Radioactive Iodine Treatment of Angina Pectoris and Congestive Heart Failure

By Herrman L. Blumgart, M.D., A. Stone Freedberg, M.D., and George S. Kurland, M.D.

Dr. Herrman L. Blumgart: The purpose of this conference is to review a decade of experience in the treatment of intractable heart disease with radioactive iodine. By inducing hypothyroidism, the systemic circulatory requirements are reduced so that they may be within the limits of cardiac reserve. Following the induction of hypothyroidism or myxedema, each patient is maintained at the lowest level of metabolism consistent with comfort. In all our patients, small daily doses of thyroid, 6 to 30 mg. daily, are administered.

We believe that the radioiodine treatment of angina pectoris and congestive failure is necessary only for that small group of patients, probably less than 5 per cent, who remain disabled and in great discomfort despite all standard methods of therapy. For these patients with severe angina pectoris, various surgical methods have been advocated, such as pericardial injury, sympathectomy, posterior rhizotomy, omentectomy, pericoronal neurctomy, or arterialization of the coronary sinus. The radioactive iodine treatment of heart disease obviates the risk and discomfort attendant on surgery.

Case 1

Mr. W. T. was admitted to the Beth Israel Hospital on May 14, 1955, for evaluation of his angina pectoris and consideration of possible radioactive iodine treatment. He was referred by Dr. Paul D. White, who had seen the patient in 1944 and repeatedly since that time. The patient was 66 years of age. He stated that he had first become aware of his heart disease in 1928, at the age of 39, when he experienced a severe episode of substernal pain radiating to both shoulders and down both arms necessitating bed rest for 6 weeks. A diagnosis of acute myocardial infarction was made. He then experienced little discomfort until 1938 when, at the age of 49, he had a similar episode again interpreted as acute myocardial infarction. Following this episode he began to have fairly frequent attacks of substernal pain radiating to both shoulders on exertion and often radiating down the left arm to the fingertips and through to the back. These attacks occurred particularly while walking in cold weather, after eating, and during the night, waking him from sleep. The patient stated that in 1942, 1945, and 1948, additional episodes of severe cardiac pain occurred accompanied by electrocardiographic changes, elevated temperature, and sedimentation rate, and that each was treated with 6 weeks of bed rest.

In 1951 he was placed on a rigid “rice diet” and experienced improvement in that the anginal attacks were less frequent and less severe. During the year 1954 to 1955, preceding his first admission to the Beth Israel Hospital, despite faithful adherence to the rice regimen, the patient continued to have such frequent attacks of severe angina that he was incapacitated and unable to attend business. He had received various xanthine preparations, pentaerythrityl tetranitrate, and other medications without discernible benefit. Although nitroglycerin alleviated the attacks, frequently well over 100 tablets were taken over a 24-hour period. Oxygen was also helpful and was administered for hours at a time each day. The pains increased in severity and frequency until he was confined to bed and required meperidine for relief of pain at 2- to 3-hour intervals and constant nursing and medical care. Anginal pains of great intensity followed the slightest exertion, meals, any controversy, prolonged conversation, dreams, unusual noises, etc.

On physical examination, the blood pressure in both arms was 120/80. The thyroid gland was not enlarged. Examination of the heart revealed regular rhythm and no enlargement, the aortic second sound was slightly louder than the pulmonic second sound,
the heart sounds were of good quality, and there were no significant murmurs. The physical examination revealed otherwise normal findings. Laboratory examinations of the blood and urine revealed normal findings. The serum cholesterol was 250 mg. per 100 ml. Serum protein-bound iodine was 5 μg. per 100 ml. Two determinations of the basal metabolic rate were -13 and -24 per cent. On x-ray the heart was normal in size and shape. The radioactive iodine uptake by the thyroid gland 24 hours after a tracer dose was 60 per cent. The electrocardiogram showed no abnormalities except that the T waves in the chest leads over the left ventricle were diphasic or inverted.

A consultation was held by Dr. William H. Higgins, Jr., the patient's personal physician, Dr. Paul D. White, who had referred the patient for study, Dr. A. Stone Freedberg, and Dr. Herrman L. Blumgart. It was agreed that the patient presented no clinical evidence of altered thyroid function. Elevated radioactive iodine uptakes such as those observed in this patient have been described previously in patients who have been on a low iodine diet like the rice diet for considerable periods of time.

In general it was considered that the salient features of this case met the criteria that we have found to be suitable indications for treatment. The patient had continued to have attacks of angina pectoris on the slightest activity during the day and also had attacks at night despite optimal medical management. He had no other disease that made rehabilitation unlikely and he was emotionally stable and cooperative. The clinical course had not been progressively deteriorating. Although the angina pectoris was severe, it had remained at approximately the same levels for some time. Because of these considerations it was decided to recommend radioactive iodine therapy.

Accordingly, 4 doses of radioactive iodine of approximately 10 mc. each were administered at weekly intervals beginning June 20, 1955. In accordance with our general experience, the thyroid uptake of the first therapeutic dose was approximately the same as the tracer dose. Uptakes of the succeeding doses decreased to approximately 20 and 10 per cent. During the patient's stay in the hospital, he continued to have occasional attacks of angina pectoris. On returning home he again had frequent, very severe attacks of angina pectoris requiring meperidine and as many as 50 nitroglycerin tablets daily. The exacerbation of angina pectoris after treatment may have represented spontaneous variation of the condition or may have been due to thyroiditis consequent to the relatively large radiation of the thyroid gland. Even though the administered dosage was small, the estimated radiation delivered by the first dose of 10 mc. was of the order of 30,000 equivalent roentgens, a dose large enough to produce a marked radiation thyroiditis. The patient's personal physician, moreover, noted some thyroid tenderness that suggested thyroiditis.

During the last week of July 1955, 8 weeks after the first dose of I131, the patient noted decided improvement. He was able to walk as much as 250 yards against the wind without anginal pain. On examination in the hospital, the basal metabolic rate was still within normal limits, the cholesterol was 235 mg. per 100 ml., and the protein-bound iodine was 4.4 μg. per 100 ml. An additional dose of 9.3 mc. of I131 was administered. The 24-hour uptake was but 9 per cent. During the next month he had only occasional episodes of angina pectoris and showed many clinical and laboratory evidences of hypothyroidism. Accordingly he was started on 1/10 gr. of desiccated thyroid.

Subsequently and up to the present time, the patient has been under supervision of his personal physician and has returned for follow-up studies to us at approximately 6-month intervals. Twenty-one months after I131 therapy he continues to be free of attacks of angina pectoris on markedly increased activity, enjoys uninterrupted sleep at night, and has returned to some active participation in his business.

Approximately 6 months after treatment, he experienced paresthesias in his fingers and feet and, although reluctant to take more than 6 mg. of thyroid daily, he was persuaded to increase his dosage to 12 mg. daily. While his basal metabolic rate remained between -20 and -30 per cent, he noted disappearance of the paresthesias without any recurrence of chest pain. When last examined in October 1956, the basal metabolic rate was -30 per cent. The transverse diameter of the heart was the same as that recorded in June 1956, 13.8 cm. The serum cholesterol was 283 mg. per 100 ml. Minimal symptoms of hypothyroidism were present; consequently desiccated thyroid was increased to 18 mg. daily.

Summary. This 66-year-old man with angina pectoris for 17 years before treatment, incapacitated for several years despite long periods of rest and other therapy, showed significant improvement 2 months after I131 therapy and for the past 18 months he has been maintained in the hypometabolic state, free of pain despite greatly increased activity.

A Physician: The criteria used in the evaluation of the results of treatment in patients with angina pectoris and congestive failure are not clear to me.

Dr. Blumgart: Since both angina pectoris and congestive failure frequently have an irregular clinical course, treatment was administered particularly to the group of patients who had been in a relatively constant state.
at least 6 months. For each patient the pre-
treatment level of disability could be con-
sidered as a comparative control for that case.
The interval between I\textsuperscript{131} therapy and the
onset of hypometabolism, usually several
months in duration, constituted an additional
control period of observation and minimized
the effect of emotional reaction or suggestion
to the taking of an “atomic cocktail.” Conse-
quently any striking improvement could be
confidently attributed to I\textsuperscript{131} treatment.

The evaluation of the effects of treatment
has been designated as excellent, worthwhile,
and not worthwhile. An excellent result denotes
that the patient is markedly improved over
pretreatment status, with either no recurrence
of symptoms or a marked decrease in the fre-
quency and severity of angina pectoris or con-
gestive failure, despite markedly increased
activity; in many instances rehabilitation and
return to gainful employment occurred. A good
or worthwhile result denotes definite improve-
ment, with a decrease in frequency and severity
of attacks of angina pectoris or congestive
failure on the same amount of activity as be-
fore treatment. The remainder of the patients
were thought to have received no worthwhile
benefit.

A Physician: What have been the results
in your patients with angina pectoris?

Dr. Blumgart: Eighty-four of our patients
have been followed long enough for evalua-
tion: 36 (43 per cent) had an excellent result,
20 (24 per cent) had a worthwhile result, and
28 (33 per cent) had no benefit. Figure 1 shows
these results as well as those previously re-
ported from 49 other clinics. These results also
are in accordance with various other pub-
lished reports.\textsuperscript{5-9}

A Physician: What objective evidence of
improvement has been obtained? Were stand-
ardized exercise tolerance tests done?

Dr. A. Stone Freedberg: Exercise toler-
ance tests were not carried out in this patient
and have not been carried out in similar cases
because of the severity of the angina and the
possible risks attendant to such tests under
these circumstances. Previous studies from
this laboratory\textsuperscript{10} have demonstrated a marked
increase in the standardized exercise tolerance
test during induced hypothyroidism.

A Physician: Can you attribute the ben-
eficial result to any effect on the blood pressure?

Dr. Freedberg: No. The blood pressure in
our patients is approximately the same after
treatment as before. We have observed no
changes in blood pressure in any of our pa-
tients that might be responsible for improve-
ment in angina pectoris or congestive heart
failure.

A Physician: Can you anticipate an im-
provement in life expectancy following the
successful treatment with I\textsuperscript{131}?

Dr. George S. Kurdian: An adequate
answer to this question must await the col-
lection of extensive data in a large number of
patients. Such data must include not only the
duration of life after therapy but the duration of
angina before I\textsuperscript{131} and the severity of
angina. Future studies may answer this point.

A Physician: Is there any hazard to I\textsuperscript{131}
three?
reported to us of the administration of I$^{131}$ during Dicumarol therapy in which severe hemorrhage into the thyroid gland resulted. We therefore currently regard this combination as hazardous.

A Physician: This patient received 5 therapeutic doses of I$^{131}$. Do all patients receive so many?

Dr. Freedberg: No. The exact dosage schedule has not been worked out, since no satisfactory method is available to determine in vivo the thyroid radiation delivered by I$^{131}$. We have estimated that approximately 30,000 to 40,000 equivalent roentgens are required to destroy the normal thyroid gland. The dosage schedule we have evolved is as follows. If the 24-hour uptake of the tracer dose is 30 to 40 per cent, an initial dose of approximately 10 mc. is administerd. At the present time, therefore, in a situation such as we had in Mr. W. T., we would administer a smaller initial dose of 7 to 8 mc. If the 24-hour tracer uptake is approximately 20 per cent, we would administer approximately 15 mc. as an initial dose. Correspondingly, with a tracer uptake of approximately 15 per cent, we would administer 20 mc. as an initial dose.

In each instance 2 subsequent doses are administered at weekly intervals, usually 5 mc. larger than the first dose. In recent years we have not administered doses larger than 20 to 25 mc. In an occasional patient additional doses have been administered 6 to 10 weeks later if hypothyroidism has not ensued. Since the thyroid uptake of these doses is very small and the turnover rapid, the doses have been, on the average, 15 to 20 mc.

With this dosage schedule, clinical thyroiditis has been observed only infrequently.

A Physician: I notice that this patient was hospitalized. Is that necessary?

Dr. Kurland: The majority of our patients are treated on an ambulatory basis. Only when angina is so advanced that travel to the I$^{131}$ laboratory precipitates severe pain do we advise hospitalization.

A Physician: Do diabetic patients in the hypothyroid state have a decreased insulin requirement?

Dr. Kurland: Yes. In several patients who had diabetes and required insulin, hypoglycemic reactions were encountered during hypothyroidism when they continued to take the same dose of insulin. In general, diabetic patients require somewhat less insulin in the hypothyroid state, i.e., approximately 10 or 15 units of insulin less than before.

It has been shown that the glucose tolerance is normal in nondiabetic patients with induced hypothyroidism. Previous studies have shown that the degree of hyperglycemia following glucose ingestion in diabetic patients is less during hypothyroidism.

A Physician: What is the effect of the hypothyroid state on heart size in your patients?

Dr. Kurland: We have studied the effect of hypothyroidism on the size and configuration of the cardiac silhouette in 27 patients by comparing roentgenograms taken before and after I$^{131}$ therapy. Ten of 13 patients who achieved good to striking relief of angina pectoris exhibited no increase in the cardiac silhouette after 2 to 48 months of hypometabolism. Two others showed increase in size only during an exacerbation of cardiac pain. On the other hand, 5 of 6 patients not benefited by treatment showed a progressive increase in heart size. In 2 patients with angina pectoris and congestive heart failure, I$^{131}$-induced myxedema was followed by progressive cardiac enlargement, despite striking therapeutic benefit. The remaining 6 patients with chronic congestive heart failure showed no cardiac enlargement during most of 19 to 53 months of hypometabolism.

We should now like to present a second patient who exemplifies many aspects of the radioactive iodine treatment of intractable congestive failure.

**Case 2**

J. K., a 43-year-old woman, had suffered attacks of acute rheumatic fever at 12 and 13 years of age. Although a murmur was recognized after the first episode, she remained well until the occurrence of dyspnea, 6 months before her first Beth Israel hospitalization in October 1951. At this time, she was admitted because of prolonged cough, fatigue, dyspnea, and cyanosis. Examination revealed cardiomegaly; the murmurs of mitral and aortic
stenosis and insufficiency, and rapid atrial fibrillation. There were basal rales and a small pleural effusion. The liver was enlarged but not tender. No evidence of hyperthyroidism, acute rheumatic fever, or bacterial endocarditis was found. When a chest roentgenogram showed previous pulmonary infarction, Dicumarol was administered for 12 days.

After discharge, cardiac decompensation and rapid atrial fibrillation recurred despite vigorous therapy in the cardiac clinic. Five doses of $^{131}$I totaling 125 mc. were administered from January to August 1952. The 24-hour uptake of the initial dose was 44 per cent. Mild transient thyroiditis occurred. During therapy a second hospital admission was required for severe congestive failure. In August 1952 definite hypothyroidism ensued and the patient noted increased work tolerance without dyspnea or fatigue. The rapid fibrillation was now replaced by slow sinus rhythm. Basal metabolism was $-24$ per cent; serum cholesterol 263 mg. per 100 ml. Mercurial diuretics, previously necessary weekly or every 2 weeks, were omitted for a while and then resumed only at monthly intervals. A daily dose of 6 mg. of desiccated thyroid was prescribed. She maintained this improvement until October 1954 when, because of a mild increase in dyspnea and ankle edema, mercurials were again administered weekly. Chronic cardiac decompensation was maintained under good control with this regimen until October 1956, when increased frequency of diuretics was required.

**Summary.** A 43-year-old woman with longstanding rheumatic heart disease and disabling congestive failure despite vigorous therapy was strikingly improved for the first 2 years after $^{131}$I therapy and moderately improved for the following 2 years.

A Physician: What are the results in congestive failure?

**Dr. Blumgart:** Thirty-four patients with congestive heart failure have been treated by us: 8 (24 per cent) were strikingly improved, 10 (30 per cent) had a worthwhile result. In 16 (46 per cent) no benefit was obtained. These results and the similar results obtained in 49 other clinics are shown in figure 2.

A Physician: In congestive failure, are the results better in the arteriosclerotic or rheumatic heart disease patient?

**Dr. Blumgart:** We have been unable to observe any difference in the results in these two groups. We have had striking improvement as well as good and not worthwhile results among both groups of patients.

A Physician: I notice that in the last case sinus rhythm replaced atrial fibrillation after

the development of hypothyroidism. Is that common?

**Dr. Kurland:** In 23 euthyroid patients with rheumatic heart disease and severe congestive heart failure treated with $^{131}$I, 16 had chronic atrial fibrillation. In 3 of these patients with long-standing atrial fibrillation, the induction of hypothyroidism was accompanied by the spontaneous return of sinus rhythm that then persisted. In no patient did atrial fibrillation develop after the treatment with $^{131}$I.

Encouraged by these events we have subsequently induced hypothyroidism in 5 patients with uncontrollable paroxysmal supraventricular arrhythmias (3 with atrial fibrillation, 1 with atrial tachycardia, and 1 with both). Four had rheumatic heart disease and 1 hypertensive heart disease. In all, the effect was beneficial. The paroxysms of arrhythmia were abolished or notably diminished in frequency. The bouts that did occur were more readily controlled without precipitation of angina or pulmonary edema.

A Physician: Have you observed the myxedema heart in the sense of a condition precipitating congestive failure in any of your cases?

**Dr. Blumgart:** As mentioned, certain of our patients showed an increase in the size of the cardiac silhouette, diminished amplitude
of cardiac contraction, lowered voltage of the electrocardiogram, and decreased velocity of blood flow. In no case, however, have we noted evidence of the precipitation of congestive failure in any patient in our series.

A PHYSICIAN: What is the reaction of these patients to other drugs they may be taking, such as digitalis or sedatives?

DR. FREEDBERG: We do not have quantitative data on this question. It is our impression that in some patients less digitalis is required to maintain digitalization. In others, we have been surprised by the continued tolerance to a large maintenance dose. We have also not observed any altered tolerance of these patients to sedatives or, in 6 patients undergoing operation, to meperidine, pentothal, or ether anesthesia. This experience, which is contrary to that in untreated myxedema, may be related to the fact that all our patients receive small doses of thyroid. We do have the impression, however, that similar tolerance to morphine is not present in our patients.

A PHYSICIAN: Have you studied the effects of hypothyroidism on the various lipid fractions?

DR. KURLAND: The serum lipoprotein and cholesterol concentrations have been studied in 15 euthyroid patients with heart disease before I\(^{131}\) treatment, during subsequent hypothyroidism, and after administration of desiccated thyroid.

The patients ranged in age from 32 to 82 years; 8 were male; 7 were female. Six suffered from rheumatic heart disease. Two of the rheumatic patients had elevated cholesterol levels before I\(^{131}\) treatment. Nine patients had atherosclerotic coronary artery disease with severe angina pectoris. Two or more control serum specimens were generally studied while the patient was euthyroid and from 1 to 6 specimens during the period when the patient was myxedematous.

Additional specimens were obtained after small doses of desiccated thyroid were given to maintain a somewhat higher level, usually \(-15\) per cent to \(-25\) per cent, at which maximum relief of cardiac symptoms and the least possible discomfort from hypometabolism occurred.

Elevation of the most dense lipoprotein fractions, \(S_1\) 0–11 and \(S_1\) 12–20 correlated better with the presence of hypometabolism than did the less dense fractions above \(S_1\) 20. Thus, the initial concentration of \(S_1\) 12–20 material ranged from 20 to 72 mg. per cent. Most of these values were within the limits found in normal people of the same age and sex. After the induction of myxedema, the \(S_1\) 12–20 values ranged from 27 to 135 mg. per cent and averaged 79 mg. per cent. The data reveal an increase greater than 15 mg. per cent in \(S_1\) 12–20 in 9 patients, and none or a small increase, less than 15 mg. per cent, in 6 patients. The 4 patients with rheumatic heart disease and without initially elevated lipids showed a mean initial value of 38 mg. per cent and a value in myxedema of 55 mg. per cent, an average increase of only 17 mg. per cent; however, 3 of these 4 patients showed only minimal increases. Additional studies were obtained in 9 of these 15 patients following the administration of small doses of desiccated thyroid. Two patients showed no change in the concentration of \(S_1\) 12–20 or a slight increase. In all the others, there was a downward trend of level that was largest in those cases that had previously shown the greatest increase; in about half the \(S_1\) 12–20 level returned to the pretreatment level.

In the \(S_1\) 30–35, \(S_1\) 35–100, and \(S_1\) 100–400 fractions no striking changes were observed.

The serum cholesterol levels showed more marked changes. The initial cholesterol values averaged 223 mg. per 100 ml. in the rheumatic patients; 263 mg. per 100 ml. in the angina patients. In 13 of the 15 patients, the serum cholesterol rose after myxedema and averaged 304 and 359 mg. per 100 ml. for the rheumatic and atherosclerotic patients respectively. With one exception, there was a decline following the administration of thyroid. The serum cholesterol levels correlated better with changes in metabolic state than did the lipoproteins.

A PHYSICIAN: Has any therapy except thyroid been effective in lowering the serum cholesterol in these patients?

DR. KURLAND: We have administered a sus-
pension of sitosterols* to 1 patient with marked hypercholesterolemia associated with I®-induced hypometabolism. The serum cholesterol fell from approximately 700 mg. to 400 mg. per 100 ml. This is similar to the effect observed by Best and Duncan. It is too soon to evaluate the duration or effectiveness of this agent. Experience with other agents such as high unsaturated fat diet, low-fat diets, thyroxin, and triiodothyronine analogues, while promising, is too limited for a definite statement.

In the treatment of congestive failure by radioactive iodine certain other aspects are exemplified by the following case:

**Case 3**

Patient N. B. was a white man, 35 years old at death. He had had chorea and several attacks of rheumatic fever in childhood.

Physical examination had disclosed cardiac enlargement and the murmurs of aortic and mitral stenosis and insufficiency. He had carried on fairly successfully but finally entered the Beth Israel Hospital in January 1950 at the age of 29 because of increasing exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, occasional precordial aching unrelated to exertion, nonproductive coughing, and rare episodes of dysphagia during the preceding 4 months. Examination disclosed a tall, thin man whose respirations were labored at a rate of 30 per minute; the apical pulse was irregular at a rate of 108 per minute. The initial blood pressure was 160/100 mm.; all subsequent blood pressure determinations were within normal limits. The heart was greatly enlarged. There were loud, rough apical systolic and diastolic murmurs and thrills, softer aortic systolic and diastolic murmurs, a loud pulmonic second sound, and a soft aortic second sound. There was slight cyanosis but no clubbing of the fingers. The neck veins were not distended, the lungs were clear, the liver edge was palpable, and edema was absent. Laboratory studies, including complete blood counts, plasma nonprotein nitrogen, Hinton serologic reaction, and urinalysis were normal except for 2+ to 4+ albuminuria. The arm-to-tongue circulation time was 32 seconds. The vital capacity was 2.1 L. (normal 4.3 L.). Chest fluoroscopy disclosed enlargement of all cardiac chambers, most marked in the left atrium. The lungs appeared slightly congested, and the costophrenic angles contained a small amount of fluid. Electrocardiograms showed atrial fibrillation, right axis deviation (120°), and probable right ventricular hypertrophy. Treatment with rest, low-salt diet, continuation of digitalis, and mercurial diuretic injections every other day resulted in lessening of dyspnea and a 12-pound weight loss, whereupon he was discharged.

Because of gradual relapse on this regimen he was rehospitalized from March to May 1950. Additional studies disclosed a venous pressure of 18.5 cm. of saline and an icterus index of 28 units. Basal metabolic rates averaged +5 per cent, and the 24-hour thyroid uptake of radioiodine was 37 per cent. As a final therapeutic measure, this euthyroid patient was given 32 mc. of radioiodine in 2 divided doses in April 1950.

His condition was unchanged until September 1950, when hypothyroidism appeared. Thereafter, exertional capacity improved considerably, and mercurial injections were required only every 2 weeks. Chest roentgenograms during this period showed slight diminution in cardiac size and clearing of pulmonary congestion. In January 1952, thyroid, 6 to 18 mg. daily, was instituted to alleviate symptoms of myxedema. The basal metabolic rate was maintained at an average of -25 per cent and the serum cholesterol level varied from 280 mg. to 400 mg. per 100 ml. He was able to return to full-time work for the next 4 years.

In August 1955, exertional dyspnea reappeared. In October, the appearance of mild cough, chills, and fever necessitated rehospitalization. The cardiac findings were unchanged. There were now neck vein distention, dullness, decreased breath sounds, and crepitations over the right lower posterior chest, moderate hepatomegaly, and slight leg edema. No evidence of thrombophlebitis was found. The chest roentgenogram showed increased cardiac enlargement and consolidation of the right middle lobe that was interpreted as a possible pulmonary infarct. The electrocardiogram disclosed increased evidence of right ventricular hypertrophy. In conjunction with the cardiac therapy, heparin was administered intravenously every 4 hours, in 50-mg. doses. Dyspnea increased, cyanosis, hypotension, stupor, and periodic breathing developed, and he died on the third hospital day.

**Postmortem examination** revealed marked stenosis and calcification of the mitral valve, minimal commissural fusion between 2 of the aortic cusps, and slightly thickened and rolled borders of the tricuspid valve with slight thickening and shortening of the chordae tendineae. The pulmonic valve was normal. There was marked dilatation and hypertrophy of the ventricles. The left atrium was huge and contained more than 2 L. of blood; the right atrium contained approximately one third this volume. The coronary arteries examined by the injection and dissection technic of Schlesinger had only a few discrete, nonstenosing atheromatous plaques in the main left and right stems.

The final pathologic diagnoses were moderately active rheumatic heart disease, mitral stenosis and

* Cytellin, supplied through the courtesy of Eli Lilly & Co.
insufficiency, slight commissural fusion of the aortic valve, cardiomegaly, enormous atria with fibrosis and calcification, chronic passive congestion of the lungs, recurrent chronic pneumonia of the right middle and lower lobes, severe pulmonary atherosclerosis, pulmonary emboli, cardiac cirrhosis of the liver, healed renal infarcts, and thyroid fibrosis and atrophy following radioiodine therapy.

In summary, a 35-year-old draftsman, invalided by rheumatic heart disease and refractory congestive heart failure, was treated with I\textsuperscript{131}. Following development of hypothyroidism, improvement was striking and the patient was able to return to work. He died of a pulmonary complication after 4 years of improvement. Despite hypometabolism for 4 years and hypercholesterolemia of 250 to 400 mg. per 100 ml. for at least 2 of these 4 years, careful study of the coronary arteries revealed no occlusions or major narrowing and only a few nonstenosing plaques.

A PHYSICIAN: To what degree does the increased serum cholesterol level of hypothyroidism cause increased coronary arteriosclerosis in the patient with angina pectoris of atherosclerotic etiology?

DR. FREEDBERG: I presume you are referring to the question whether the high cholesterol values of myxedema dispose the patient to an increased progression of arteriosclerosis. The situation in our patients is not strictly analogous to untreated complete myxedema, since we prescribe or administer small doses of thyroid and we have indicated above the effect that this may have on the serum lipoproteins. We have reviewed the clinical course and postmortem findings of patients who survived from 1 to 11 years after surgical total thyroidectomy and in whom hypometabolism with elevated cholesterol values was present.

We have been particularly interested in the younger patients with rheumatic heart disease. In them only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed post mortem in such patients, the lesions might well be attributed to the myxedematous state. In a study reported previously,\textsuperscript{14} the clinical and postmortem findings are described in 8 such patients with rheumatic heart disease or cor pulmonale, in whom hypothyroidism or myxedema was present and who survived from 1 to 13 years (average, 7.4 years) following surgical total thyroidectomy. None of the 8 cases showed complete occlusion of any of the coronary arteries; 5 of the 8 showed no narrowing of any of the main stems or branches of the coronary arteries; only 3 of the 8 showed slight narrowing of 1 of the main stems. In the other arteries, atheromatosis and atherosclerosis varied greatly, but was similar to that usually observed in similar euthyroid patients.

Our results do not, of course, disprove a role of cholesterol in the production of atherosclerosis; these results do demonstrate, however, that over the observed period of time, the hypothyroid state, controlled with small daily doses of desiccated thyroid, is not necessarily, in itself, sufficient cause for the production of coronary atherosclerosis.

It is of particular interest in patient N. B., case 3, that after hypometabolism was induced by I\textsuperscript{131}, the basal metabolic rate was maintained at a level of approximately -20 per cent for 4 years and the serum cholesterol was significantly elevated as high as 400 mg. per 100 ml. for at least 2 years. When the heart was carefully examined by the technic of Schlesinger, there was no evidence of coronary occlusion or major narrowing of any of the coronary vessels.

A PHYSICIAN: How do you deal with the problem of increasing angina pectoris or congestive failure in your hypothyroid patients when you cannot lower the thyroid medication further without causing intolerable symptoms of myxedema?

DR. BLUMGART: It is fortunately a relatively small group of patients in which one is confronted with this difficult problem. The patient cannot tolerate any further lowering of the metabolic state and has now progressed so that his angina pectoris or congestive failure is similar to that before treatment. Under such circumstances nothing further can be done than the usual methods of treatment; in the instance of angina pectoris, surgical methods of treatment must be considered, including alcohol injections of nerves, ganglionectomy, introduction of foreign substances within the pericardium, or even posterior rhizotomy.

A PHYSICIAN: What do you believe are the mechanisms whereby improvement is achieved?
Dr. Freedberg: Various considerations lead to the conclusion that the reduction in cardiac work consequent to induced hypometabolism is, in all probability, the most important factor. The beneficial effect of rest, and the consequent reduction in cardiac work, in the successful treatment of congestive failure, has long been known. Means in 1924 in discussing the treatment of cardiac dyspnea noted:

First of all comes treatment directed towards reduction of the metabolic rate. This is seen most strikingly in treatment by rest, particularly in heart failure. Mere confinement to bed, of course, makes total metabolism closely approach basal and, therefore, greatly diminishes the work both of the heart and the respiratory organs and consequently, the dyspnea... In the dyspnea of hyperthyroidism... those measures which reduce the hyperthyroidism and therefore the metabolism by the same token diminish or abolish dyspnea.

In 1930, it was noted that the velocity of blood flow in patients with myxedema, in the absence of circulatory insufficiency or congestive heart failure, was slower than in normal individuals; in fact, the rates were similar to those observed in patients with congestive heart failure. This led to the concept that reduction of the metabolic demands to a level more closely approaching the blood supply by the institution of hypothyroidism or myxedema might be beneficial to the patient with congestive heart failure. The general validity of this concept has been confirmed by the results obtained following surgical total thyroidectomy, by thiourea derivatives, and, as reported here, by radioactive iodine.

A recent paper by Davies, McKinnon, and Platt suggests another mechanism whereby myxedema may benefit the patient with congestive failure. They observed that patients with myxedema, in contrast to patients with congestive heart failure, had unimpaired ability to excrete salt and water. It was particularly striking that a patient with mitral stenosis and spontaneous myxedema had a glomerular filtration rate and renal blood flow similar to that observed in congestive heart failure, but the administration of a 10-Gm. salt intake and 1,500 ml. of fluid daily did not result in an increase in body weight or a rise in venous pressure, as in patients with congestive failure.

Certain of these considerations are applicable to angina pectoris. It is well established that many patients with angina pectoris and thyrotoxicosis are markedly improved or show a disappearance of angina pectoris when the metabolic rate is reduced to normal. The cost of cardiac work in hyperthyroidism has been shown by Plummer and Boothby to be increased, so that the cardiac work of the thyrotoxic patient at rest is like that of a normal person doing light work. A general reduction in body metabolism in euthyroid individuals with a consequent reduction in requirements for cardiac work would be of obvious importance in improving angina pectoris occurring at rest. It is difficult, however, to relate the small increase in cardiac efficiency and the decreased cost of cardiac work, noted by Briard and co-workers in myxedema to the marked increase in tolerance of exercise noted by patients with angina pectoris in whom hypothyroidism is induced. Moreover, though in most instances clinical improvement in angina pectoris occurs pari passu with the drop in metabolic rate, in a few instances clinical improvement is noted early in the period of reduced metabolism and in others only after several months or longer.

Other possibilities suggested as the mechanisms for the improvement that occurs in intractable angina pectoris after induction of controlled hypothyroidism include (1) a decrease in sensitivity of the cardiovascular system to adrenergic mediators, (2) an alteration in pain perception, and (3) an increased rate of development of intercoronary arterial collateral circulation. There is much evidence to indicate an interrelationship between the thyroid hormone, the adrenal cortical hormones, and the catecholamines, epinephrine and noradrenaline. Raab recently summarized the evidence, "that the thyroid hormone affects the myocardial metabolism by markedly potentiating the hypoxia producing calorigenic and toxic action of the adreno-sympathogenic cortical amines." Since in myxedema there not only is reduction of the thyroid hormone but also in the adrenal cortical hormones, the pos-
sibility cannot be excluded that some local myocardial or coronary vascular change explains the beneficial effect of induced hypothyroidism. Our own data have revealed little change in the systemic pressor response to norepinephrine in euthyroid patients with cardiac failure before and after I\textsuperscript{131}-induced hypothyroidism; Riseman and co-workers also observed little alteration in blood pressure response to epinephrine after surgical total thyroidectomy in patients with angina pectoris until the basal metabolism had fallen to $-30$ per cent. Of the other possibilities, no evidence exists that the beneficial effect of hypothyroidism is to alter pain perception or to effect a beneficial change in the rate of development of the intercoronary arterial circulation. Much further work is necessary to elucidate these various possibilities.

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