Staff Meeting Bulletin
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University of Minnesota

Thiouracil Therapy in Hyperthyroidism

Volume XV | Friday, June 2, 1944 | Number 28

STAFF MEETING BULLETIN
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INDEX

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I.

No. 28

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
June 5 - June 10

Monday, June 5

9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff, Todd Amphitheater, U. H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U. H.

12:30 - 1:30 Pediatric Seminar; Metabolic Studies in Asthmatics; Dr. Stoesser; W205 U. H.

Tuesday, June 6

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff, Main 515 U. H.

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff, Eustis Amphitheater, U. H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff, Main 515, U. H.

12:30 - 1:30 Pathology Conference; Autopsies, Pathology Staff, 104 I. A.

4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Station 54, U. H.

4:00 - 5:00 Pediatric Grand Rounds; I. McQuarrie and Staff, W-205 U. H.

5:00 - 6:00 Roentgen Diagnosis Conference; Drs. Kelby and Beiswanger, M-515 U.H.

Wednesday, June 7

9:00 - 11:00 Neuropsychiatry Seminar; J. C. McKinley and Staff, Station 60 Lounge, U. H.

10:30 - 12:30 Otolaryngology Case Studies; Out-Patient Ear, Nose and Throat Department; L. R. Boies and Staff.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Staphylococcic Pyemia; E. T. Bell, C. J. Watson, O. H. Wangensteen, and Staff, Todd Amphitheater, U.H.

12:30 - 1:20 Physiological Chemistry Journal Club; Current Literature Reviews; Staff, 116 M. H.

4:00 - 5:00 Obstetrics and Gynecology Journal Club; J. L. McKelvey and Staff, Station 54, U. H.

Thursday, June 8

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Rounds; C. J. Watson and Staff, East 214 U. H.

12:30 - 1:30 Physiology Chemistry Seminar; The Use of Heavy Isotopes as Tracers; H. G. Wood, 116 M. H.

Friday, June 9

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

8:30 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U. H.

11:45 - 1:15 University of Minnesota Hospital General Staff Meeting; Special Movies, Summary 1943-44, Powell Hall Recreation Room.

1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff, Eustis Amphitheater.

1:00 - 2:50 Dermatology and Syphilology; Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U. H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton and Staff, Todd Amphitheater, U. H.

Saturday, June 10

9:00 - 10:00 Medicine Case Presentation, C. J. Watson and Staff, Main 515 U. H.

9:15 - 11:30 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff, Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff, E-214 U. H.

II. THIOURACIL THERAPY IN HYPERTHYROIDISM

E. B. Flink
G. T. Evans

Introduction

In May of 1943 E. B. Astwood of Boston[1] published a report on the reduction of basal metabolic rate and abolition of signs and symptoms of hyperthyroidism in 3 cases using thiourea and thiouracil by mouth. The results in their first case are shown in Slide 1 which is taken from their paper. It shows, in a 9-month period, 2 remissions each with thiourea and thiouracil. Characteristic increase in body weight and elevation serum cholesterol were also found to occur with the lowering of basal metabolic rate.

In July of 1943 a report by Williams and Bissell[2] recorded the successful application of thiouracil in 9 cases of hyperthyroidism.

Following these reports we obtained a supply of thiouracil* and it has been applied in 16 cases on the Medical Service and on 2 in Pediatrics. The cooperation of these departments is gratefully acknowledged.

Since no attempt was made to do any special studies in our cases they will be reported only in brief. The purpose of this discussion is to 1) review the fundamental developments which have led to this new form of thyroid therapy, 2) report the systematic clinical studies which have appeared to date. Judging from recent reports this drug is finding increasing favor and in view of its expanding local use it was thought that a review of developments would be welcome.

Early Developments

It is always difficult to decide on the origin of a new idea. In the minds of some the present development of thiouracil might be thought of as having its origin in the work concerned with cabbage or thiocyanate goiter. However, the report which appeared in Science by MacKenzie, MacKenzie, and McCollum[3] has been accepted by most observers as a significant turning point. In their paper they reported a remarkable enlargement of the thyroid in animals which had been fed sulfaguanidine. Two years later a thoroughly definitive paper by them appeared (MacKenzie and MacKenzie[4]). In the intervening time papers by two other groups had appeared which bore very definitely on the subject, viz., Richter and Clisby[5,6] in the study of the graying of hair in rats had noted that phenyl thiourea when fed produced an enlargement of the thyroid. Kennedy[7] in investigating goiters produced by the feeding of rape seed were led to the demonstration that allyl thiourea and thiourea produced enlargement of the thyroid; the histology of these thyroids and also of the pituitary glands of these animals resembled that which is to be shortly described. Without in any way wishing to pass over the contribution made by these authors, it is convenient to review briefly the paper by the two MacKenzies[4] which gives an excellent orientation in the earlier fundamental studies.

Thyroid Enlargement in Rats with Sulfaguanidine

The MacKenzies[4] used 5 animal species. Rats gave the most striking results. Sulfaguanidine was fed as a 0.5 to 3.0% constituent of the food to young rats. Slide 2 (being Figures 1 and 2 of their paper) shows the striking results obtained. It will be noticed in Figure 2 in which 2% sulfaguanidine was fed that a 34% enlargement of the thyroid occurred as early as the second day of feeding; at 55 days the glands were approximately 5 times normal size. In Figure 1 in which varying percentages of sulfaguanidine were fed for two weeks it is to be noted that there is a linear dependence of enlargement upon dose. Their photographs of the thyroids are not satisfactory for slide

*Kindness of Dr. Benjamin W. Carey, Lederle Laboratories, Pearl River, New York.

reproduction but Slide 3 from the paper of Astwood, Sullivan, Bissell and Tyslowitz[8] in the same number of Endocrinology shows for a similar experiment the marked thyroid enlargement. Hyperemia which is a marked feature is seen as early as the third or fourth day. The enlargement is uniform and symmetrical. The histological appearance of the thyroid glands of the MacKenzies[4] is shown in Slide 4. (Figures 5-10 of their paper). There is a progressing heightening of the thyroid epithelium with diminished or absent colloid. Mytotic figures were frequently encountered. The glands then resemble the histology of acute iodine deficiency in animals or of human toxic diffuse goiter. No necrosis was observed in this series although it has been seen by others.

It should be noted that at the 2% dietary level of sulfaguanidine the growth of the young rats was well maintained. Concretions in the urinary tract were seldom produced even after many months of treatment. 4% sulfaguanidine was lethal for most of the young animals. Thirty days after cessation of sulfaguanidine, the histological appearance of the gland had returned to approximately normal.

Adult rats required a larger dose of sulfaguanidine to produce less marked thyroid changes. In old female rats a significant enlargement of the thyroid occurred only after feeding 2% sulfaguanidine for 14 days. The histological changes in these glands although less marked than in young animals were quite definite.

Other Chemical Agents

Sulfapyridine, sulfadiazine, sulfamethyldiazine gave effects which were in the same range of those given by sulfaguanidine. Sulfathiazole and sulfanilamide itself were less effective, the former probably because of lower blood levels occurring with standardized sulfathiazole feeding.

Thiourea, allyl thiourea and diethyl thiourea were also found to be active. On the same or larger dose levels such substances as thiocyanate, urea, cystine and cysteine gave negative results.

Other species

In mice the results were less definite than in rats. Dogs gave positive though less striking results. Changes in the thyroid of guinea pigs were difficult to obtain but the MacKenzies are inclined to explain this on the low blood levels which were found in those animals; on this basis they do not believe this to be a true species difference. On the other hand in the chicken blood levels higher than those which obtained for rats were without effect on the thyroid. They believe this to be a true species difference but point out that the chicken like the rate is susceptible to the goitrogenic agent present in soy beans.

Metabolic Rates

Because sulfaguanidine produces in rats thyroig hyperplasia with diminished or absent colloid, thus resembling the histological picture of diffuse toxic goiter in humans it might have been expected that the basal metabolic rates of these animals would have been elevated. The reverse however is found to be the case. After 2 weeks of sulfaguanidine feeding in rats, the basal rates were -20%. Although as has been already recorded, the glands have been seen to return to an approximately normal histological picture after cessation of the drug, they found for two animals maintained for 52 days on sulfaguanidine that as much as 5 weeks after removal of the drug, the basal metabolic rates were still depressed. This was a minor observation at the time but assumes new significance in the light of recent clinical experiences to be mentioned subsequently.

Effect of Iodine and Thyroid Extract on Sulfaguanidine-induced Hyperplasia

On the supposition that a deficiency state was produced by sulfaguanidine, concurrent feeding of inositol, liver

powder, fresh liver, cysteine, cystine, vitamin C, calcium pantothenate was tried; the thyroid enlargement was not prevented by any of these. Para-aminobenzoic acid which lessens or abolishes the bacteriostatic effect of the sulfonamides actually enhanced the thyroid effect of sulfaguanidine.

The goiter produced by cabbage in rabbits (Webster and Chesney[9]), by soy beans in rats and chickens (Sharpless, Pearsons and Prato[10]); (Wilgus, Gassner, Patton and Gustavson[11]) and by thiocyanate in rabbits and man (Rawson, Hertz and Means[12]) can be prevented or abolished by iodine administration. This is not the case with sulfaguanidine goiter; the glands of animals given sulfaguanidine and iodine weighed slightly more than those given sulfaguanidine alone and showed as great hyperplasia. There was actually a greater depletion of colloid in the iodine-supplemented group. This is also in contrast to the iodine effect on diffuse hyperplastic goiter in humans where regression of cells and accumulation of colloid results.

In sharp contrast are the results when thyroid extract or thyroxin is given concurrently with sulfaguanidine. The enlargement and histologic change were entirely prevented. The lowest dosage of thyroxin used not only prevented thyroid enlargement but reduced the weight of the gland below that of normal controls. Slide 5 (being Figures 19-22 in the paper by the MacKenzies) illustrates these last two effects. In Figure 19, 0.1% sulfaguanidine was given for 14 days concurrently with 0.1% sodium iodide. The hyperplasia is the same as produced with this dose of sulfaguanidine alone and the absence of colloid is even more striking. On the other hand Figures 21 and 22 respectively show the results with concurrent thyroid and thyroxin (1 microgram per 10 grams/body weight). The low cells and plentiful colloid are striking.

The Pituitary

Following thyroidectomy and in animals receiving Brassica seed, the pituitary manifests characteristic changes, namely, decrease in acidophils, an increase in basophils with hyalinization, vacuolization and signet-ring formation ("Thyroidectomy cells"). Similar changes are seen in the pituitaries of animals fed sulfaguanidine. Despite the pituitary changes the ovaries of a number of sulfaguanidine treated females showed no detectable change.

Estrous cycles were normal and one female gave birth to a litter of living young.

In the same issue of Endocrinology as contains the paper by the MacKenzies there appeared a paper by Astwood, Sullivan, Bissell, and Tyslowitz.[8] This paper covered much the same ground as that just reported. In addition it was shown that in hypophysectomized animals thyroid hyperplasia did not occur as a result of sulfaguanidine; furthermore hypophysectomy in animals previously treated with sulfaguanidine caused marked thyroid regression.

Astwood and his co-workers also showed that the calorigonic action of thyroid extract was not inhibited by these compounds in normal and hypothosectomized rats.

The balance of evidence in these two papers favors the view that sulfaguanidine produces a specific block to the formation of thyroid hormone, as a consequence of which the pituitary acts to produce thyroid hyperplasia. Accessory evidence on the validity of this theory is to be found in papers reported below.

Before continuing with an account of added fundamental evidence, however, present purposes will be best served if the clinical reports are now given.

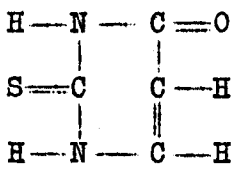
Clinical Application

To date, 122 cases of hyperthyroidism treated with thiouracil have been reported in the literature. The results in general have been good.

The initial clinical paper by Ast-

wood[1] was mentioned in introduction. Since his general results are better represented in later papers they will not be commented on here. But particular points about this paper deserve comment. As a result of his careful examination of 106 compounds[13] thiouracil made its appearance as a compound of choice.

2-thio-uracil has the formula



Slide 6

It is a white crystalline powder, readily soluble in NaOH, soluble 1:2000 in water, insol. in acids, alcohol, ether. It is fairly stable as solution or powder, has no odor but a bitter taste. Uracil, a pyrimidine, is a constituent of plant nucleic acid.

Using a dose of this drug of 2 grams daily, which is considerably higher than that now employed, he produced in one patient an agranulocytosis which, however, remedied itself upon stopping the drug. Some malaise was also produced with this dose level. The slide of his first case, as previously shown indicated that the signs and symptoms of hyperthyroidism soon returned after the drug was stopped.

Papers by Williams and Bissell[14,2] next appeared. They reported the results with thiouracil on 9 cases of hyperthyroidism. In all of these the toxic manifestations disappeared; the basal metabolic rate which initially averaged +60% fell to below +20% in 25 days and to normal (zero) in 35 days. In 4 of the charted cases the basal rate reached approximately -10%. The average weight gain in these patients was 12 lbs. Four of the cases were ambulatory, one was pregnant and one had been previously lugolized. Blood iodine studies in 4 cases showed a fall of protein-bound iodine to a normal or subnormal level.

Dosage

The authors used at this time a daily dose of 1.0-1.2 grams administered as 0.2 gram tablets by mouth 5-6 i.d. Using a method which has not as yet been published they determined that the drug is rapidly absorbed. The maximum blood level from a single dose of 0.2 gm. was found to be 2.3 mg.% which was reached in 15 minutes. 0.2 gram q.4 h. gives a blood level of 3 mg.% approximately. This paper together with the findings of Williams and Clute[15] indicate that the tissues with the greatest concentrations are pituitary, thyroid, adrenal, bone marrow. Thiouracil in blood is chiefly in the cells, particularly the white cells. One-third of ingested drug is excreted in the urine. Anticipating it should be noted while dosage is being discussed that subsequent publications have recommended 0.6 grams as the maximum dose (0.1 gram 6.i.d.) with a drop to 0.4 gm. on clinical improvement or when the basal metabolic rate has returned half-way to normal. After the basal metabolic rate is normal, the daily maintenance dose has been 0.1-0.2 gms.

Toxic Manifestations

In the 9 cases reported by Williams and Bissell[14,2] no serious toxic manifestations were encountered. Renal involvement was particularly excluded. Frequent leukocyte counts were done in view of the report of agranulocytosis by Astwood but no disturbances were found.

In 2 cases slight pitting edema with elevation of serum chlorides occurred but disappeared in spite of uninterrupted treatment. In this connection it will be recalled that thiouracil is concentrated in the adrenal and pituitary. In other studies Williams, Bissell, Jandorf and Peters[16] observed in a small proportion of patients that Na, Cl, and N_2 retention occurred, with some edema but no nephritis. No correlated change in androgenic or carbohydrate function, such as might be associated with the adrenal was found.

The MacKenzies[17] found in rats that thiourea produced pulmonary edema.

Kennedy and Purves[18] found hypertrophied adrenal cortices in rats fed

Brassica seed. However, Richter and Clisby[5] and Williams with other associates (to be published) found no change in adrenal size or histology with phenyl thiourea and thiouracil.

Effect on Thyroid and Pituitary

Williams and Bissell[2] were able to show in myxedematous patients that thiouracil did not inhibit the usual effect of thyroid administration.

In 3 treated hyperthyroid cases slight enlargement of the thyroid was observed in the first 2 weeks of treatment; this later receded. In the other 6 cases, the thyroid became smaller returning to normal size in 2 of these. In one case the eye signs increased during the general clinical improvement but improved when gr.i. daily of thyroid was given. This method of control of eye signs is based upon the as yet unproved assumption that circulating thyroid hormone keeps the pituitary in check in respect of thyrotropic hormone. It is consistent with the observation that administered thyroid does not produce eye signs whereas[19] thyrotropic hormone does. The concept of using thyroid extract in both normal and thyroidectomized animals to control pituitary function has some reasonableness in the light of the studies by Means, Hertz and Williams[20] of dissociated oculopathy in Graves' disease. Reinhoff[21,22] having observed the ability of administered thyroid to shrink colloid goiter administered it to 9 hyperthyroid patients; this treatment resulted in a reduction of signs and symptoms of hyperthyroidism with shrinkage of the gland and an average fall in basal metabolic rate of 20%. All patients did well postoperatively. Attention is drawn to this possible effect of administered thyroid because of the possibilities of 1) controlling the thyroid hyperplasia induced by thiouracil, 2) treatment of thyroid oculopathy.

Thiouracil in Severe Hyperthyroidism Preoperatively

Bartels[23] has reported the use of thiouracil preoperatively in 11 patients with severe hyperthyroidism. Clinical improvement occurred in all and the basal metabolic rate of all returned to or near normal in 20 days to 6 months, the delayed responses being obtained in previously lugolized cases or in those with very large thyroids. No toxic manifestations were encountered. The BMR and weight changes in 8 of these cases are shown in his chart 1 (Slide 7).

Rawson, Evans, Means, et al[24] reported a series of cases including 19 in which thiouracil was used as a preparation for surgery, 3 patients who were given iodine and thiouracil simultaneously and 3 patients who have been maintained on thiouracil as treatment in itself.

They used the doses recently advocated by Astwood, namely 0.6 gms. by mouth with a reduction to 0.4 gms. per day after the basal had dropped half way to normal. Slide 8 shows the basal metabolic response in these patients. It will be noticed that between the 10th to 14th day half of these cases have basal metabolic rates under +10%. The cases who had received iodine prior to treatment had the most delayed response. The heavy solid line in the graph is the plotted average of all cases. The heavy dotted line is the iodine response curve earlier found by Means and Lerman.[25] Because of the similarity of the curves to each other and to the curves for the drop in basal metabolic rate following thyroidectomy or removal of thyroid therapy from myxedematous patients. Means apparently favors the view that the effect merely represents the using up of the hormone that was present when the therapy began. As an explanation for the curves in lugolized patients he suggests the possibility of more hormone originally being stored.

Histology

The paper by Rawson, Evans, Means, et al[24] gives the best account available to date of the histologic changes. In general all of the thyroids showed

moderate hypertrophy to marked hyperplasia. In most cases colloid was markedly diminished or absent. In 5 patients biopsies were taken before thiouracil was started and compared to the operative specimen. In three of these 5 cases there was only minimal increase in the height of the cells as a result of the thiouracil therapy. In the other two there was a significant increase in mean acinar cell heights. Both of these last 2 cases exhibited good prompt clinical response to the treatment. Slide shows the histological picture before and after thiouracil in one of these cases. The results seen at operation in the cases in which no original biopsy was done varied widely. Slide 9 shows the histological picture at operation in one case whose basal metabolic rate fell from +35% to +7% in 12 days. Dental abscesses developed at this time and thiouracil was continued for 4 more weeks at which time the basal rate was -16%. This gland shows marked hyperplasia and replacement of acinar structure by cellular elements with loss of colloid. Slide 10 shows on the right hand side the gland of a patient who had a goiter for 15 years, it having only recently become toxic. Involution seems to dominate the picture. The photograph on the left shows the gland of a patient who had received iodine up to the time of admission to the hospital. The basal rate fell from +41% to +12% in 30 days. Compared with a preceding biopsy there was no change in the height of the cells as a result of thiouracil therapy in this case. Means and his co-workers comment on the increased vascularity of the thiouracil glands at operation.

Metabolism

A careful study of weight, pulse, blood pressure and the metabolism of Ca, P, N and creatine in the thiouracil treatment of hyperthyroidism has been made by Sloan and Shorr.[26] All of the features studied showed a return to normal, thus indicating the physiological nature of the remissions produced by thiouracil.

Long Maintained Thiouracil Therapy

Astwood[27] in a recent report records successful thiouracil therapy in 51 hyperthyroids. The slowest responses were obtained in 1) lugolized patients, 2) toxic nodular goiter, 3) acromegalics. Added iodine was used in two cases of large diffuse goiter who showed thyroid enlargement and increase in bruit on thiouracil therapy; as a result the BMR fell further and the bruit disappeared. Four cases had a febrile reaction about the 10th day.

In 9 cases maintained for 6-8 months (maintenance dose 0.1-0.2 gms. daily) thiouracil was discontinued. All have remained normal to date (2-8 months later). This is a highly significant development since it offers hope for a long-time medical treatment of hyperthyroidism. Eleven normal people were treated with the usual doses of thiouracil for 6 weeks without observable effect.

Added Fundamental Contributions

Since the early work of the MacKenzies, Astwood, Richter and Clisby, and Kennedy considerable added definition of the disturbances has been reported. Some of this has been given under the clinical papers. That which remains is divisible into three groups:
1) Studies of iodine metabolism,
2) Involvement of the pituitary,
3) Miscellaneous.

Iodine Metabolism

According to Rawson, Evans, Means, et al[24] the thyroids removed from patients with Graves' Disease who have been prepared for thiouracil contain 1/4 to 1/3 of the iodine which one would expect to find in normal human thyroid or in the gland of thyrotoxic patients treated preoperatively with iodine. The thyroglobulin prepared from these glands contained a substandard amount of iodine. The material so prepared was administered to myxedematous patients; judging this material either on a weight basis or on the basis of iodine content, the response in the myedematous patients was distinctly substandard.

These same authors found that the ability of the thiouracil treated glands to collect tracer iodine was greatly diminished by comparison to that found by Hertz, Roberts and Salter[28] for untreated hyperplastic thyroids of Graves' disease.

Franklin, Lerner and Chaikoff[29] fed rats thiouracil and examined the disposition of tracer iodine in the thyroids at various times following the cessation of the thiouracil. Their results (Slide 11) show that thiouracil depressed the total uptake of iodine and that the radioactive thyroxin and diiodotyrosine were correspondingly reduced. Return to normal as indicated by the curves was practically complete in two weeks.

The marked loss of thyroid iodine concurrent with the hypertrophy produced by thiouracil feeding in rats is shown in the next slide (12), taken from a paper by Astwood and Bissell[30]. Withdrawal of the drug reversed the effect. The same authors showed that thyrotropic hormone of the anterior pituitary induced a marked thyroid enlargement but that iodine content was but little affected. These data support the view that thiouracil inhibits hormone formation in the thyroid.

Similar evidence on iodine function in relation to thiourea and sulfonamides have been provided by Franklin and Chaikoff[31] and Baumann, Metzger and Marine.[32]

Dempsey[33] on the basis of histochemical reactions believes that thiouracil inhibits peroxidase activity in the thyroid while leaving the cytochrome oxidase system intact.

Rawson, Tannheimer and Peacock[34] compared the thyroid hyperplasia produced by thiocyanate and by thiouracil. The thiouracil glands were larger. Tracer doses of radioactive iodine were administered after the hyperplasia was established and four hours before the animals were sacrificed. The thiocyanate glands took up more tracer iodine (87% of dose given), and the thiouracil glands less (10% of dose) than did the controls (56% of dose).

The weights and uptake of iodine are shown in Figure 2 from their paper (slide 13).

These authors offer a diagram to illustrate their concept of the two sets of circumstances (Slide 14). The thiocyanate block stands between the thyroid and the tissues and demands more iodine. The thiouracil block stands between the iodine supply and hormone production, thus preventing iodine uptake. In both cases the pituitary is believed to be overactive in respect of thyrotropic hormone, the assumption being that it reacts thus in the absence of back-effect of the thyroid hormone.

Thyroid-Pituitary Relationship

Although the thyrotropic hormone of the anterior pituitary has not been isolated in pure form its existence is not doubted. Time does not permit nor do the circumstances require that this aspect be covered in any detail. Reviews are available, viz., those of Rynearson[35]; Collip[36]; Lerman[37]; Elmer[38]; Salter[39]. Although thyrotropic action has been demonstrated in animals and in clinical cases, the results have not always been reproducible at will; resistant states develop. Its increased presence in the blood of hyperthyroid patients has been demonstrable in only a fraction of the cases. Similar non-uniform results have also been found in irradiation of the pituitary in hyperthyroidism; thus recently Thompson and Thompson[49] radiating 38 cases obtained permanent total remission in 7, temporary partial remission in 16, and negative results in 15.

The back-effect of the thyroid upon the pituitary is thoroughly established. The ability of thyroxin to prevent or abolish the thyroid hyperplasia due to the new goitrogenic agents is added evidence of this effect. That this is due to the effect of circulating thyroid hormone directly on the pituitary has not been vigorously demonstrated.

Miscellaneous Recent Evidence

By treating rats from birth with thiouracil Hughes[41] was able to produce cretins (Slide 15). By giving thyroxin concurrently with thiouracil this effect was not produced. Newborns of thiouracil treated mothers appeared grossly normal but showed thyroid hyperplasia and subsequently some retardation of development; this favors placental or mammary transmission. No adverse effect of thiouracil have been reported for the one pregnant hyperthyroid case treated by Williams and Bissell.[2]

The MacKenzies[42] have recently given sulfaguanidine for long periods to rats from the time of weaning. Though the basal metabolic rate fell to thyroidectomy levels and typical thyroidectomy cells appeared in the pituitaries, the histology of thyroid epithelium varied from normal to extreme hyperplasia. Most people have been inclined to view the varied histologic pictures in human hyperthyroidism as reflecting a complex etiology and varied course. It is, therefore, interesting that here in inbred animals with uniform treatment the picture should vary so widely.

By interrupting treatment they were able to show regression in the thyroids and that no hypersensitive or resistant states developed.

"Summer" and "winter" hearts of frogs can be differentiated on the basis of their response to temperature changes. Carter, Mann, Harley-Mason and Jenkins[43] identified paraxanthine as the inhibitory substance in mammalian urine which will convert "summer" hearts to "winter" hearts. This appears as an interesting finding in view of the close similarity to the new goitrogenic agents.

Mechanism of action

The currently accepted explanation of the effects of thiouracil is that it inhibits the usage of iodine and the formation of thyroid hormone by the thyroid gland; in the absence of normal thyroid function the pituitary overacts producing epithelial hyperplasia of the thyroid. Alternate explanations are commented on below. (See (4)).

Theory	Contra-argument
Inhibition of formation of some essential metabolite in gastro-intestinal tract.	Thiourea is effective parenterally.
General toxic effect.	Some of the most toxic agents are least effective. The effective agents do not interfere with growth and development if thyroid is fed.
Retention of thyroxin by thyroid gland.	Not retained.
Elevation of tissue requirement for thyroxin or Destruction of the thyroid hormone.	Thyroxin is normally effective despite the drugs.
Locally induced thyroid hyperplasia.	Hyperplasia not seen in hypophysectomized animals.

- - -

U. of M. Hospitals Cases

In these cases we have adhered to the larger doses earlier recommended, viz., 1.0 - 1.2 grams daily initially with graded reduction as improvement occurred. This was done for several reasons: (1) Most of the cases had been Lugolized; (2) Attempts to lower dosage according to the rules laid down by the Boston groups resulted in two cases in return of signs and symptoms and an elevation of the basal rate; (3) For further evaluation of toxicity; in this as will be seen we have been successful.

The individual case summaries follow:

Case Summaries

1. This 68-year old woman has had a goiter all her adult life. During the 5 years prior to hospitalization she had some heat intolerance, nervousness, sweating, dysphagia, dyspnea, hoarseness and a weight loss of 50 pounds. She has had recurrent attacks of right upper quadrant abdominal pain and fever associated with definite jaundice for two years. On examination she had a very large, stony-hard, irregular thyroid which extended substernally. She had a stare and lid-lag. Her skin was warm, moist and moderately pigmented. The heart was normal in size; tachycardia and auricular fibrillation developed during her hospital stay. Preparation for thyroidectomy was started and was progressing satisfactorily, but when she was about ready for operation, she had a severe attack of gall stone colic with fever, leukocytosis, severe anorexia and abdominal tenderness. She recovered incompletely from this and her hyperthyroidism was definitely aggravated in spite of continued use of Lugol's solution. Her B.M.R. which was +38% at time of admission, rose to +46% (after subsidence of fever). Physical exhaustion was marked. Because of the progression of symptoms thiouracil was started and she was given 1.0 Gm. daily for 30 days after which time she was much improved clinically, and her B.M.R. was +12%. A left thyroid lobectomy was performed with removal of 270 Gm. thyroid adenoma. Her blood pressure rose to 220 systolic during the operation, but she tolerated the surgery well. Her temperature rose to 102°postoperatively but it was normal on the third day. She has not been back to clinic since discharge, but she has written that she is feeling well and is able to do her own work. The histology of the thyroid tissue removed was that of an adenoma.

2. This 18 year old woman developed nervousness, weakness of the muscles, increased appetite, heat intolerance and palpitation 4 months prior to hospital admission. She had received Lugol's solution for 3 weeks before admission. She had a diffusely enlarged thyroid gland, tachycardia, high pulse pressure, prominent pulmonary conus, a systolic murmur at the cardiac apex, marked purposeless motion, smooth, moist skin, fine tremor of the hands and tongue, and exophthalmos. Details of laboratory procedures and successful course in the hospital are shown in the Slide. The B.M.R. fell to +8% in 33 days; she gained 15 kg. in weight. She received thiouracil for 6 weeks and demonstrated no real toxic manifestations. She did develop questionable non-pitting edema of the ankles and complained of tightness of the skin. She tolerated a bilateral subtotal thyroidectomy well with no rise in pulse rate during a two hour operation. Sixty grams thyroid tissue were removed. The gland was friable and bled a great deal. Histologically there was marked hyperplasia such as is present in an untreated Grave's disease. Postoperatively her temperature rose to a high of 102.6° on the second but was normal on the 4th day. Subsequent course has been very satisfactory.

3. This 46 year old woman developed nervousness, heat intolerance, exertional dyspnea, weakness, palpitation, tremor and sme increase in size of her thyroid gland (which has been large for 3 years), during 5 months prior to hospitalization. She lost 10 pounds in one month. No iodine had been administered at any time. She had a ruptured appendix with peritonitis in 1938, carcinoma of the cervix treated by roentgen therapy in 1941, and a pankysterectomy in 1942 for adenocarcinoma of the left ovary. On admission she had definite exophthalmos with stare, lid-lag, and poor power of convergence. Her skin was diffusely pigmented, moist, and warm. She had a tachycardia, and palpitation, increased pulse pressure, a diffusely enlarged firm thyroid gland, a marked fine tremor and quadriceps weakness. Her initial B.M.R. was +78% and a resting pulse at that time was 116. After receiving only thiouracil for 11 days the B.M.R. dropped to +14% and the pulse to 76. Clinically too her symptoms have been remarkably relieved. She will have a thyroidectomy in the near future. There have been no toxic manifestations.

4. This 12 year old girl developed a firm goiter, nervousness, excessive appetite, exophthalmos, irritability and had signs of hyperthyroidism at the age of 8. She had an elevated basal metabolic rate, +31%, and a good response to Lugol's solution. A right subtotal lobectomy was performed then. She had return of symptoms at the age of 12 years. She failed to gain weight, in fact she lost a few pounds prior to starting therapy, and she was quite irritable, had crying spells and an excessive appetite. She had slight exophthalmos and lid-lag, had a tremor, tachycardia and an enlarged left lobe of the thyroid. Her initial B.M.R. was +22%. After 18 days of thiouracil she was better, her B.M.R. was -6% and she had gained 5 pounds in 3 months. She received 0.5 Gm. daily for two months and now receives 0.1 Gm. daily (for 75 days). She is feeling fine and her father says she is the best she has been since onset of her illness at age of 8. There have been no toxic symptoms. Operation is not contemplated at least for the present.

5. This 64 year old woman noted dyspnea on exertion, nervousness, occasional palpitation, heat intolerance, profuse sweating and a 10 pound weight loss in spite of a good appetite for a year prior to hospitalization. She had definite symptoms of chronic sinusitis and had noted a flare-up of symptoms just prior to hospital admission. She had a tachycardia, increased pulse pressure, auricular fibrillation, left ventricular cardiac enlargement. Her eyes were prominent and lid-lag, stare and poor convergence were present. She had an assymetric nodular goiter. There was slight pitting edema of the ankles and legs, and the liver was enlarged. The mild evidence of heart failure responded to bed-rest and digitalization. She was given Lugol's solution and thiouracil simultaneously. She received 20 gm. of thiouracil in 25 days in the hospital with very satisfactory response. Her B.M.R. decreased from +50% to +12% with corresponding clinical improvement. She refused to have surgery so she was discharged from the hospital and was instructed to take 0.2 Gm. of thiouracil a day. On first visit to the clinic she exhibited definite evidence of recurrence of all her symptoms of hyperthyroidism so the dose of thiouracil was increased to 0.4 Gm. per day along with Lugol's solution. She improved very definitely again in two weeks and for the past 6 months has been maintained on a dose of 0.2 Gm. of thiouracil without any Lugol's solution. Auricular fibrillation disappeared spontaneously after two months of therapy. She complained of tightness and numbness of her feet on one visit but this complaint disappeared, and she has demonstrated no other toxic manifestations. The plan is to discontinue treatment now to see if she can get along without medications. There can be no doubt that she has benefited a great deal from the use of thiouracil.

6. This 17 year old girl developed symptoms of hyperthyroidism in the spring of 1943. She was given Lugol's solution 2weeks out of 3 continuously until hospitalization here in May, 1944. Initial slight subjective benefit from Lugol's was obtained but her symptoms recurred. Her illness was complicated by pneumonia in December and rheumatic fever in January. She had lost 7 to 8 pounds. She is moderately underdeveloped and has never menstruated. Her thyroid gland is diffusely enlarged, firm, and there is a to-and-fro bruit over both poles. There is a systolic murmur at the cardiac apex and a definite prominence of the conus pulmonalis. She had a marked fine tremor of the hands, much purposeless movement, and moist, warm fine skin. Initial B.M.R. was +77%; after 10 days therapy with thiouracil the B.M.R. has fallen to +40%, her pulse has decreased from 135 to 96 and her weight has increased from 78 to 83 pounds. There has been no evidence of toxicity of thiouracil. She is under treatment at the present time.

7. This 59 year old man was admitted to the hospital because of cardiac decompensation of short duration. A goiter was discovered shortly before admission to the hospital and he

had received iodine prior to coming here. He had gradually lost 75 pounds weight in spite of a good appetite during a period of 3 years. On examination he had auricular fibrillation, hypertension, and evidence of both right and left heart failure. He had a large nodular goiter with extension of the left lobe substernally and with a left vocal cord paralysis. His heart was enlarged to the right and left and there was a prominence of the pulmonary conus. Initial B.M.R. (after subsidence of the dyspnea at rest) was +55%. After 40 days of treatment with thiouracil (1.0 Gm. daily for 16 days and 0.4 Gm. daily for 24 days) his B.M.R. had fallen to +23% and his cholesterol had risen from 143 to 245 mg.%. A subtotal thyroidectomy was performed without any difficulty and 196 Gm. of adenomatous thyroid tissue was removed. His post-operative course was unusually uneventful. Histologically the thyroid tissue was adenomatous, not diffuse hyperplastic.

8. This 51 year old woman lost 20 pounds in 5 weeks following an attack of "flu." She had palpitation, tremor of her hands and her body, heat intolerance, and muscular weakness for 5 years, but had been able to compensate apparently by an increased appetite. She received Lugol's solution for one month irregularly (because of nausea and vomiting induced by Lugol's solution before coming here. She had an assymetrically enlarged thyroid gland, marked brownish pigmentation of her skin, wavy and brittle finger-nails, and a tachycardia. The covers of her bed demonstrated the remarkable tremor of her hands and feet. Initial B.M.R. was +57%. She received thiouracil for 42 days (1.0 Gm. daily for 12 days and 0.4 Gm. daily for 30 days) with a fall of B.M.R. to +17%. A bilateral subtotal thyroidectomy was performed and the surgeon encountered considerable bleeding, which he thought was more than usual for thyroidectomy. Her postoperative course was very uneventful. Sections of the thyroid revealed very small acini with many cellular areas without acini or colloid. It is possible that thiouracil caused some nausea but no severe nausea or vomiting as was encountered from iodine.

9. This 50 year old woman had chronic pulmonary tuberculosis and had a thoracoplasty in 1939 with control of the tuberculosis. She had a goiter for 30 years but developed tachycardia, palpitation, a 12 pound weight loss in spite of a good appetite, nervousness and irritability 18 months before hospitalization. There was evidence of development of right bentricular heart strain during the past 9 months of life. She received a full course of x-ray therapy and continuous administration of Lugol's solution for 4 months before death. B.M.R.'s were thought to be unreliable because of a diminished vital capacity, but a series of galactose tests were carried out. Before x-ray therapy the peak value was 103 Mg.%, after the second course of x-ray and just before thiouracil therapy it was 86 Mg.%. After 30 days of thiouracil (1.0 Gm. daily) the peak value was 63 Mg.% and after 46 days it was 23 Mg.%. Her weight increased from 99 to 106 pounds during this time. She was not edematous. She died of chornic cor pulmonale and bronchopneumonia. She had no recognized signs or symptoms of thiouracil toxicity. The thyroid gland was chiefly one large adenoma. Because of the complications it is difficult to say whether she actually received any benefit, but the data cited above would tend to suggest some improvement.

10. This 64 year old diabetic woman had recurrence of hyperthyroidism 12 years after a thyroidectomy. The hyperthyroidism was present for 3 years before admission. Here diabetes was definitely made worse and she had gradually lost weight and strength. She had auricular fibrillation and a diffuse cardiac enlargement with prominence of the conus pulmonalis. She received Lugol's solution for 2 weeks before thiouracil was started and also received it during therapy. She had a fairly good response to iodine when thiouracil was started. Sge gad a total of 14 Gm. of thiouracil in 18 days anf continued to improve subjectively without much change in B.M.R. (+32 to +29%). Thyroidectomy was carried out with ease and postoperative course was uneventful. The thyroid gland had typical histologi-

cal appearance of regressing Grave's disease. It is difficult to determine whether benefit was obtained because of the relatively short administration in a previously Lugolized patient. There were no toxic symptoms or signs.

11. Nine months before coming here this 67 year old Indian woman noted the onset of nervousness, muscle weakness, palpitation, dyspnea on exertion, heat intolerance, tremor of the hands and weight loss of 50 pounds. She had a very good response to iodine at the onset, stopped taking it in 10 days, had a recurrence of symptoms not relieved by continued (4 mo.) use of Lugol's, and came here because of lack of improvement. She had a tachycardia (100) and increased pulse pressure, moist warm skin, some overactivity, no eye signs, a nodular enlargement of the thyroid gland, and a systolic murmur at the cardiac apex. She received 1.0 Gm. of thiouracil daily for 17 days and though there was no significant change in B.M.R. (which was +29% to start with) her pulse decreased to normal, she gained 11 pounds weight, had a very uneventful operative and postoperative course. The thyroid gland was typical of "regressing Grave's disease" with a few areas of definite cellular hyperplasia. There were no toxic symptoms attributable to thiouracil. It is questionable whether thiouracil appreciably influenced her course; only a short course of treatment.

12. This 50 year old woman had had pernicous anemia for four years. About 9 months before hospital admission she had increasing nervousness, heat intolerance, tremor of hands, a good appetite, palpitation, dyspnea on exertion and a weight loss of 30 pounds. Iodine was given for three months with initial improvement but with return to her former state prior to being seen here. She had a moderately enlarged firm diffuse goiter, a stare and lid-lag, tachycardia, a blood pessure of 158/98, a systolic murmur at base and apex of heart, muscle weakness, and warm moist skin. She received 1.0 Gm. of thiouracil for 31 days and 0.8 Gm. for 16 days. There was a gradual weight gain from 85 pounds to 93 pounds but there was only very moderate improvement in the B.M.R. She tolerated a two hour operation well and her postoperative course was uneventful. If one relies only on objective measurement one would have to say the thiouracil had little effect. On the other hand she improved clinically and tolerated operation quite well. The histological appearance was that of regressing Grave's disease; 38 Gm. of thyroid tissue was removed.

13. This 32 year old woman had symptoms of hyperthyroidism for 1 year and had received Lugol's solution for about 8 months before admission here, but this was discontinued when thiouracil was started. Initial B.M.R. was +34% and weight was 117 pounds; after 32 days of thiouracil therapy the B.M.R. was +22% and the weight was 124 pounds. At operation 44 Gm. of thyroid tissue were removed. She tolerated a two hour operation without any rise of pulse rate and her postoperative course was very uneventful. Histological appearance of thyroid gland was very hyperplastic with tall columnar cells, very little colloid, and many papillary infoldings. This patient undoubtedly benefited from thiouracil but it was not administered long enough to get a complete remission of symptoms. There were no toxic symptoms attributable to thiouracil.

14. This 15 year old girl noted exophthalmos, swelling of the neck, sweating, nervousness, palpitation, excitability at age of 12. She had an unhappy home situation which undoubtedly aggravated her condition. She was given Lugol's solution for four months with some improvement. A year later thyroidectomy was contemplated but cancelled because of an unfavorable reaction to anesthetic. Her symptoms have remained about the same but she has gained weight and development has been normal. She has exophthalmos, lid-lag, and stare, constant tachycardia (132 - 100), blood pressure of 148/60, moist, flushed and warm skin. B.M.R.'s have never been very high. She had not received iodine for at least 18 months. She was given 1.0 Gm. of thiouracil for 20 days and 0.2 Gm. for an additional 26 days with a decrease of B.M.R. from +23% to -2%. No change in status occurred after discontinuing

the drug. There was subjective improvement. No toxic symptoms occurred.

15. This 51 year old woman developed irritability, nervousness, insomnia, weight loss of 30 pounds and cardiac irregularity rather suddenly four and one-half months before coming here. She had received Lugol's solution for 2 months without benefit and continued to receive it until operation. Initial B.M.R. was +74% and the final B.M.R. was +46% (1 week before operation and 5 days after starting thiouracil). She received 1.0 Gm. thiouracil daily for 12 days. Operation and postoperative course was uneventful. Histologically the gland had the appearance of regressing Grave's disease. This patient received the drug too short a time for any definite conclusions. She did improve on hospital management enough to permit successful uneventful thyroidectomy. No toxicity.

16. This 46 year old woman developed symptoms of hyperthyroidism 2 years ago with progressive increase in symptoms during the 6 months prior to hospitalization. She had a diffusely enlarged thyroid gland, was very overactive, and had lid-lag, stare and poor power of convergence. She had received Lugol's solution for 1 month before coming here. She was given 1.0 Gm. of thiouracil daily for 14 days and 0.6 Gm. daily for 10 days. She had a mild neutropenia during most of her treatment but severe neutropenia developed on the 24th day of treatment. Bone marrow biopsy at this time revealed arrest of the myeloid development at the myelocyte stage. Her total W.B.C. count fell to 1400 with 6% neutrophiles. Note the rapid rise in neutrophiles and total leukocytes after stopping thiouracil. Her B.M.R. decreased from +54% to +20% with a corresponding clinical improvement. Lugol's solution was administered for one more week and she had a subtotal thyroidectomy 34 days after starting therapy. She tolerated a two and a half hour operation well and her post-operative course was uneventful. Bone marrow biopsy performed ten days after the first one revealed a hyperplasia of all bone marrow elements with a rise of the myelo-erythroid layer from 3% to 12%. Histologically the appearance of the thyroid was that of regressing Grave's disease with some areas of persistent marked hyperplasia.

She received undoubted benefit from the thiouracil, but she also suffered a serious toxic manifestation which fortunately subsided promptly.

17. This 21 year old woman has had symptoms of hyperthyroidism for 13 months, has lost 17 pounds in 3 weeks, and had received Lugol's solution for 2 weeks prior to hospitalization with some amelioration of symptoms. She has a moderate diffuse firm enlargement of the thyroid gland, tachycardia, blood pressure of 130/58, marked palpitation, fine tremor, moderate overactivity, warm moist skin and moderate exophthalmos. Initial B.M.R. was +43% and cholesterol 127 Mg.% changed to +55% and 156 Mg.% respectively after 10 days of therapy. She received 1.0 Gm. of thiouracil for 14 days. It had to be discontinued because of the appearance of cutaneous purpura; thrombocytopenia (77,000 platelets), increased bleeding time, and positive cuff test were found. The purpura disappeared in a few days and the platelet count rose to normal. She has had a follicular tonsilitis to complicate her course further, but now seems to be improving.

She received no benefit from thiouracil and suffered a serious toxic manifestation which cleared spontaneously. No case of purpura has thus far been reported in the literature. Because of the possibility of thrombocytopenia it certainly will be advisable to check for bleeding tendency before submitting any patient to operation.

18. This 70 year old woman has symptoms and signs of toxic thyroid adenoma (substernal) with basal-metabolic rates of +40 to +45%. After only 4 days of thiouracil therapy she developed an erythematous rash of the face with some edema around the eyes. This rash disappeared after discontinuing thiouracil without stopping other medications, so it undoubtedly represents a toxic skin eruption due to thiouracil. She had previously manifest-

ed sensitivity to sulfonamide.

Summary of U. of M. Cases

Eighteen patients have received thiouracil for periods varying from 4 days to 7 months. Only 3 patients have been unlugolized (one adult patient). One patient developed neutropenia, one thrombocytopenic purpura and one toxic erythema, but all recovered promptly from these toxic manifestations on withdrawal of the drug. One case showed questionable edema. Nine patients have improved very definitely from therapy and some of them dramatically. Four patients received the drug for too short a time for much improvement to occur. One patient failed to improve after 32 days of therapy. Several patients obtained questionable benefit either because of the mildness of the process in one patient or because of the serious complicating disease in another. Ten patients have undergone subtotal thyroidectomies successfully. The histological appearance of the thyroid tissue removed at operation in two of the ten patients is that of marked hyperplasia. The rest of the glands showed either typical adenomata or had the usua; appearance of regressing Grave's disease.

Summary of thiouracil therapy

Dosage — Initially- 0.6 gm. daily, orally as 0.1 gm. tablets distributed throughout the day.

Reduction -to 0.4 gm. on clinical improvement or when B.M.R. has returned halfway to normal.

Maintenance - 0.1 - 0.2 gm. daily.

NB. It remains to be shown that these doses will be sufficient for all cases in all parts of the country.

Toxicity — Watch for:
malaise
rash
fever
edema and hyperchloremia
leucopenia
increased bleeding tendency.

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III. GOSSIP

Where did we get our tropical diseases in this country? Although none of the United States lies in the tropics, much of it is sub-tropical country. The American Indian had malnutrition at times, many skin diseases, certain intestinal worm infections, dysentery, relapsing fever, and Rocky Mountain spotted fever. He was not troubled by syphilis, tuberculosis, smallpox, measles, malaria, typhus fever, hook worm disease, cholera, and plague until these diseases were brought to him. Immigrants from Spain, Portugal, France, Italy and England introduced malaria. Tuberculosis flourished in the northern colonies and syphilis among the Spanish. The Indians contracted all of these infections and others. Cortez brought typhus to Mexico and eventually it came to Texas and the southwest before the Irish and the Poles introduced it directly. The slaves from Africa brought hook worm disease and virulent malaria, filariasis, leprosy, and yaws. Yellow fever and dengue came from the West Indies. We were spared the spread of schistosomiasis and onchocherosis, not because the diseases did not reach here but there were no spreaders. Cholera came from India, bubonic plague came to San Francisco from China and so the diseases came to us. Most of our large cities in the earlier days had outbreaks of these infections. Their control and extermination has been brought about by the development of immunity, improvement in sanitation (spreaders) and nutrition. It is likely that we will see a temporary recurrence of some of these infections, especially in those areas of the United States where they now tend to be prevalent. It is not likely according to most observers that the parts of the country which have been least hospitable to these infections will show much recurrence. We must not be lulled into a sense of false security, however, although Minnesotans are believed to be relatively safe from the spread of most of them. The one weakness in our setup is the possible spread of amebic dysentery through defective plumbing. For a long time our sanitary experts have been telling us about the defective plumbing in our homes and institutions....The problem of nervous and mental disease among service men is widely discussed. Two statements are often requoted. The first estimates that "six million men will come back from service with a changed personality." In some the change will be favorable and others, unfavorable. The other statement is that "50% of all the beds in the Veterans Hospitals are used for nervous and mental disease" and this is supposed to indicate the influence of war on men's minds. One must not forget that 50% of all hospital beds are used for patients with nervous and mental disease which suggests that civilian conflicts are also as frequent a cause of these disorders....Medical rehabilitation of civilian victims of accidents, diseases and emotional conflicts is a larger program than that for military casualties where a change in occupation is necessary (up to now). I visited a small factory the other day where everyone was disabled except the foreman. These men and women were engaged in a highly technical phase of manufacture in the optical industry. The group had a high work output, low absentee rate, few conflicts and less stalling than so-called normal individuals. It would appear that the special training of disabled individuals for certain types of work is to be recommended over the training of able-bodied individuals for the same job. Other types of work are in order for the able-bodied especially.....The shortage of physicians is beginning to tell in certain locations where specialists in small town clinics drop out, through illness or death, as it is practically impossible to replace them. All of these men have been carrying a specialized load for large communities....The number of University men and women who are retiring this year because they have reached the age of 68 is more striking than usual. Industry has devised a procedure in which the last years of a man on the job show a decrease in the number of hours of work and in the pay. This method permits him to develop outside possibilities or to start on his leisure time program.....