiouracil treated groups is much greater than in the iodine group (Table 4). However, in many instances patients were first treated with iodine and when it was evident that an incomplete response was being obtained, thiouracil was begun. This is evidenced by the fact that the average duration of thiouracil therapy was 26 and 37 days compared with 44 and 48 preoperative hospital days for the two groups. At the present time it is unnecessary to hospitalize the majority of patients for propylthiouracil therapy and a long preoperative hospital stay can be eliminated. Multiple stage thyroidectomies were eliminated entirely in the thiouracil treated patients. One lobectomy was carried out in a patient who had a previous subtotal thyroidectomy and only one lobe was enlarged. In reviewing the charts it was not always possible to determine why a decision was made to do a stage thyroidectomy in iodine treated patients, but there must have been adequate reason. There were no deaths in the patients with toxic diffuse goiter.

Table 6 summarizes some of the information on thiouracil therapy. There were no frank failures in the toxic

Table 6

	Thiouracil Therapy		
	Toxic Diffuse Goiter Surgery (19)	Toxic Nodular Goiter Surgery (26)	Thiouracil Maintenance Therapy (10)
Average Days of Thiouracil	26.5 d	37 d	9 mo
Average Decrease in Metabolism	30%	20%	25% (42 d)
Average Weight Gain	9.5#	7.6#	15.3#
Use of Iodine before Thiouracil	77%	73%	50%
Toxic Reactions	15%	15%	10%
Leukopenia	5.5%	7.5%	10%
Remissions	13	10	3
Deaths	0	1	1
Recurrence	0	0	2
Inadequate Follow-up	6	13	4

diffuse goiters but two patients with adenomatous goiters were maintained on thiouracil for 79 and 108 days with only partial or no response. Both were subjected to thyroidectomy and one patient died immediately preoperatively. Perhaps this patient should not have been operated on, but the circumstances were such that it was thought to be the best procedure at the time. Both of these patients had iodine for long periods before starting thiouracil so the results must also be considered a failure of iodine therapy as well. The total incidence of toxic reactions was 14%. Thiouracil therapy had to be interrupted in 5 out of 55 patients because of fever, thrombocytopenia, or

leukopenia. One additional patient developed leukopenia and neutropenia with fever several days after discontinuing the drug. Of the patients with adequate follow-up, there was no recurrence of hyperthyroidism after surgery. Of course there are multiple factors involved and one cannot ascribe an absence of recurrence to thiouracil alone.

Table 7 summarizes the final results of therapy. The most striking defect in the whole group of patients is the poor follow-up after therapy. In some charts both medical and surgical clinics were satisfied with a follow-up of just

Table 7

Summary of Results of Therapy	Toxic Diffuse Goiter Female	Toxic Diffuse Goiter Male	Toxic Nodular Goiter Male & Female	Toxic Diffuse Thio. & Surgery	Toxic Nodular Thio. & Surgery	X-Ray Therapy Non-Op.	Op.
Good Results (B.M.R. below 20 or feeling well 6 months)	46	10	40	13	10	11	4
Residual Symptoms or Recurrence	10	2	5	0	0	4	5
Postoperatives Deaths	0	0	1	0	1		
Follow-up Less 6 weeks	14	4	14	2	11	2	
6 wks. - 6 mos.	6	5	14	4	3		
Complications Recur. N. Paral.	6	2	1	2	0	0	
Hypoparathyroid	0	1	0	2	1	0	
Myxedema	7	1	2	2	1	2	
Malignant Exophthalmos	0	1	0	0	0	0	

6 weeks and then discharged the patients from the clinic. In other instances, the only notes made were those referring to the surgical wound and its healing. In still others, no basal metabolic rates were obtained postoperatively. A patient has not been observed adequately postoperatively unless he has had a basal metabolic rate determined at least 6 months

after surgery.

Complications

Two patients died in the postoperative period (0.9%). Both deaths were in elderly women with nodular goiters. Hypoparathyroidism occurred in 2% of the patients. Recurrent nerve paralysis

occurred in 5% of the surgical patients. Myxedema occurred in 6% of the surgical patients and in 7% of patients treated with X-ray. Progressive exophthalmos was present in one patient but unfortunately his follow-up was only 6 weeks. At this point it may be well to review the findings of Mayo Soley⁶ regarding exophthalmos. The eyes of over 50% of the patients with toxic diffuse goiter became measurably more prominent after subtotal thyroidectomy and they became less prominent in only a small percentage of persons. It is generally agreed that subtotal thyroidectomy may make the exophthalmus worse in patients with a severe degree of proptosis.

Good results were obtained in only 54.5% of surgical patients and 55.5% of the whole group of patients. This low figure, of course, is largely due to the fact that 33.8% of patients were inadequately followed. It is very likely that a large percentage of the 79 patients with inadequate follow-up could also be considered to be good results but one cannot assume that to be so. Of the patients followed adequately 90% of surgical patients can be considered to be in a prolonged remission. Myxedema, nerve paralysis and hypoparathyroidism were considered to be complications and these patients are included in the "good result" group.

Discussion

Vander Laan and Swenson⁷ have reported the results of operations at the Peter Bent Brigham Hospital in the period 1933-1940. Nineteen of 149 patients failed follow-up. Of the 130 patients followed for 6 months or longer 87% had satisfactory results. The mortality rate was 3.1% and the recurrence rate was 8.3%. These results correspond reasonably well with those reported above. The incidence of hypothyroidism is distinctly greater than in our series indicating in all probability that more radical surgery was carried out. In hospitals reporting a high incidence of recurrence of persistent hyperthyroidism the incidence of myxedema is low.

Mortality statistics in toxic diffuse goiter vary greatly. Thompson, Taylor and Myer⁸ reported a 13.1% mortality in

toxic diffuse goiter at the Cooke County Hospital. The factor of careful pre-operative preparation is important. They found that better preoperative care and selection of time for surgery without changing surgeons or surgical technique brought about a decrease of mortality rate from 13.1% to 4%. Maes, Boyce and McFettridge⁹ reported a mortality rate of 15.8% for toxic diffuse goiter at the Charity Hospital in New Orleans. Lahey² reported a case mortality of only .88% in a series of 22,000 patients (this includes operations on non-toxic goiters). Bartels¹⁰ reported a case mortality of 1.49% for the years 1939-1942 at the Lahey Clinic for toxic goiter operations. In 1945 and 1946 the mortality rate was .17% and .19%. This decrease in mortality is attributable to the use of thiouracil in preoperative preparation of the more severe cases of hyperthyroidism. It is evident that our mortality statistics compare favorably with that of any other group and are better than many.

The superimposition of cardiac failure in patients with hyperthyroidism adds considerably to the risk of any form of treatment and particularly surgery. Lahey and Hurxthal¹¹ reported a mortality rate of 4.25% in a group of 300 "thyrocardiac patients". When one compares this rate with that of the Lahey Clinic for all hyperthyroidism one can appreciate the increased hazard. Compensation returned in 95% of the survivors and 71% of cases with auricular fibrillation reverted to regular rhythm. Likoff and Levine¹² reported cure of all 21 patients (out of 409 thyrotoxic patients) who had heart failure secondary to hyperthyroidism. The importance of a careful evaluation of the cardiac status in patients with hyperthyroidism should be emphasized repeatedly. The number of patients in our series with auricular fibrillation was 16 of 174 patients treated with iodine and 11 of 55 patients treated with thiouracil. Some of these patients had frank signs of heart failure whereas others had signs and symptoms only on mild exertion. One of the two deaths in the series was in a patient with auricular fibrillation. The actual num-

ber of reversions to regular rhythm cannot be stated because of inadequate notes in many instances.

At this point allow us to digress a moment to state that response to digitalis with slowing of the pulse and apical rate to 70 to 80 per minute can occur in hyperthyroidism and does not exclude the diagnosis. There are five patients with auricular fibrillation in our series who had undoubted hyperthyroidism but had a normal response to digitalis before any definitive therapy for the hyperthyroidism was given or when the basal metabolic rates were plus 50% or higher. It is true that, when a patient with auricular fibrillation does not respond to digitalis as expected, one should consider hyperthyroidism or some other toxic condition, but the reverse is not true. A more careful search would uncover more cases without doubt, but these five cases are cited to illustrate the fact that digitalis can slow an auricular fibrillation to a normal rate in spite of the presence of hyperthyroidism.

The problem of recurrence of hyperthyroidism is probably best summarized by two papers by Thompson and his co-workers^{13,14}. At the Massachusetts General Hospital recurrence or persistence of hyperthyroidism after subtotal thyroidectomy occurred in 19.5% of 190 cases of hyperthyroidism. Most of these were in patients with toxic diffuse goiters. At the Presbyterian Hospital of Chicago recurrence of persistence occurred in 17.5% of 212 patients with toxic diffuse goiters. Most of the patients had persistent and not recurrent hyperthyroidism. It is interesting to note that the prolonged use of iodine was sufficient to keep approximately two-thirds of the patients in normal condition with normal basal metabolic rates. Some patients recovered spontaneously after ten months to three years. Patients who did not respond to iodine satisfactorily were subjected to further surgery. Regeneration of the thyroid so that it became palpable again was observed in 74% of those with recurrence, whereas the thyroid became palpable in only 15% of those with permanent remission. In over 80% of cases the basal metabolic rate drops to normal or below and stays there. Thompson and his co-

workers are of the opinion that the more careful the follow-up the higher is the incidence of persistence or recurrence. Surgeons with the most experience and therefore those who do more radical resections of the thyroid have fewer recurrences than the less experienced surgeons. Thompson and Preston¹⁴ state that there is general agreement that 2.7% to 6.5% of patients have severe enough post-operative thyrotoxicosis to require a second thyroidectomy.

Three male patients and one female patient in our series illustrate the complexity of the problem of recurrence. The first one had to have three operations before his hyperthyroidism was controlled. A total of only 62 grams of tissue was removed, so it is entirely possible that he had too conservative surgery initially. A second patient had bilateral polar ligations and three operations in stages, with removal of 96 grams of hyperplastic thyroid tissue. The final recurrence 5 years later was treated satisfactorily with X-ray therapy. The third male patient had two lobectomies with removal of 62 grams. Two years later a bilateral subtotal thyroidectomy was carried out with the removal of an additional 114 grams. A third recurrence was treated with propylthiouracil. A girl, fourteen years old at the onset, had three operations over the course of 4 years. Each time she had basal metabolic rates of -30%, -24%, and -11% six weeks after the three operations respectively, only to have a recurrence later. These patients must represent the group which has a powerful force causing regeneration of tissue. Vander Laan and Swenson⁷ report one patient who is comparable to the third patient mentioned above.

Fulton, Schnitker and Cutler¹⁵ could find no distinguishing feature of the preoperative state of patients showing persistence or recurrence. There was no relation to the amount of thyroid tissue removed at surgery. In our series there was an insignificant difference between those with residual or recurrent hyperthyroidism, those who had myxedema and those with normal postoperative

basal metabolic rates. (Actually the averages for the recurrences were 42 grams, 46.5 grams for the normals and 48.3 grams for the hypothyroid patients. It must be concluded that there is a striking tendency of some patients to have recurrence of hyperthyroidism sometimes occurring at long intervals throughout adult life.

Since the introduction of thiouracil and related compounds in 1943 many significant contributions to our knowledge of thyroid diseases have been made. A review of the thiouracil literature will not be attempted but a few pertinent references will be made to the literature. The rate of response of basal metabolic rates to thiouracil varies in minor respects with each report but there is a general agreement among all users of thiouracil. Bartels and Bell¹⁷ treated 400 cases with thiouracil and found the following averages: 1.3% drop in B.M.R. per day for diffuse toxic goiters of short duration without previous iodine, 1% drop per day for diffuse toxic goiters of long duration or of short duration with previous iodine, 0.64% drop per day in toxic nodular goiter without previous iodine and 0.45% drop in toxic nodular goiter with previous iodine therapy. These figures point out the facts with which most people agree, namely that toxic diffuse goiters respond best and the toxic nodular goiters treated previously with iodine respond the slowest, and some are actually completely resistant to thiouracil. Naturally there are many individual variations.

The greatest hindrance to the use of thiouracil is the frequency with which toxic reactions occur. Williams¹⁸ reports an incidence of toxic reactions of 14.5% and the drug companies and cooperating clinics¹⁹ report an incidence of toxic reactions of 13.0% of 5,745 patients. The toxic reactions in our series corresponds with these figures. Agranulocytosis is the most serious and therefore the most important. Leukopenia, fever, skin rash, salivary gland enlargement, arthralgia, neuritis, nausea and vomiting, thrombocytopenia, jaundice, periarteritis nodosa, and delirium may occur.

The use of thiouracil and propyl-

thiouracil as maintenance therapy has been studied extensively. Barr and Schorr²⁰ treated 100 patients with thiouracil. In 48 patients from whom thiouracil has been withdrawn 76% have not relapsed. Williams¹ reported 49 remissions out of 100 patients. Some of these patients relapsed, for in a later report²¹ 51 out of 111 patients maintained on thiouracil for many months had no evidence of hyperthyroidism 3 to 31 months after cessation of therapy. Most relapses occur within a month or two after cessation of therapy. Grauer, DeWalt and Elkin²² treated 15 patients for many months and 10 of the 15 have had a remission of from 7 to 23 months. Incidentally they found liver extract did not prevent agranulocytosis. McCullagh, Hibbs and Schneider²³ treated 218 patients for an average of 8 months with propylthiouracil but are unwilling to state how many remissions can be expected. Beierwaltes and Sturgis²⁴ report 13 patients treated for an average of 10 months, and of these 8, or 60%, have experienced a relatively persistent remission. It is clear that thiouracil and its derivatives are not satisfactory for prolonged treatment of all patients. There is a definite incidence of relapse even after prolonged therapy, especially in males and in patients with large glands and severe hyperthyroidism. Such therapy requires considerably more time on the part of the doctor for follow-up than thyroidectomy or X-ray therapy. There is always the danger of serious toxic reaction. However, in patients who are considered to be poor candidates for surgery, such as those who have had multiple thyroidectomies, and in patients who refuse other forms of therapy, the thiouracils are definitely indicated and very useful. It is our opinion that thiouracil and propylthiouracil therapy is still too recent for full and adequate evaluation of maintenance therapy, and that the main and very real usefulness of these drugs is the preparation of seriously ill hyperthyroid patients for thyroidectomy. Literally hundreds of cases have been reported in which thyroidectomy has been made safe in patients who would have been in greater danger of untoward reactions before the

use of these drugs. The most striking example is the thyrotoxic heart disease patient.

One form of therapy which has decreased in popularity recently is X-ray therapy. Only a small number of patients were treated with X-ray in this series. As judged by the basal metabolic rate and other criteria, the hyperthyroidism was somewhat less severe than in the other groups. Nevertheless, a satisfactory result by inducing remission of hyperthyroidism, was obtained in 15 out of 24 patients or in 60%. Some of the patients in the operative group had had multiple operations with residual or recurrent hyperthyroidism. One index of the efficacy of X-ray therapy in certain individuals is the occurrence of myxedema in two of 16 patients who had not had previous or subsequent operation. Smith and Stenstrom²⁵ reported 78.0% satisfactory results in a series of 350 cases of toxic diffuse goiter. The criterion of satisfactory result, however, is not as rigid as that applied by others - "by satisfactory is meant the ability to do all their previous work and carry on practically all of their other activities with little, if any, inconvenience". Soley and Stone²⁶ studied 43 patients intensively and found that 25 or 58% were clinically free of hyperthyroidism in an average time of 8.7 months from the onset of treatment and 8 or 18.6% were markedly improved. Both groups had a coincident decrease in the size of the thyroid to within normal limits. The average basal metabolic rate was plus 35.7% before treatment and -2% after treatment. Esophagitis and tracheitis occurred in 15 of their patients, but a change of technique corrected this fault. Two of the 43 patients died of cardiac failure before the effect of X-ray could occur. We wish to point out several pertinent facts. Radiation therapy produces a higher percentage of remissions than do the thiouracils and with less risk. The expense and time involved is the least of any form of therapy - as is attested to by the average weight of the charts of these patients compared with those treated by other means! We believe that radiation therapy should be used in selected cases.

This series of patients does not in-

clude any treated with radioactive iodine. Iodine 130 and iodine 131 have been used by many investigators for the treatment of hyperthyroidism. Iodine 131 is now available in sufficient quantities so that it is possible to treat many patients. There still are certain unknown factors in the use of radioactive iodine, such as the possible role in production of cancer, so that it cannot be recommended for routine use as yet. It has been used only in 7 patients here. All of these patients had a special indication of one kind or another for the use of the substance rather than some of the other forms of therapy. Satisfactory remission with return of the basal metabolic rate to normal has occurred in four. The other three have been given the iodine just 2 months ago. It appears that radioactive iodine will afford a higher percentage of remissions than x-ray therapy and probably even than surgery.

Summary and Conclusions

A review of 244 patients with hyperthyroidism treated by various agents and methods during the period from 1937 to 1946 has been made. The results of therapy - chiefly thyroidectomy after various forms of preoperative preparation - corresponds well with several other reported series of patients. The incidence of recurrent nerve paralysis is greater but the mortality is less than most reported series. The number of stage thyroidectomies in the iodine prepared patients may have been unnecessarily high.

The most discouraging part of the study is the high percentage of inadequately followed patients in the post-operative period and the dearth of specific information in some of the follow-up material. Much of the study was unusually laborious because pertinent information was 'buried' in many different places on the same record and among many pages of words.

The results of thiouracil therapy in the preparation for thyroidectomy are similar to the results of others. These patients were more seriously ill than the

average of the whole group. Several frank failures of thiouracil are recorded in toxic nodular goiter patients. Prolonged hospitalization for thiouracil therapy is unnecessary now since propylthiouracil has been substituted and fear of serious reactions is much less. All patients with moderately severe to severe hyperthyroidism or those with complications such as diabetes or heart disease should be prepared for surgery with propylthiouracil. A long enough time should be allowed to bring the basal metabolic rate to normal. Our series of patients on thiouracil maintenance therapy is too small to conclude much about effectiveness. Three out of 10 patients attained prolonged remissions.

X-ray therapy is certainly effective in many cases, is economical, and is probably superior to thiouracil or propylthiouracil in the number of permanent remissions achieved.

We believe that at the present time the most effective therapy for hyperthyroidism is preparation of the patient with iodine for the mild cases and propylthiouracil for the more severely ill patients and then thyroidectomy when the patient is in the most ideal condition possible.

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III. MEDICAL SCHOOL NEWS

Minnesota Medical Foundation

It is a pleasure to welcome the Minnesota Medical Foundation as co-publisher of this Bulletin. The idea for such a Foundation was conceived in the spring of 1939 when plans were being made for the celebration of the fiftieth anniversary of the University of Minnesota's Medical School. By the fall of that year the committee of the Minnesota Medical Alumni Association which was charged with the duty of exploring this idea was able to report that such a foundation had been incorporated under state laws. The purpose of the Foundation as given in the articles of incorporation are: "to promote the welfare of the community by the cooperation of alumni and friends of the Medical School of the University of Minnesota in improving the undergraduate, graduate and research functions of that Institution; to establish scholarships, lectureships, professorships, research and student loan funds in that Institution; to publish and promote the publication of a representative medical Bulletin; and in general, by all legitimate and usual means, to advance the interests of the University of Minnesota Medical School and its alumni, without consideration for benefits bestowed".

Classes of membership to the Foundation are:

1. Foundation Patrons, persons contributing \$1,000 or more.
2. Life Members, persons contributing \$100 or more.
3. Annual Members, persons contributing \$10 annually.
4. Student Members, contributing \$1 annually.

All classes of members receive the Bulletin.

During the war years the Foundation was relatively inactive. The organization

is active again and membership and participation of all who are interested in furthering the objectives stated above is earnestly requested.

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Minnesota Medical Alumni Association

The Minnesota Medical Alumni Association which has also been inactive during the war years is also in the phase of re-activation. A preliminary meeting of interested physicians has already been held and an official meeting of the organization will be held soon. The date will be announced in the Bulletin. Formerly the Medical Alumni held a meeting on the Campus the day of or preceding the Homecoming Football Game. A clinical program was usually presented. Meetings of the Alumni Association were also held at the annual meetings of the Minnesota Medical Association and the American Medical Association.

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One of the functions which the Bulletin hopes to perform is that of informing friends of the Medical School of the activities going on here on the campus. The activities of the clinical and full time members of the faculty cover a wide area geographically and in terms of subject matter. It is hoped that we will be able to present this picture of the Medical School as a vital force in the scientific life of our state, nation, and the world. The editorial staff will welcome information concerning activities of the medical school faculty for publication in these pages.

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A course in Surgery for general practitioners and surgeons will be given in the Center for Continuation Study of the University on April 8, 9, and 10. Participating in the teaching will be a large number of Twin City staff members. Out of town faculty members are Dr. Nelson W. Barker of Rochester, Minnesota; Dr. Kenneth Campbell of Ann Arbor, Michigan; and Dr. George Gomori of Chicago, Illinois.

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