Hypothyroidism Produced by Radioactive Iodine (I\(^{131}\)) in the Treatment of Euthyroid Patients with Angina Pectoris and Congestive Heart Failure

Early Results in Various Types of Cardiovascular Diseases and Associated Pathologic States

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

Hypothyroidism, induced by I\(^{131}\) to lessen the work of the heart, is proposed as a means of treating certain patients with angina pectoris and congestive failure who are refractory to the standard medical measures. Eighteen such patients have been treated. The period of follow-up averages thirteen months. Eight of the 13 patients with angina pectoris and 3 of 5 patients with congestive failure showed worthwhile improvement. In 6 of the 18 patients, the improvement was striking. Tentative criteria for the selection of patients, their pre- and post-treatment management, and detailed descriptions of the results are presented.

Previous studies which showed that the work of the heart is lessened in myxedema led to the employment of total thyroidectomy,\(^1,\)\(^2\) and more recently, antithyroid drugs,\(^3\)\(^-\)\(^10\) to induce hypothyroidism in patients with intractable angina pectoris and/or congestive heart failure. Concomitant clinical improvement has been witnessed, but with each method certain disadvantages have been apparent.\(^2\)\(^,\)\(^6\) The availability of radioactive iodine (I\(^{131}\)) led us to investigate its possible use for this purpose.\(^11\)

This communication is a report of the therapeutic results of hypothyroidism induced by I\(^{131}\) in 18 euthyroid patients with advanced angina pectoris or congestive heart failure. Each patient was selected, for reasons to be detailed, from the relatively small group of cardiac cripples who remained seriously disabled and in great discomfort despite all medical measures including regulation of their activity, assistance in their emotional problems and medicinal treatment.

Plan of Investigation

The first problem was to learn whether persistent hypothyroidism could be induced safely by one or more doses of I\(^{131}\). It is well known that thyrotoxicosis can be controlled by I\(^{131}\) with a reduction of the basal metabolic rate to normal. Three to eight millicuries are commonly used. The avidity of the normal thyroid gland for I\(^{131}\) is much less, however; the uptake is usually 20–50 per cent of the administered dose, as indicated by urinary excretion, and averages 50 per cent as measured by external counting.\(^13\) Before the therapeutic studies of the present communication were undertaken, observations were made with gradually increasing doses in euthyroid patients in terminal state due to hemiplegia or other conditions such as carcinoma. The results of these studies indicated that persistent hypothyroidism could be induced by one or more appropriate doses without any toxic effects.\(^13\)\(^,\)\(^14\)

Since November 1947 we have induced persistent hypothyroidism in the 18 consecutive cardiac patients of the present report in whom the duration of the follow-up is sufficient for clinical evaluation of the therapeutic results.

Methods of Study

The clinical appraisal of the post-treatment as well as of the pretreatment condition of each patient was carried out independently by several observers. We also have evaluated the pretreatment as well as the post-treatment condition of our patients by as
many objective criteria as possible. Detailed clinical and laboratory studies were performed before, and at frequent intervals after treatment. With a few minor exceptions, the treatment of cardiac disease in each patient was the same after treatment as before treatment.

Routine examinations of the blood and urine, electrocardiograms and roentgenograms of the chest taken at a distance of 7 feet were performed before treatment and at frequent intervals after treatment. Blood for cholesterol measurements was drawn from the antecubital vein with minimal stasis after a fast of fourteen hours or more. Measurements of serum cholesterol were made in duplicate by the method of Myers and Wardell, using the apparatus for continuous extraction described by Ling. The averages of the duplicate determinations, which checked within 5 per cent, have been reported. Where the clinical state of the patient indicated, special studies of the blood were performed. These included non-protein nitrogen, glucose, total protein, calcium, corrected sedimentation rate, and prothrombin time.

The basal metabolic rate, the vital capacity of the lungs and its subdivisions were measured with a Collins Benedict-Roth apparatus. Patients with orthopnea were allowed to lie in a semirecumbent position. On each occasion, measurements were made in duplicate or triplicate and were repeated before treatment until it was evident that the patient had attained the basal state. The Dubois normal standards as modified by Boothby and Sanford were used.

The venous pressure was measured by the direct method of Moritz and Tabora. When possible, the readings were obtained with the patient recumbent, the right auricle being assumed to be 5 cm. below the level of the fourth costochondral junction. When orthopneic, the patient was allowed to sit up at an angle of 45 degrees, the right auricle then being assumed to be 2.5 cm. below the fourth costochondral junction.

The arm to tongue circulation time was performed with sodium dehydrocholate (Decholin) according to the methods of Winternitz, Deutsch and Brull and Gargill.

Each patient received a tracer dose of I\textsuperscript{131} before treatment. Quantitation of the uptake in the thyroid gland following tracer and therapeutic doses was made by a four-tube method previously described. The seventy-two-hour urinary excretion of I\textsuperscript{131} was determined by a modification of this method by the method described by Marinelli and Hill and by one of us. We are indebted to Dr. Douglas J. Riggs for determination of the serum protein-bound iodine in some cases.

Many of our patients with angina pectoris were too ill to be subjected to an exercise tolerance test. When the hazard was not considered significant and when the patient could undertake the necessary effort, exercise tolerance tests as described by Rise-
Table 1.—The Dose, Urinary Excretion, Retention, and Side Effects of I\textsuperscript{131} Administered to Eighteen Euthyroid Cardiac Subjects

<table>
<thead>
<tr>
<th>Case</th>
<th>1st Administered (mc.)</th>
<th>72-Hour Urinary Excretion (%)</th>
<th>Amount Retained in Body (mc.)</th>
<th>Thyroiditis†</th>
<th>Transitory Thyrotoxicosis</th>
</tr>
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<tbody>
<tr>
<td>1. J. L.</td>
<td>29</td>
<td>64</td>
<td>10.3</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>96</td>
<td>1.7</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>83</td>
<td>4.9</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>97</td>
<td>1.2</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>150</td>
<td>18.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. R. A.</td>
<td>24</td>
<td>62</td>
<td>9.0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>87</td>
<td>3.6</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>92</td>
<td>3.1</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>15.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. J. K.</td>
<td>42.5</td>
<td>45</td>
<td>23.5</td>
<td>+++</td>
<td>Probable</td>
</tr>
<tr>
<td>4. H. R.</td>
<td>25.5</td>
<td>Not feasible</td>
<td></td>
<td>++</td>
<td>None</td>
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<tr>
<td>5. M. G.</td>
<td>42.5</td>
<td>58</td>
<td>17.8</td>
<td>++</td>
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</tr>
<tr>
<td></td>
<td>25.5</td>
<td>82</td>
<td>4.6</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>68.0</td>
<td>22.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. S. F.</td>
<td>42.5</td>
<td>44</td>
<td>23.8</td>
<td>+</td>
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<tr>
<td>7. B. S.</td>
<td>25.5</td>
<td>80</td>
<td>5.1</td>
<td>+</td>
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<tr>
<td></td>
<td>27.0</td>
<td>92</td>
<td>2.2</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>52.5</td>
<td>7.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8. M. H.</td>
<td>39</td>
<td>70</td>
<td>11.7</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>72</td>
<td>9.5</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>21.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. M. C.</td>
<td>15.5</td>
<td>64</td>
<td>5.4</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>24.0</td>
<td>88</td>
<td>2.9</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>32.0</td>
<td>1.6</td>
<td></td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>71.5</td>
<td>9.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. R. S.</td>
<td>30.5</td>
<td>70</td>
<td>9.2</td>
<td>0</td>
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<tr>
<td>11. H. Y.</td>
<td>25.5</td>
<td>Not feasible</td>
<td>—</td>
<td>++</td>
<td>None</td>
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<tr>
<td>12. J. E.</td>
<td>25.5</td>
<td>Not feasible</td>
<td>—</td>
<td>++</td>
<td>None</td>
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<tr>
<td>13. M. S.</td>
<td>42.5</td>
<td>71</td>
<td>12.2</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>56.0</td>
<td>71</td>
<td>16.2</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Total</td>
<td>98.5</td>
<td>28.4</td>
<td></td>
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</table>
Hypothyroidism Produced by Radioactive Iodine

Table 1.—Continued

<table>
<thead>
<tr>
<th>Case</th>
<th>I(^{131}) Administered (mc.)</th>
<th>72 Hour Urinary Excretion (%)</th>
<th>Amount Retained in Body (mc.)</th>
<th>Side Effects*</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thyroiditis†</td>
</tr>
<tr>
<td>14.</td>
<td>25.5</td>
<td>17</td>
<td>21.2</td>
<td>0</td>
</tr>
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<td>15.</td>
<td>27.0</td>
<td>28</td>
<td>19.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30.5</td>
<td>35</td>
<td>19.5</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>57.5</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>8.5</td>
<td>71</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>24.0</td>
<td>62</td>
<td>9.0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>32.5</td>
<td>11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>27</td>
<td>43</td>
<td>15.7</td>
<td>0</td>
</tr>
<tr>
<td>18.</td>
<td>39</td>
<td>48</td>
<td>20.4</td>
<td>+</td>
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</tbody>
</table>

* No toxic effects on the blood or kidney, and no radiation sickness was observed in any case.
† ++++ severe; ++ moderate; + mild, tenderness on palpation but no symptoms; 0 none

ment was reflected by the fact that twelve attacks of acute myocardial infarction had occurred in the 13 patients with angina pectoris. The etiologic basis for angina pectoris in all patients was arteriosclerotic heart disease; in 5, arterial hypertension was present. Eleven were men, 2 were women. The ages ranged from 38 to 72 years; the average was 57 years. The duration of angina pectoris prior to treatment was 1–18 years and averaged 5 years. The period of observation following I\(^{131}\) therapy was seven to nineteen months and averaged twelve months.

The 5 patients with congestive failure (table 3) had all been treated by prolonged bedrest and regularly showed evidence of congestive failure on getting out of bed. Three of the patients had rheumatic heart disease; the other 2, arterial hypertension and arteriosclerotic heart disease. The ages of the patients ranged from 43 to 59 years. The duration of decompensation varied from 1 1/2 to 17 years and averaged 7.3 years. The condition in each case was such that definite improvement could be confidently attributed to the hypothyroidism induced by I\(^{131}\).

In some of the patients of this series, the probability of achieving a worthwhile result was admittedly small. Thus, Patient 5 had already suffered two attacks of acute myocardial infarction and several other episodes of prolonged exeruciating pain but without progressive characteristic electrocardiographic changes. Similarly, Patient 18 had shown a rapidly progressive course of congestive failure with multiple embolic episodes. In all patients included in this report, reliable information regarding the characteristics and severity of the clinical course was available. Some patients had been observed for years in the cardiac clinic of the Beth Israel Hospital and on the wards; others were referred by highly competent physicians who placed their records at our disposal. Each patient was appraised independently by several of us before a decision was reached; in many instances, our appraisal was based on observation and study of the patient, including exercise tolerance and other tests, over a period of weeks or many months before radioactive iodine therapy was instituted.

No patient was chosen whose prognosis for life was good. In each instance the procedure was explained to the patient with a full account of its experimental status and the necessity for frequent follow-up studies. In some patients the treatment was inaugurated while they were still
hospitalized; in others, all studies were carried out with the patients on an ambulatory basis.

No patient showed positive evidence of hyper- or hypothyroidism before treatment. In addition to the clinical criteria, the following indices revealed normal thyroid function: the basal metabolic rate, serum cholesterol, and, in some instances, the serum protein-bound iodine. Tracer doses of $^{131}$I were administered and in all cases the percentage of urinary excretion was that observed with normal thyroid function. In patients with congestive failure, the urinary excretion is lower than that observed in edema-free individuals. Direct measurements of the thyroid uptake in patients with congestive failure have revealed uptakes in the euthyroid range.

The patients selected had diverse types of cardiovascular disease i.e., arteriosclerotic heart disease with congestive failure, arteriosclerotic heart disease with angina pectoris, arteriosclerotic heart disease with hypertension and paroxysmal dyspnea, rheumatic valvular heart disease with normal rhythm or with auricular fibrillation.

To obtain patients who met these requirements, only certain patients were selected from among the larger group with intractable heart disease. Some rejected patients failed to give sufficient objective confirmation of their incapacity when carefully studied; others were afflicted with associated diseases (such as bronchiectasis with advanced pulmonary emphysema, renal disease, cirrhosis of the liver, cerebral arteriosclerosis, active rheumatic fever, subacute bacterial endocarditis) which would render evaluation of the therapeutic result difficult. In others, the anticipated duration of life of weeks or a few months was insufficient to permit the induction of hypothyroidism which similarly requires weeks or months.

Case Histories with Comment

Case 1.—Angina pectoris one year, increasing in frequency and intensity; patient almost completely incapacitated. Coronary arteriosclerosis; old myocardial infarction. Four doses of $^{131}$I, totaling 150 mc., with temporary hypothyroidism and clinical improvement after each of the first three doses; persistent myxedema and disappearance of angina after fourth dose. Myxedema controlled by 30 mg. thyroid daily. Practically complete disappearance of all symptoms. Patient feeling well past seven months and gainfully employed. Striking therapeutic result.

Pretreatment History. J. L., a 41 year old man, B.I.H. $\#69433$, referred through the courtesy of Dr. J. E. F. Riseman, received 29 mc. $^{131}$I on April 27, 1948. One year prior to $^{131}$I therapy, attacks of substernal pressure on exertion and emotion were first noted. He was hospitalized for eight months before treatment because of "clawing, tearing" substernal pain with momentary loss of consciousness, due to probable acute myocardial infarction. The anginal attacks increased in severity and frequency, lasted from one to ten minutes and were relieved by nitroglycerine. He had been unable to work for the previous nine months and had been restricted largely to the house because walking even a hundred feet precipitated an attack. He was awakened by anginal attacks, often suffering three or four episodes nightly. He noted increasing dyspnea and was uncomfortable unless he used two pillows. In the month prior to $^{131}$I therapy, he had used over 500 tablets of nitroglycerine. During his illness, he had received the following treatment: theobromine sodium acetate, potassium iodide, sedatives, quinidine, atropine; nitroglycerine alone was of slight help. There was no history of arterial hypertension or of rheumatic or syphilitic infection.

Pretreatment Physical Examination. Physical examination revealed entirely normal findings. The heart was of normal size and contour. The first sound was split. The sounds were of good quality and there was a Grade I apical systolic murmur. The blood pressure was 110/80.

Pretreatment Laboratory Examinations. (See table 2.) The urine and blood were normal. On x-ray examination, the heart was normal in size and shape. The electrocardiogram was consistent with an old posterior infarct. The administration of 150 microcuries $^{131}$I was followed by a three-day urinary excretion of 45 per cent (euthyroid range).

Post-treatment Course. On April 27, 1948 he received 29 mc. $^{131}$I; three additional doses of 43, 39 and 59 mc. were administered on July 23, August 19 and November 22, 1948, respectively (table 1). Five weeks after the first dose of $^{131}$I, definite clinical improvement was noted with disappearance of all but a few attacks of angina pectoris. The serum cholesterol level had risen and clinical signs consistent with hypothyroidism were present. During the next few weeks, anginal episodes recurred to the pretreatment severity and frequency. The hypothyroid state was transient. Five weeks after the third dose, the serum cholesterol values rose, and the basal metabolic rate became lower. The patient experi-
<table>
<thead>
<tr>
<th>Case, Initials, Sex, Age</th>
<th>Diagnoses In Addition To Angina Pectoris and Arteriosclerotic Heart Disease</th>
<th>Duration of Angina Pectoris</th>
<th>Basal Metabolic Rate</th>
<th>Serum Cholesterol</th>
<th>Other Findings</th>
<th>Comment</th>
<th>Therapeutic Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. J. L. M, 41</td>
<td>Prior myocardial infarction</td>
<td>1 Years Before 15 daily</td>
<td>%</td>
<td>328</td>
<td>ETT—32; Dyspnea; angina at night and rest</td>
<td>Thyroid 30 mg. daily</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 one monthly</td>
<td>−10</td>
<td>770</td>
<td>ETT—45†; No attacks at night or rest; no dyspnea; actively employed</td>
<td>Thyroid 6–12 mg. for 6 mos.</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 None</td>
<td>−20</td>
<td>350</td>
<td>Actively employed; no parox. noct. dysp. or dyspnea; C.T. 27 sec.</td>
<td></td>
<td></td>
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<tr>
<td>3. J. K. M, 44</td>
<td>Probable prior myocardial infarction</td>
<td>5 Before 4-5 or more nitroglycer. tablets daily</td>
<td>−11</td>
<td>325</td>
<td>Parox. noct. dysp.; C.T. 12 sec.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 None</td>
<td>−24</td>
<td>380</td>
<td>None; C.T. 33 sec. Marked dyspnea on exertion, par. noct. dysp., edema, rales</td>
<td>Thyroid 6–24 mg. for 3 mos.</td>
<td>++++</td>
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<tr>
<td>4. H. R. M, 72</td>
<td>Marked congestive failure; aortic sten. and insuff.; hypertension</td>
<td>10 Before Many daily</td>
<td>Not feasible</td>
<td>220</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 None</td>
<td>Not feasible</td>
<td>399</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. M. G. M, 38</td>
<td>2 Prior myocardial infarctions; episodes of coronary failure</td>
<td>2 Before Frequent</td>
<td>−3</td>
<td>280</td>
<td>Noct. angina. Unable to work; C.T. 14 sec.</td>
<td>Thyroid 24 mg.</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 None</td>
<td>−23</td>
<td>450</td>
<td>No noct. attacks. Doing heavy labor; C.T. 18 sec. Housebound; edema of legs; palpitation; orthopnea; dyspnea; C.T. 28 sec.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. S. F. M, 59</td>
<td>Hypertension, cardiac enl., congestive heart failure; chronic pyelonephritis</td>
<td>5 Before 2-5 weekly</td>
<td>+3</td>
<td>178</td>
<td>Up and about; no edema; no palpitation; less dyspnea; no orthopnea; C.T. 24 sec.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 Rare</td>
<td>−20</td>
<td>444</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7. B. S.</td>
<td>2 Prior myocardial infarctions; hypertension</td>
<td>2.5 Before 4 daily</td>
<td>−6</td>
<td>275</td>
<td>Par. noct. dysp.; C.T. 14 sec. Emotional lability</td>
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</table>

*Therapeutic Result: +++, ++, +, 0.
<table>
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<tr>
<th>M, 52</th>
<th>tension</th>
<th>17</th>
<th>Rare</th>
<th>−20</th>
<th>450</th>
<th>No par. noct. dysp.; C.T. 27 sec.</th>
<th>+ +</th>
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</thead>
<tbody>
<tr>
<td>8. M. H. F, 65</td>
<td>Prior myocardial infarction; diabetes mellitus</td>
<td>1.5</td>
<td>Before 1-12 daily 11-17 nitro. weekly 2-5 weekly</td>
<td>Not feasible</td>
<td>305</td>
<td>Palpitation</td>
<td></td>
</tr>
<tr>
<td>9. M. C. M, 58</td>
<td>2 prior myocardial infarctions</td>
<td>3</td>
<td>Before Frequent on moderate effort</td>
<td>+2</td>
<td>307</td>
<td>ETT 12-15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td>530</td>
<td>ETT 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Angina recurred but less than control period 5-6 weekly</td>
<td>−18</td>
<td>380</td>
<td>ETT 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>Before 2.5 12</td>
<td>None Occasional</td>
<td>−25 25</td>
<td>240</td>
<td>Thyroid 24 mg. daily for previous 3 mos.</td>
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<tr>
<td>10. R. S. M, 69</td>
<td>Hypertension; intercostal neuritis following alcohol nerve block T2-T6; prior thyroid de-nervation</td>
<td>5</td>
<td>Before 8-10 daily</td>
<td>−5</td>
<td>207</td>
<td>Frequent angina at night, at rest, after meals; C.T. 30 sec.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 daily 8-10 daily</td>
<td>−27 25</td>
<td>400 285</td>
<td>None; C.T. 29 sec. Recent exacerbation of angina on increased thyroid dosage</td>
<td></td>
</tr>
<tr>
<td>11. H. Y. M, 67</td>
<td>Probable prior myocardial infarction</td>
<td>15</td>
<td>Before 2-3 daily at restricted activity</td>
<td>−12</td>
<td>210</td>
<td>Sedentary existence; noct. angina</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change</td>
<td>−30</td>
<td>500</td>
<td>Still sedentary. no noct. angina</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6-8 per week on minimal effort or eating</td>
<td>−6</td>
<td>250</td>
<td>ETT 18, C.T. 26 sec.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change on effort. None on eating</td>
<td>−24</td>
<td>400</td>
<td>ETT-30, C.T. 31 sec.</td>
<td></td>
</tr>
<tr>
<td>12. J. E. F, 59</td>
<td>Prior myocardial infarction; hypertension</td>
<td>4</td>
<td>Before 2-3 daily at restricted activity</td>
<td>−12</td>
<td>210</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change</td>
<td>−30</td>
<td>500</td>
<td>Thyroid 36 mg.</td>
<td></td>
</tr>
<tr>
<td>13. M. S. M, 61</td>
<td></td>
<td>5</td>
<td>Before 5-6 per week on minimal effort or eating</td>
<td>−6</td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No change on effort. None on eating</td>
<td>−24</td>
<td>400</td>
<td>Thyroid 60 mg.</td>
<td></td>
</tr>
</tbody>
</table>

* ++++ striking; +++ excellent; ++ good; + fair; 0 not worthwhile.
† ETT-Exercise Tolerance Test stopped by fatigue; no angina.
‡ Arm to Tongue Circulation Time.
enced marked improvement. He was able to undertake much more effort despite which he used only approximately 8 nitroglycerine tablets a week. Five weeks after the fourth dose, complete disappearance of angina pectoris was observed despite the fact that he spent much of every day walking about the city in search of a job. In repeated exercise tolerance tests, forty-five to fifty trips were performed without anginal pain; the patient stopped exercise at our request or because of fatigue. His facies became myxedematous; the blood cholesterol values increased and the basal metabolic rate was -22 per cent. Desiccated thyroid, 30 mg. daily, was prescribed. At the present time he has been gainfully employed, working eight hours a day for the past seven months, experiences no angina except on very strenuous exertion, and is not troubled by symptoms of myxedema. The basal metabolic rate is maintained at -25 per cent; the serum cholesterol is 770 mg. per cent.

Comment: A 41 year old man, with almost completely incapacitating angina pectoris and an old myocardial infarction was treated with 4 doses of I$^{131}$. Transient hypometabolism and clinical improvement in the frequency of angina pectoris followed the first 3 doses. Myxedema followed the fourth dose and was accompanied by complete disappearance of anginal pain in daily life. Correspondingly, a marked increase in the standardized exercise tolerance test was observed. He is gainfully employed, working eight hours a day as a laboratory assistant for the past seven months. On 30 mg. desiccated thyroid, he is not troubled by symptoms of myxedema. The clinical improvement is striking.

Case 2.—Arterial hypertension; arteriosclerotic heart disease. Acute posterior myocardial infarction and pulmonary edema fourteen months before treatment. Angina pectoris of three years' duration, increasing in severity with resulting invalidism. Frequent attacks of paroxysmal nocturnal dyspnea. Myxedema induced by three doses of I$^{131}$ with complete remission of symptoms and rehabilitation to an employed state.

Pretreatment History. R. A., a 62 year old bricklayer, B.I.H. #98406, received 24 mc. I$^{131}$ on February 12, 1948. Nine years before treatment, he was examined because of headaches, weakness and depression. The blood pressure was 170-190/115-130. Five years before I$^{131}$, at the time of suprapubic prostatectomy, the blood pressure was 150/100, the heart was enlarged to the left. Three years before I$^{131}$, he developed mild angina pectoris and dyspnea on exertion, relieved by rest and by nitroglycerine. Fourteen months before treatment he was admitted to the hospital critically ill, with severe substernal pain, acute pulmonary edema and the characteristic clinical and electrocardiographic evidence of an acute postero-lateral myocardial infarction and right bundle branch block. Thereafter, he was confined at home because of slight exertion precipitated angina. He suffered five to ten attacks of angina pectoris daily and increasing breathlessness, despite limitation of activity and the use of nitroglycerine, digitalis, various xanthines and vitamins. When examined in the Cardiac Clinic during the period before treatment, he was dyspneic, weak, unable to walk without suffering substernal pain, and had had several attacks of nocturnal dyspnea.

Pretreatment Physical Examination. The blood pressure was 160/110. The retinal vessels were somewhat narrowed and tortuous. There was moderate emphysema of the lungs. No rales were heard. The heart was enlarged to the left; the rhythm regular and there were no murmurs.

Pretreatment Laboratory Examinations. (See table 2.) The blood, urine and stool were normal. The non-protein nitrogen was 35 mg. per cent. Electrocardiograms revealed old postero-lateral myocardial infarction and right bundle branch block. The serum protein bound iodine was 5.8 gamma per cent. After an I$^{131}$ tracer dose, the urinary excretion was 54 per cent in seventy-two hours.

Post-treatment Course. On February 12, 1948, I$^{131}$ was administered, and again on May 27 and July 24, 1948 (table 1). In late August 1948, the basal metabolic rate, serum cholesterol and physical appearance were unchanged, but the patient was able to undertake considerable effort without angina pectoris, dyspnea or paroxysmal nocturnal dyspnea. On September 25, 1948, the serum cholesterol was 400 mg. per cent. His voice was very deep, eyes and face puffy, the hands cool and slightly moist. At this time the patient became employed, for the first time in two years, as a supervisor on a bricklaying job, requiring that he rise early, travel for one hour in a street car, walk one mile to his place of employment and be ambulatory for an eight hour day. He was able to perform these tasks without dyspnea or angina. In the ensuing six months the basal metabolic rate was consistently approximately -22 per cent and the serum cholesterol between 380 and 500 mg. per cent. The patient experienced only occasional episodes of "jumping" or "fluttering" in the chest, thought to be paroxysmal tachycardia. He stated that he experienced breathlessness on climbing three flights of stairs. In February 1949, five months after hypometabolism had become evident with an elevated serum cholesterol and a lowered basal metabolic rate, the patient complained of undue sensitivity to cold, chronic sleepiness and fatigue, muscular pains, rhinorrhea. Accordingly, 12 mg. thyroid daily was administered, with improvement in these symptoms. He returned to work. Up to the present, he experiences no precordial pain, but has some
shortness of breath on climbing, without stopping, 2 to 3 flights of stairs. There is no orthopnea, cough or paroxysmal nocturnal dyspnea nor any evidence, on physical examination, of congestive failure.

Comment. This 60 year old patient with a past history of a posterior myocardial infarction and three years of angina pectoris, dyspnea on exertion and paroxysmal nocturnal dyspnea was invalided at home for fourteen months before I\textsuperscript{131} treatment. Following the induction of hypometabolism, he has experienced complete freedom from precordial pain and has only slight dyspnea on climbing three flights of stairs without stopping. For 9 months since the induction of hypometabolism, he has been gainfully employed on a job requiring considerable physical and mental activity. On 12 mg. thyroid daily, the basal metabolic rate is – 20 per cent, the serum cholesterol 350 mg. per cent, and he is not troubled by symptoms of hypometabolism. A striking result.

Case 3.—Arteriosclerotic heart disease; severe angina pectoris of five years' duration, preventing employment and markedly limiting activity. Probable old anterior myocardial infarction four and one-half years before I\textsuperscript{131}. Orthopnea and paroxysmal nocturnal dyspnea. Myxedema induced with one dose of I\textsuperscript{131}. Striking relief of angina pectoris.

Pre-treatment History. J. K., a 44 year old former bartender and shipyard worker, B.I.H. #87843, received 42.4 mc. of I\textsuperscript{131} on January 27, 1949. Five years previously the patient first experienced characteristic angina pectoris relieved by nitroglycerine. He was hospitalized for two weeks after one episode of severe pain. Four and one-half years before treatment, recurrent attacks of angina pectoris awakened him from sleep and occurred every few hours despite frequent use of nitroglycerine. He was hospitalized at another institution for thirty days, where, following prolonged cardiac pain and dyspnea after an exercise test, electrocardiograms revealed evidence of definite myocardial damage. For eight months he had received injections of testosterone without relief; theobromine sodium acetate and digitalis were also without benefit. Anginal attacks, accompanied frequently by dyspnea and occasionally by nausea and vomiting, were precipitated by as little effort as dressing or undressing, excitement, cold, or meals. He had attacks awakening him from sleep. He had been unable to work because even a limited amount of effort produced pain; he invariably developed an anginal episode on walking more than one block. The average intake of nitroglycerine was four to five tablets daily; in the period before treatment the attacks were increasing in frequency. For the five years before treatment he had also experienced dyspnea on exertion, orthopnea requiring three pillows and had had two episodes of paroxysmal nocturnal dyspnea.

Pretreatment Physical Examination. The thyroid was not palpable. Blood pressure was 130/80. The heart was enlarged to the left; the rhythm was regular. There was a soft aortic systolic murmur. The lungs were clear. The non-tender liver was felt two fingersbreadth below the right costal margin. Spleen was not palpable.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. The electrocardiogram was consistent with an old anterior myocardial infarction. On x-ray the heart shadow was increased. Circulation time was twelve seconds. After an I\textsuperscript{131} tracer dose, the urinary excretion was 85 per cent in seventy-two hours.

Post treatment History. On January 27, 1949, 42.5 mc. of I\textsuperscript{131} were given. Three days later he developed a painful throat, with thyroid gland tenderness. The pharynx was normal. During the next week chills, nausea, and vomiting, and increased throat pain were experienced. The thyroid gland was two times normal size, firm and acutely tender. In this period, i.e., two to three weeks after treatment, the patient observed increased angina pectoris. Despite marked restriction of activity, four or five attacks occurred daily; the slightest effort produced an attack. It was believed that the patient had experienced thyroiditis with mild thyrotoxicosis, manifested by a rise in the basal metabolic rate and a drop in the serum cholesterol (fig. 1), accompanied by increased angina pectoris. During the next one to two weeks this reaction gradually subsided and the serum cholesterol, basal metabolic rate and the severity of the angina pectoris were approximately the same as before treatment (fig. 1). Eight weeks after I\textsuperscript{131}, the patient noted that for the first time in five years he was able to go for a number of days without requiring any nitroglycerine. He had no night pain, no meal pain, no prolonged pain and was able to undertake more effort without developing angina. During the the prior five years he had never experienced a comparable remission. The basal metabolic rate was – 24 per cent and the serum cholesterol was 400 mg. per cent. He showed no clinical evidence of myxedema. During the next few weeks further improvement was noted and he went an entire week without taking nitroglycerine. He was able to walk three blocks rapidly without pain; he dressed and undressed without pain and he had no pains at meals, at night or during conversations; all had previously precipitated attacks. Fourteen weeks after treatment, six weeks after the onset of improvement, the patient observed weakness of the hands, fatigability and postnasal discharge. The cholesterol was 625 mg. per cent and the basal metabolic rate was – 25 per cent. His face appeared fuller and less florid. During the next week he noted loss of energy,
marked weakness, fatigability, rhinorrhea, sleepiness and nasal speech. On 24 mg. of thyroid daily these symptoms disappeared. The basal metabolic rate was −24 per cent and the serum cholesterol was 380 mg. per cent.

Comment: This 44 year old patient had had angina pectoris for five years, a probable acute anterior myocardial infarction and two episodes of paroxysmal nocturnal dyspnea. Anginal attacks were produced by minimum effort such as walking one block or undressing; they occurred at night.

Case 4.—Arteriosclerotic heart disease; aortic stenosis and insufficiency; auricular fibrillation; angina pectoris of ten years’ duration of increasing severity; marked congestive heart failure refractory to all accepted types of therapy. Paroxysmal nocturnal dyspnea. Induction of myxedema with one dose of I^{131}. Complete remission of symptoms of both angina pectoris and congestive failure past twelve months. Striking therapeutic result.

FIG. 1.—J. K., Case 3. The serum cholesterol, the basal metabolic rate and the clinical course following the administration of 42.5 millicuries I^{131}. To conform to the activity of the millicurie used by the Bureau of Standards and also used throughout this paper, the millicurie stated in the above figure should be multiplied by the factor of 1.7.

and after meals and required four to five nitroglycerine tablets daily. He had experienced no remission during this entire period. With the induction of hypometabolism after I^{131} the patient noted no night pain or meal pain and went long periods without any anginal episodes or paroxysmal nocturnal dyspnea. He required only about one nitroglycerine tablet every twenty days. His exercise tolerance was increased from one to three and one-half blocks, and he can perform all his usual tasks about the house without development of angina pectoris. No symptoms referable to hypometabolism are present on a daily dosage of 24 mg. of thyroid. The relief from angina pectoris is striking.

Pretreatment History. H. R., a 72 year old white male, B.I.H. 98225, received 25.5 mc. of I^{131} on February 26, 1948. Ten years before, the patient had noted precordial pain on slight exertion and on walking upstairs, gradually increasing in severity. During the seven years before treatment, he was observed in the Cardiac Clinic. Three years before I^{131} therapy, increasing frequency of angina on the slightest exertion, and even when at rest, was associated with dyspnea and ankle edema. At this time, fine moist rales were heard at both bases. The tender liver edge was felt three fingers below the right costal margin. The patient was maintained on digitals, theobromine sodium acetate and nitroglycerine. Eighteen months before treatment, anginal attacks
occurred on effort and at rest, and as often as five to six times nightly, accompanied by dyspnea.

Ankle edema was present. The blood pressure was 150-200/60-90. There was a loud, musical, apical systolic murmur, obscuring the first sound, and a loud, high pitched aortic systolic murmur transmitted to the neck vessels and the right upper back. There was a short aortic diastolic murmur. The second aortic sound was diminished. A diagnosis of aortic stenosis and insufficiency was made. Fifteen months before treatment, auricular fibrillation was observed.

During the year before I\textsuperscript{12}, dyspnea became markedly worse and he became short of breath on walking fifteen steps. On a rice diet regimen, he appeared to show some improvement, with diminution in exertional dyspnea and relief of angina, but was unable to maintain the diet. Five months before I\textsuperscript{12}, he again suffered angina and dyspnea on the slightest exertion. Despite theobromine sodium acetate, digitalis and mercurial diuretics by mouth and intravenously during the period immediately preceding I\textsuperscript{12}, increasing dyspnea, paroxysmal nocturnal dyspnea, ankle edema and very frequent attacks of angina pectoris were noted.

Pretreatment Physical Examination. The patient was dyspneic, cyanotic and the neck veins were distended. There were rales at both lung bases. The heart was enlarged to the left; the rhythm was grossly irregular with a ventricular rate of 68. The signs of aortic stenosis and insufficiency were noted. The tender liver edge was palpable three fingers below the right costal margin. There was 2+ pitting edema at the ankles. The blood pressure was 185/65.

Post-treatment Clinical Course. On February 26, 1948 the patient received 25.5 mc. of I\textsuperscript{12}, followed a week later by sore throat on swallowing which gradually decreased during the next two weeks. In June 1948, four months after treatment, he reported conspicuous improvement. He had no exertional dyspnea, ‘could walk for two hours and could run without short breath.’ He had had no chest pain whatsoever. He had discarded all medication. Physical examination showed no venous distention, a few, medium rales at the right base, a barely palpable nontender liver and only minimal ankle edema. There was no clinical evidence of myxedema, and the patient refused basal metabolic studies. The serum cholesterol had risen from 220 to 283 mg. per cent. During the following two months the patient maintained this improvement, the basal rales cleared and, for the first time in a long period, he could sleep flat in bed. He had no cough, no dyspnea and no angina pectoris. The serum cholesterol had risen to 331 mg. per cent. His skin was cool and there was some puffiness below the eyes. On August 9, 1948, five and a half months after I\textsuperscript{12}, the patient showed definite evidence of myxedema.

He had maintained his cardiac improvement. At this time, he was instructed to take thyroid 6 mg. daily, and later this was increased to 18 mg. However, he continued to complain of symptoms due to myxedema, and it was discovered that the patient had failed to take thyroid as ordered. In May 1949, the patient was seen because of severe pain in the right upper quadrant, due to herpes zoster. At this time he was having no angina pectoris and no symptoms of congestive failure. He was taking no cardiac medication or thyroid. He had no dyspnea, orthopnea, ankle edema and suffered minimal discomfort from myxedema. X-ray examination showed the heart to be greatly dilated with small amplitude of contraction. The heart rhythm was grossly irregular, rate 57 to 110, and the electrocardiogram showed auricular flutter with varying auriculo-ventricular block. The serum cholesterol was 399 mg. per cent.

Comment: This 72 year old male, with a ten year history of angina pectoris and an eight year history of congestive heart failure, showed striking improvement following the administration of radioactive iodine with remission of all his cardiac symptomatology. Five and one-half months after treatment, he went into frank myxedema, the symptoms of which were troublesome, but the patient refused to take thyroid as ordered. When last seen, fifteen months after I\textsuperscript{12}, he had maintained his cardiac improvement and was only minimally troubled by myxedema. He has continued to refuse to take thyroid.

Case 5.—Severe, frequent angina pectoris, two years. Two attacks of acute myocardial infarction and many other attacks of excruciating and prolonged cardiac pain without electrocardiographic changes, i.e., “coronary failure.” Myxedema induced by two doses of I\textsuperscript{12} with marked relief of angina pectoris. Myxedema controlled by 24 mg. of thyroid daily. Doing heavy work and gainfully employed for past eight months. Excellent therapeutic result.

Pretreatment History. M. G., a 38 year old painting and construction supervisor, B.I.H. #92857, received 42.5 mc of I\textsuperscript{12} on June 4, 1948. Beginning in June 1946, attacks of mild substernal pressure occurred following meals, exercise and emotional disturbance and also occasionally awakened the patient from sleep. The first hospital admission in February 1947 had been preceded by marked increase in severity and duration of attacks which culminated in acute posterior myocardial infarction attended by shock, a pericardial friction rub, electrocardiographic changes, fever, leukocytosis and increased corrected sedimentation rate. He was hospitalized for six weeks. After discharge from the hospital, the attacks of angina pectoris continued
with increased severity, and were associated with nausea, heartburn and epigastric fullness. During the fifteen months prior to I\(^{131}\), the patient had many severe and excruciating attacks of cardiac pain during the night as well as during the day, only slightly relieved by nitroglycerine and preventing steady employment. Nine months prior to I\(^{131}\) he suffered an acute anterior myocardial infarction, and on two subsequent occasions he was similarly hospitalized because of severe prolonged cardiac pain, although serial electrocardiographic changes were not evident on these latter two admissions; minor T wave changes were observed.

During the hospital admission immediately before I\(^{131}\), the patient was placed on dicumarol\(^{26-27}\) and maintained at a satisfactory prothrombin time level with 50 mg. alternating with 100 mg. daily. The number and severity of attacks of angina pectoris became somewhat less on complete bed rest but did not disappear. All other medical measures having failed, it was decided, despite the grave prognosis, to administer I\(^{131}\).

**Pretreatment Physical Examination.** The findings were normal. The heart was not enlarged; the sounds were of good quality; no murmurs were heard. The blood pressure was 122/84.

**Pretreatment Laboratory Examinations.** (Table 2.) The blood and urine were normal. Electrocardiographic tracings were consistent with old posterior and anterior myocardial infarcts. X-ray examination revealed the left ventricle slightly enlarged to the left.

**Post-treatment Course.** The patient received 42.5 mc. of I\(^{131}\) on June 4, and 25.5 mc. on July 23, 1948 (fig. 2). During the second week after the first dose he noted profuse perspiration, increased palpitation and dyspnea and more frequent severe attacks of angina pectoris. The skin was warm and flushed; the thyroid palpable and very tender. The basal met-

![Fig. 2.—M. G., Case 5. The serum cholesterol, the basal pulse rate, the basal metabolic rate and the clinical course following the administration of two doses of 42.5 and 25.5 millicuries of I\(^{131}\). To conform to the activity of the millicurie used by the Bureau of Standards and also used throughout this paper, the millicurie stated in the above figure should be multiplied by the factor of 1.7.](http://circ.ahajournals.org/doi/10.1161/01.cir.11.9.1116)
clinical improvement, was able to undertake considerably more effort and had only occasional slight momentary sticky pain not related to effort or emotion. He observed increased tolerance to hot weather and no pain on exertion or emotion. On August 4, nine weeks after the first dose and twelve days after the second dose, the basal metabolic rate was -17 per cent; the serum cholesterol values rose to approximately 400 mg. per cent. He re-entered the hospital, however, for the sixth time on September 1, 1948, because of severe persistent chest and left axillary pain. Electrocardiographic and other laboratory studies failed to reveal any evidences of fresh involvement of the myocardium. Dicumarol therapy was continued.

Four months after the first dose the cholesterol was 700 mg. per cent and the basal metabolic rate -30 per cent. On 12-24 mg. of thyroid he experienced a variable amount of disability from myxedema, feeling perfectly well on some occasions and complaining of symptomatology on others. The patient was subject to a high degree of emotional stress and aggravation and continued to have atypical precordial pain. The precordial symptoms were unusual in that they did not occur on undertaking even fairly severe work but rather occurred at the end of the day when the patient sat down to rest. It was the opinion of a number of observers that these precordial sensations were not of cardiovascular origin.

In April 1949, eleven months after the first dose, he went to work in another city and dicumarol was stopped. Despite marked physical labor including the lifting of heavy materials up to 50 lbs. in weight, and working at least eight hours daily, the patient experienced no chest pain and did not tire easily until he returned to the region of his home, when he again began to experience fleeting momentary stabbing precordial pain. At the present time, thirteen months after the first dose of I\textsuperscript{131}, he is receiving thyroid 24 mg. daily and has no troublesome symptoms from hypothyroidism.

Comment. This 38 year old man with severe disabling angina decubitus was incapacitated during the fifteen months prior to I\textsuperscript{131}. He obtained almost complete freedom from cardiac pain following the induction of myxedema by I\textsuperscript{131}. He has been gainfully employed at heavy manual labor for the past eight months. He experiences fleeting momentary stabbing precordial pain, unrelated to effort and occurring at the end of the day when resting. On 24 mg. thyroid daily he has no troublesome symptoms of hypothyroidism. An excellent result.

Case 6.—Recurrent acute pyelonephritis; hypertension and cardiac hypertrophy; angina pectoris and congestive heart failure with orthopnea for five years. Induction of myxedema with one dose of I\textsuperscript{131} with marked decrease of angina pectoris and improvement in congestive heart failure. Minimal discomfort from hypothyroidism. Good, worthwhile therapeutic result.

Pretreatment History. S. F., a 59 year old insurance and real estate agent, B.I.H. \$6279, referred through the courtesy of Dr. Paul M. Zoll, received 42.5 mc. of I\textsuperscript{131} on December 30, 1947. In September 1942, he noted the onset of dyspnea on exertion, and angina pectoris on exertion and emotion, relieved by nitroglycerine. There was a past history of recurrent, acute pyelonephritis. Physical examination revealed the blood pressure 194/128, cervical venous engorgement, and fine basal rales. The liver was four fingers below the costal margin and there was slight pitting edema of both ankles. On rest, digitalization, theobromine sodium acetate and phenobarbital, he noted some improvement in dyspnea. Attacks of angina pectoris continued and he was unable to work.

In June 1947 he suffered an exacerbation of congestive failure with orthopnea and peripheral edema. Walking even short distances produced dyspnea and palpitation. Although house bound, he suffered two to five attacks of angina pectoris weekly.

On a chair-and-bed regimen, digitalis and a low salt diet, purines and nitroglycerine for the three months before I\textsuperscript{131} therapy, there were continued peripheral edema, dyspnea on climbing one flight of stairs, orthopnea and palpitation. Attacks of angina pectoris continued unchanged.

Pretreatment Physical Examination. The neck veins were distended, the lungs were clear. The heart was enlarged, the rhythm regular. The blood pressure was 228/118. The liver was percussed three fingersbreadth below the costal margin. There was moderate pitting edema of the legs.

Pretreatment Laboratory Examination. (See table 2.) The blood was normal. The urine showed a 1 + albumin content and 0-3 red blood cells in the sediment. The specific gravity was 1.016. The electrocardiogram was consistent with left ventricular hypertrophy. On x-ray examination the heart was markedly enlarged to the left, the aorta dilated and the hilar shadows and lung markings increased, indicating left ventricular hypertrophy and dilatation and moderate pulmonary congestion.

Post-treatment Course. I\textsuperscript{131} was administered December 30, 1947; ten days later he noted sore throat, pain on swallowing and slight cough, but no thyroid tenderness or swelling. Three serum cholesterol measurements during the next six weeks were 178, 177 and 178 mg. per cent. Approximately 13 weeks after I\textsuperscript{131} the basal metabolic rate was -25 per cent, the serum cholesterol 340 mg. per cent. A tracer dose of I\textsuperscript{131} was followed by a urinary excretion of 81 per cent during the next three days. Thyroid 15 mg. daily was prescribed and discomfort from hypothyroidism became minimal. Associated with the
hypometabolic state, there was distinct improvement with absence of palpitation, lessened dyspnea and disappearance of peripheral edema. A definite decrease in the number of attacks of angina pectoris occurred; nitroglycerine consumption decreased from 2 to 5 tablets per week to 2 tablets per month. There was, moreover, considerable concomitant increase in the amount of activity, in that he was leaving the house and undertaking considerable exertion.

With an increase in thyroid to 24 mg. daily in August 1948, angina pectoris and congestive failure increased, and he suffered an attack of paroxysmal nocturnal dyspnea. In September 1948, nine months after \( I^{131} \), he suffered a cerebrovascular accident but recovered with little residual disability. Thereafter he remained at home, except for trips to the hospital, until recently, when he has increased his activity and taken short walks. Thyroid dosage was reduced to 15 mg. daily. In the ten months since the cerebrovascular accident, he has had only a rare episode of angina pectoris, has had no orthopnea, dyspnea, ankle swelling, cough or paroxysmal nocturnal dyspnea. X-ray examination showed the heart size to be unchanged and the lungs clear.

Comment: A 59 year old man with marked hypertension, congestive failure and angina pectoris, complicated by chronic renal disease, received one dose of \( I^{131} \). Myxedema was induced with concomitant decided improvement in congestive failure and in angina pectoris. On a dosage of 15 mg. thyroid daily, there has been minimal discomfort from hypometabolism, congestive failure is absent, orthopnea has disappeared and only a rare attack of angina pectoris is experienced. The result is considered good and worthwhile.

Case 7.—Arterial hypertension; arteriosclerotic heart disease. Angina pectoris of two and one-half years' duration. Two attacks of acute myocardial infarction, fifteen and six months before treatment. Orthopnea, paroxysmal nocturnal dyspnea. Myxedema induced by two doses of \( I^{131} \) with relief of the symptoms of angina pectoris but some discomfort from the hypometabolic state. Good, worthwhile result.

Pretreatment History. B. S., a 52 year old white man, B.I.H. M2922, received 25.5 mc. \( I^{131} \) March 11, 1948. Two and one-half years before treatment severe angina pectoris developed once or twice daily, precipitated by effort, and relieved by rest and nitroglycerine. Fifteen months before treatment, increasingly frequent angina pectoris culminated in an attack of severe and prolonged cardiac pain, weakness, sweating, collapse, slight fever and electrocardiographic tracings characteristic of acute posterior myocardial infarction. After discharge, he had frequent attacks of angina pectoris, with dyspnea on minimal effort such as bending over to tie his shoes, or having a bowel movement. The patient was orthopneic and experienced several attacks of paroxysmal nocturnal dyspnea. Six months before \( I^{131} \), a second episode of severe precordial pain lasting twenty minutes occurred, with electrocardiographic changes of anterior myocardial infarction. During the period of pretreatment study, various observers noted emotional lability, anxiety, easy fatigability, weakness, occasional dizziness and marked hyperventilation. Despite frequent angina pectoris he continued to do light work three to four hours daily. Propylthiouracil, 500 mg. daily, was administered for two weeks before \( I^{131} \) therapy, but had to be discontinued because of leukopenia.

Pretreatment Physical Examination. The arterioles of the fundus showed increased tortuosity and narrowing. The blood pressure was 170/100. The heart was enlarged to the left, the rhythm regular, the sounds normal. There was a short, Grade I apical systolic murmur. There was moderate pulmonary emphysema. The tender liver was felt two to three fingersbreadth below the right costal margin. The spleen was felt two fingersbreadth below the left costal margin.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. Complete gastrointestinal and gall-bladder x-ray examinations were normal. Chemical tests of liver function were within normal limits. During the seventy-two hours after a tracer dose of \( I^{131} \) he excreted 79 per cent in the urine. The electrocardiogram was abnormal; the pattern was not diagnostic.

Post-treatment Clinical Course. On March 11, 1948, he received 25.5 mc. and on May 27, 1948, 27 mc. of \( I^{131} \) (table 1). On July 7, 1948, coincident with evidence of slight myxedema and serum cholesterol 400 mg. per cent (table 2), angina pectoris markedly decreased and he required no nitroglycerine for several weeks despite at least the same level of activity. There were no further attacks of paroxysmal nocturnal dyspnea and no orthopnea. During the next two months, he continued to experience conspicuous relief of angina pectoris. In September 1948 he had considerable discomfort from myxedema and many precordial sensations different from those previously experienced on effort and not relieved by rest or nitroglycerine. On thyroid, 12 mg. daily, the serum cholesterol decreased from over 600 to 360 mg. per cent. He also complained of right upper abdominal tenderness and pain. After thorough study in the hospital the consensus was that many of the symptoms were on a functional basis. It was, however, decided to re-establish the euthyroid state to learn the degree to which the symptoms were due to myxedema. Accordingly, the thyroid dose was gradually increased to 45 mg. daily. After three weeks the patient complained of increased frequency of angina pectoris, and required
about 6 nitroglycerine tablets daily. He noted diminution of numbness of the hands and feet, but most of the symptoms, notably fatigue and hyperventilation remained. At this time, the patient stated unequivocally that he would prefer having such hypometabolic symptoms as were necessary rather than the pain in the chest, which, by this time, was recurring on minimal effort. After reduction to 15 mg. thyroid daily, there was an increase in serum cholesterol, lowered basal metabolic rate, and definite diminution in angina from three to five attacks daily, to only that number per week, or less. There was, however, increased fatigability and stiffness and numbness of the hands.

Comment: While myxedematous, this patient was free of angina pectoris, paroxysmal nocturnal dyspnea and orthopnea but suffered from a number of symptoms, some of which could possibly be ascribed to hypometabolism. On increasing the thyroid to 45 mg. daily, he noticed a decrease of the numbness of the hands, paresthesias and some of the dizziness. Concomitantly, however, the angina pectoris returned to the pretreatment control severity. The patient unequivocally stated he preferred the hypometabolic symptoms to his chest pain. The dose of thyroid was then decreased to 15 mg. daily and the basal metabolic rate fell to -20 per cent and the serum cholesterol rose again to 450 mg. per cent. With this there was a marked diminution in the angina pectoris. Despite return of numbness and fatigability, the improvement in angina pectoris during the past eleven months was such that the patient and observers regarded the result as having been worthwhile.

Case 8.—Severe diabetes mellitus for twenty years. Angina pectoris for eighteen months. Acute myocardial infarction one year before treatment, followed by increased frequency and intensity of angina pectoris. Myxedema induced by two doses of I\(^{131}\) with marked decrease of angina pectoris and lessened insulin requirement. Some discomfort from myxedema. Good therapeutic result.

Pretreatment History. M. H., a 65 year old housewife, B.I.H. #72724, received 39 mc. I\(^{131}\) on November 6, 1948. She had had diabetes for twenty years, observed in the Diabetic Clinic for 18 years, requiring increasing doses of insulin until, at the time of I\(^{131}\) treatment, she was maintained under irregular control by 56 units of protamine and 20 units of regular insulin daily. Eighteen months before treatment the patient noted substernal pressure radiating to both shoulders, precipitated by exertion, and relieved by rest or by nitroglycerine. One year before I\(^{131}\) she was hospitalized for nine weeks because of acute myocardial infarction. Three months before treatment, examination in the Cardiac Clinic revealed frequent palpitation and attacks of angina pectoris one to twelve times daily on emotion, on slight exertion, aggravated by cold, and of much greater frequency and severity than before the acute myocardial infarction. The average weekly requirement of nitroglycerine varied from 11 to 17 tablets.

Pretreatment Physical Examination. The thyroid was not palpable. The heart was enlarged. The sounds were of good quality. There was a Grade II systolic murmur loudest in the pulmonic area and the rhythm was regular. The blood pressure was 130/80. The lungs were clear.

Pretreatment Laboratory Examinations. (See table 2.) The blood was normal. The urine showed 1+ albumin and rare red blood cells. On x-ray examination the heart was slightly enlarged and the lungs clear. Electrocardiogram was consistent with old posterior myocardial infarction and left ventricular hypertrophy. The P-R interval was 0.22 second. Because of the severity of the diabetes and our unwillingness to allow the patient to fast, basal metabolism studies were not performed. Nonfasting serum cholesterol three hours postprandially on a standard diabetic diet was 335 and 395 mg. per cent. Following a tracer dose of I\(^{131}\) the patient excreted 62 per cent in the urine in seventy-two hours.

Post-treatment Clinical Course. On November 6, 1948 she received 39 mc. and on January 21, 1949, 34 mc. I\(^{131}\) (table 1). Three weeks after the first dose, a nontender nodule 1.5 cm. in diameter became palpable at the lower pole of the thyroid. During the next month, the nodule gradually decreased in size and disappeared. In April 1949, ten weeks after the second dose, the patient definitely experienced fewer episodes of squeezing precordial pain and they were less severe. There was also a diminution in palpitation. The serum cholesterol had risen 100 mg. per cent from the previous level. Six weeks later, four months after the second dose, the patient noted further marked improvement and required nitroglycerine only once every two to three weeks. Furthermore, the urinary reductions of Benedict's solution were negative more frequently than ever before, and the Diabetic Clinic in consequence reduced the daily dose of insulin from 50 units of protamin insulin and 20 of regular insulin in the morning to 50 units of protamine insulin and 12 of regular insulin. The serum cholesterol was 540 mg. per cent. While extremely grateful for the relief of angina the patient noted many symptoms of myxedema, which were ameliorated by 24 mc. of thyroid daily. On this dosage she began to experience occasional mild episodes of angina pectoris requiring 2 to 5 nitroglycerine tablets weekly as compared with 11 to 17 tablets a week prior to I\(^{131}\).

Comment: This 65 year old woman with angina...
pectoris and severe diabetes mellitus was treated with two doses of I\(^{131}\). Myxedema was induced with marked improvement of angina pectoris, relief of palpitation and some amelioration of diabetes mellitus. On a dose of 24 mg. thyroid daily, discomfort from hypometabolism is slight and angina pectoris has remained greatly improved. This patient is considered a good therapeutic result.

**Case 9.**—Arteriosclerotic heart disease. Two prior attacks of acute myocardial infarction. Angina pectoris for three years before I\(^{131}\). Induction of myxedema with I\(^{131}\). Relief of angina pectoris and increased exercise tolerance tests for nine months. Diminished improvement with increase in thyroid medication. A worthwhile result.

**Pretreatment History.** M. C., a 58 year old former painter, B.I.H. \#40863, received 15.5 mc. I\(^{131}\) on August 9, 1948. Ten years before treatment he experienced an episode of acute posterior myocardial infarction. Thereafter, he was disabled by a variety of complaints, regarded as functional. Four years before I\(^{131}\) he was awakened from sleep by severe epicardial pain and chest pressure and was hospitalized for five weeks with acute myocardial infarction. Thereafter, the patient was disabled because of angina pectoris on slight effort such as bending over a bath tub or walking a little faster than usual, or on excitement. The pain lasted “one to two minutes” and was relieved by rest and somewhat by nitroglycerine. The number of attacks a day was directly related to the level of effort and in consequence he lived a very restricted existence. Several xanthine preparations and quinidine were without effect on the exercise tolerance or on attacks suffered in daily life.

**Pretreatment Physical Examination.** The thyroid was barely palpable and non-nodular. The blood pressure was 140/80. The heart was not enlarged. The rhythm was regular. The sounds were of good quality and no murmurs were heard.

**Pretreatment Laboratory Data.** (See table 2.) The blood and urine were normal. Electrocardiograms revealed old, posterior myocardial infarction and bundle branch block. X-ray examination showed the heart to be of average size and shape. There were marked degenerative changes of the thoracic spine with narrowing of the 5th and 6th discs.

**Post-treatment Course.** The patient received 15.5, 24 and 32 mc. I\(^{131}\) on August 9 and 24 and September 30, 1948, respectively (table 1). On September 30, seven weeks after the first treatment, the patient noted fatigue, hoarseness, some puffiness of the eyes. In the middle of October 1948, nine weeks after the first dose, he noted freedom from angina pectoris. The standardized exercise tolerance test was unchanged. Shortly thereafter, the patient became frankly myxedematous; the serum cholesterol rose to 530 mg. per cent. He remained free of angina pectoris and the standardized exercise tolerance test was twenty-one to twenty-five trips. On increased doses of thyroid from 6 to 36 mg. the symptoms of myxedema were relieved (table 2). Angina pectoris recurred, less frequent than before I\(^{131}\), and the exercise tolerance test was fifteen trips.

**Comment:** A 58 year old man with two previous myocardial infarctions and angina pectoris of three years' duration received three doses of I\(^{131}\). Myxedema was induced and angina pectoris was ameliorated. It was the independent observation of the Head of the Cardiac Clinic, Dr. Paul M. Zoll, “that the patient was unquestionably considerably improved. His angina pectoris was completely absent for several months and now occurs only infrequently. He is able to do much more than previously. There are no symptoms directly referable to myxedema at present, unless some of the fatigue is on this basis. The therapy was certainly worthwhile for this patient.”

**Case 10.—Angina pectoris for eighteen years before treatment.** Paravertebral alcohol block with postinjection neuritis twelve years before I\(^{131}\); denervation of thyroid gland eleven years before I\(^{131}\). Myxedema induced by radioactive iodine. Therapeutic effect not considered worthwhile.

**Pretreatment History.** R. S., a 69 year old male clothing cutter, B.I.H. \#M1052, received 30.5 mc. I\(^{131}\) on December 31, 1947. In 1930 and 1931 he was hospitalized for five and seven months, respectively, because of status anginosus. In 1935 and 1936, paravertebral alcohol injection (T2–T5) and thyroid denervation, respectively, were without benefit. During the previous thirteen years under the close supervision of the Angina Pectoris Clinic, approximately sixty medications were tried without significant benefit. During this entire period there had been no remission from angina pectoris for more than one week.

During the nine months before I\(^{131}\) treatment he suffered a severe reactive depression and anxiety, had numerous nightmares accompanied by angina pectoris and twice attempted suicide. Although in bed the greater part of the time, he still suffered approximately one attack daily.

**Pretreatment Physical Examination.** The blood pressure was 150/84. The heart was not enlarged; the rhythm, regular. There was a Grade II apical systolic murmur. The lungs were clear.

**Pretreatment Laboratory Data.** (See table 2.) The urine and blood were normal. The serology was negative. X-ray of the heart and the electrocardiogram were within normal limits. Following a tracer
dose of I\textsuperscript{131}, 57 per cent was excreted in the urine in three days; two additional tracer studies were similar.

Post-treatment Course. In 1935 this patient had been studied and rejected for total thyroidectomy because of a basal metabolic rate of \(-22\) per cent. Although improvement after I\textsuperscript{131} was observed likewise unlikely, the absence of symptoms of hypothyroidism, the euthyroid tracer excretions, and the failure of all other treatment led us to accept this patient on an investigative basis. Accordingly, on December 1, 1947, the patient received 30.5 mc. I\textsuperscript{131} (table 1). Ten weeks later the metabolic rate was \(-42\) per cent, and the serum cholesterol 430 mg. per cent and the patient showed marked evidence of hypothyroidism. Anginal pain had not been experienced since the first week after I\textsuperscript{131}. The exercise tolerance test, however, was unchanged. Following the administration of thyroid, 6 to 12 mg. daily, the clinical signs of hypothyroidism were alleviated and the basal metabolic rate rose to \(-25\) per cent; the serum cholesterol fell to 234 mg. per cent. During this period, the patient suffered an occasional attack of angina pectoris. He was, however, continually depressed, brooding, not interested in living and, in November 1948, approximately one year after I\textsuperscript{131} therapy, he expired, following an overdose of a sedative in what was apparently suicide.

Comment: A patient with severe, disabling angina pectoris of eighteen years’ duration, emotional instability and low metabolic rate was given I\textsuperscript{131} in December 1947. Marked hypothyroidism followed and was associated with an absence of attacks in daily life. The exercise tolerance test was not significantly changed and, following the administration of small doses of thyroid, attacks of angina pectoris recurred. In evaluating the effect of hypothyroidism in this patient, we consider that the procedure has not been beneficial to this patient and the result not worthwhile. This experience again emphasizes that low pretreatment metabolic rates and severe emotional instability constitute contraindications to this form of therapy.

Case 11.—Arteriosclerotic heart disease, probable old myocardial infarction, angina pectoris of increasing severity for five years, refractory to all types of treatment. Myxedema induced with I\textsuperscript{131} with some relief of angina pectoris but with uncomfortable symptoms of myxedema. Result considered not worthwhile.

Pretreatment History. H. Y., a 67 year old upholsterer, B.I.H. \# M2457, received 25.5 mc. I\textsuperscript{131} on April 13, 1948. Five years before treatment probable acute myocardial infarction occurred. Thereafter, angina pectoris became increasingly severe and frequent with as many as 10 to 15 attacks a day. During the three years before treatment under close supervision of the Angina Pectoris Clinic, various xanthines, Khellin, vitamin E, potassium iodide, and digitalis were administered without effect. Only nitroglycerine was of value. Eight months before treatment the patient experienced pain in the calf and anterior aspects of the legs on effort. At the time of treatment he was taking at least 8 to 10 nitroglycerine tablets every day, and had angina on slight effort, at rest, at night and with meals.

Pretreatment Physical Examination. The heart was enlarged, the left border 13 cm. from the midsternal line; the rate was 80; the rhythm regular; the sounds were of good quality; no significant murmurs were heard. Blood pressure was 130/80. The chest was emphysematous. A few scattered moist rales were heard at the right base posteriorly. There was no peripheral edema.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. The electrocardiogram was consistent with old anterior myocardial infarction.

Post-treatment Clinical Course. On April 13, 1948, the patient received 25.5 mc. of I\textsuperscript{131} (table 1). Two months later the basal metabolic rate was \(-11\) per cent; the patient observed he had the same number of attacks but they were less severe. Nocturnal attacks decreased from nightly to only once a week and he could walk a little farther without developing pain. Exercise tolerance test was unchanged.

Four months after I\textsuperscript{131} the basal metabolic rate decreased to \(-17\) per cent. The serum cholesterol rose to 328 mg./100 cc. The patient required only 2 to 5 nitroglycerine tablets a day and none at night. He no longer had attacks at meals, but climbing stairs continued to induce angina pectoris. During the next month, frank myxedema occurred; the metabolism was \(-27\) per cent, the cholesterol 400 mg. per cent. During this period there was marked diminution of angina on effort. Nitroglycerine tablets, 3 daily, were used only in an attempt to alleviate intermittent claudication. Exercise tolerance test was not of value because of the leg pain. Thyroid, 24 to 36 mg. a day, did not control the symptoms of hypothyroidism. Despite the fairly marked improvement in angina pectoris as manifested by diminution in the number of attacks from ten to fifteen to only one to two a day, the absence of night pain, and the ability to work several hours a day without pain, the patient was unhappy over the degree of discomfort arising from myxedema. On thyroid, 45 to 60 mg. daily, gradual loss of the uncomfortable symptoms of myxedema and a concomitant return of angina pectoris to the pretreatment level occurred. Intermittent claudication remained troublesome.

Comment: Angina pectoris was greatly lessened in the presence of myxedema, but when thyroid was administered to ameliorate the symptoms of
hypothyroidism, angina pectoris returned and
was approximately that obtaining before treat-
ment. The therapeutic result was considered not
worthwhile.

Case 12.—Hypertension, arteriosclerotic
heart disease, increasingly frequent and severe
angina pectoris for three years. Acute myo-
cardial infarction one year before treatment.
Myxedema induced by one dose of I\(^{131}\). No
significant relief of angina pectoris. Therapeutic
result not worthwhile.

Pretreatment History. J. E., a 59 year old female,
B.I.H. \#M265, received 25.5 mc. of I\(^{131}\) on May 13,
1948. She had had hypertension for eight years and
angina pectoris for four years before I\(^{131}\) therapy.
Attacks of angina pectoris occurred not only on
walking but on eating, exposure to cold and fre-
quently without evident precipitating factors; she
was occasionally awakened from sleep by nocturnal
attacks. For the three years before treatment the pa-
tient, although sedentary, had been incapacitated by
angina. In January 1945, severe attacks of sub-
stantial pain lasting three to four hours were diag-
nosed as coronary failure. In March 1947 the
patient suffered an acute anterior myocardial in-
farction. For one year before I\(^{131}\) the patient had
had mild diabetes requiring no insulin.

Pretreatment Physical Examination. The blood
pressure was 170/90. The cardiac rhythm was regu-
lar with an occasional ventricular premature beat;
sounds were of good quality; there were no murmurs.
The lungs were clear.

Pretreatment Laboratory Data. (See table 2.) The
urine and blood were normal. The electrocardio-
graphic tracings were consistent with an old ante-
roepal myocardial infarction. On x-ray examina-
tion, the heart was moderately enlarged to the left.

Post-treatment Course. On May 13, 1948, the pa-
tient received 25.5 mc. of I\(^{131}\) (table 1). Nine weeks
after I\(^{131}\) the serum cholesterol was 427 mg. per cent
and the basal metabolic rate was –29 per cent. The
patient noted a diminution of night attacks and re-
quired no nitroglycerine in contrast to her previous
state when she took three to four daily. During
August, 1948, three months after I\(^{131}\), frank myx-
edema occurred. On gradually increasing doses of
thyroid from 12 to 36 mg. daily, the troublesome
symptoms of myxedema cleared; angina pectoris re-
curred to approximately the pretreatment severity.
However, she no longer had night attacks.

Comment: A 59 year old woman with hyper-
tension and incapacitating angina pectoris of three
years duration, was treated with one dose of I\(^{131}\).
Myxedema was induced with significant improve-
ment in angina pectoris but with the thyroid
dosage necessary to relieve discomfort, angina
pectoris relapsed to pretreatment severity. There
have been no nocturnal attacks, and she suffers
no disability from the hypometabolic state. We
do not consider the result worthwhile.

Case 13.—Arteriosclerotic heart disease with
angina pectoris of six years’ duration. Induction of
myxedema by two doses of I\(^{131}\) with some
relief of angina pectoris but with uncomfort-
table symptoms of myxedema. Result not con-
considered worthwhile.

Pretreatment History. M. S., a 61 year old white
male, B.I.H. \#99719, received 42.5 mc. of I\(^{131}\) on
July 15, 1948. Six years before I\(^{131}\), the patient
first experienced angina pectoris accompanied by
dyspnea and relieved by rest. Attacks were precipi-
tated by walking two blocks on the level or one
flight of stairs, lasted eight to ten minutes, un-
relieved by nitroglycerine.

Pretreatment Physical Examination. The patient
appeared chronically ill. The thyroid was not pal-
pable. The heart was not enlarged, the rhythm was
regular, the sounds of distant quality. The lungs
were clear. The blood pressure was 160/100.

Pretreatment Laboratory Data. (See table 2.) The
blood and urine were normal. X-ray examination re-
vealed marked left ventricular enlargement. The
radiocardiogram was abnormal, the pattern not
diagnostic. Following a tracer dose of I\(^{131}\) the ur-
inary excretion was 77 per cent.

Post-treatment Course. On July 15, 1948, the pa-
tient received 42.5 mc. of I\(^{131}\); the seventy-two-hour
urinary excretion was 71 per cent. Two weeks later,
moderate thyroiditis was accompanied by increased
anginal pain and dyspnea despite less exertion.
Twenty-five nitroglycerine tablets per week were
used in contrast to only 5 to 6 per week in the pre-
ceding period. The exercise tolerance test was ele-
von to thirteen trips. The thyroiditis subsided during
the next two weeks. Nine weeks after I\(^{131}\), mild hypo-
thyroidism was associated with slight improvement
in the angina pectoris; the attacks were shorter, not
as severe and required more exertion to precipitate
them. The exercise tolerance tests averaged twenty-
seven trips, compared to eighteen trips before I\(^{131}\).
The basal metabolic rate was –15 per cent and the
serum cholesterol 320 mg. per cent. It was thought
desirable to lower the metabolism even more in an
attempt to effect additional improvement. Therefore,
on November 10, 1948 he received 56 mc. I\(^{131}\) (table
1). The basal metabolic rate decreased to –24 per
cent and the serum cholesterol rose to 400 mg. per
cent. Improvement in angina pectoris was main-
tained but not augmented. On gradually increasing
doses of thyroid from 18 mg. to 60 mg. daily, some
improvement in the symptoms of myxedema oc-
curred. The frequency and severity of angina pec-
 toris was slightly less than before I\(^{131}\).

Comment: A 61 year old man with angina pectoris
of six years' duration received two doses of I\textsuperscript{131}. Hypometabolism and some concomitant improvement in angina pectoris followed. The exercise tolerance test increased from eighteen to twenty-seven trips. A second dose of I\textsuperscript{131} was administered, and myxedema was induced. On increasing doses of thyroid to 60 mg. daily, there was some improvement in the symptoms of myxedema. He was able to walk three to four blocks without developing angina (compared to two blocks before I\textsuperscript{131}) and felt that there was improvement. However, in view of the fact that improvement was not marked and that he still complains of some symptoms of hypometabolism, we believe the result in this case is not worthwhile.

Case 14.—Marked systolic arterial hypertension. Congestive heart failure for five years. Multiple episodes of acute pulmonary edema. Mild angina pectoris. Myxedema induced by one dose of I\textsuperscript{131}. No further cardiovascular symptomatology. A striking therapeutic result.

Pretreatment History. R. F., a 59 year old housewife, B.I.R. #72033A, received 25.5 mc. of I\textsuperscript{131} on April 2, 1948. Twenty-four years before, acute tonsillitis was followed by migratory joint pains. Hypertension was first noted seven years before I\textsuperscript{131}. Five years before treatment, she was hospitalized because of increasing dyspnea, orthopnea, substernal oppression, weakness, and weight loss of three months' duration. The diagnoses were hypertension, hypertensive heart disease, congestive heart failure, and thyrotoxicosis. The patient was treated with digitalis, low-salt diet and potassium iodide with incomplete relief. Treatment with thiouracil was followed by icterus, pruritus and diarrhoea; biopsy of the liver revealed acute bile stasis; slow recovery followed omission of the drug.

Four years before I\textsuperscript{131} treatment, dyspnea, orthopnea, weakness and weight loss required a fourth hospital admission. Hemithyroidectomy was performed. The recurrent laryngeal nerve was cut and right cord paralysis resulted.

Potassium iodide was administered and continued, but twenty months before I\textsuperscript{131} treatment, readmission was necessary because of acute pulmonary edema. Following recovery, three basal metabolic rate determinations were ±0 per cent. Eight months before I\textsuperscript{131} treatment, potassium iodide was omitted. Two months before I\textsuperscript{131}, she noted marked dyspnea on slight exertion and anterior chest pain radiating to the left arm on moderate exertion, often relieved by nitroglycerine. During the two months before I\textsuperscript{131}, she also had had three or four episodes of acute pulmonary edema. Despite markedly restricted activity, digitalis, low salt diet and xanthines, symptoms continued.

Pretreatment Physical Examination. The patient was dyspneic; the neck veins were distended; blood pressure was 230/90. There was no tremor or tachycardia; basal pulse rate was regular, 62 to 66. The heart was markedly enlarged to the left; a basal systolic but no diastolic murmur was heard. There was slight peripheral edema.

Pretreatment Laboratory Examinations. (See table 3.) The blood, urine and stool were normal. Nonprotein nitrogen was 39 mg. per cent; total protein was 6.5 grams per cent. On x-ray examination, the heart was enlarged and the lung markings were increased. The electrocardiogram was consistent with left ventricular hypertrophy.

Post-treatment Course. On April 2, 1948, the patient received 25.5 mc. of I\textsuperscript{131} (table 1). Eleven weeks after treatment, myxedema was clinically obvious. The basal metabolic rate was —20 per cent, and 12 mg. of thyroid daily was prescribed. The patient noted definite decrease in dyspnea, no cough, no ankle swelling or orthopnea. She slept on one pillow. She had no further episodes of acute pulmonary edema, paroxysmal nocturnal dyspnea or any chest pain. Weakness and fatigability were not relieved by amphetamine sulphate. Improvement had been so striking and the decrease in metabolic rate so great that it was believed the thyroid dosage could be increased without precipitating congestive failure or acute pulmonary edema. Accordingly, the dose of thyroid was increased gradually to 60 mg., and subsequently to 100 mg. daily (table 3); ethinyl estradiol, 0.05 mg. daily, was also administered. The patient observed a sense of wellbeing with decreased nervousness and fatigability. The previous cardiovascular improvement has been sustained.

Comment: This 59 year old patient with a previous history of thyrotoxicosis received I\textsuperscript{131} for the treatment of congestive heart failure, recurrent acute pulmonary edema, paroxysmal nocturnal dyspnea and mild angina pectoris secondary to hypertensive heart disease. She had been observed in the endocrine and cardiac clinics during the five years before I\textsuperscript{131} treatment. At the time of I\textsuperscript{131} therapy there was some difference of opinion as to whether residual thyrotoxicosis was present; it was the consensus, based on the absence of symptoms and signs of thyrotoxicosis and the normal basal heart rate, that the patient was euthyroid, the increase in metabolic rate and low I\textsuperscript{131} excretion being attributed to arterial hypertension and congestive failure. Eleven weeks after 25.5 mc. I\textsuperscript{131}, myxedema was present. Thereafter, she had no acute pulmonary edema, paroxysmal nocturnal dyspnea, no angina pectoris and no symptoms of congestive failure. Fatigability and nervousness decreased with thyroid 100 mg. and ethinyl estradiol 0.05 mg. daily. The absence of cardiovascular symptoms has continued. The therapeutic result was striking.
### Table 3.—Summary of Results in Five Patients with Congestive Heart Failure

<table>
<thead>
<tr>
<th>Case, Initials, Sex, Age</th>
<th>Additional Diagnoses</th>
<th>Duration of Decompensation</th>
<th>Before and Months After Thyroid</th>
<th>Basal Metabolic Rate</th>
<th>Serum Cholesterol (mg./100 cc.)</th>
<th>Arm to Tongue Circulation Time (sec.)</th>
<th>Vital Capacity (cc.)</th>
<th>Venous Pressure (mm. Hg.)</th>
<th>Dyspnea</th>
<th>Other Signs and Symptoms</th>
<th>Comment</th>
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<tr>
<td>14. R. F. F, 59</td>
<td>Art. hypertension, mild angina pectoris, previous thyrotoxicosis</td>
<td>5</td>
<td>Before</td>
<td>+20</td>
<td>213</td>
<td>13</td>
<td>1700</td>
<td>130</td>
<td>Yes</td>
<td>Mild angina pectoris, multiple episodes of acute pulmonary edema. Slight peripheral edema.</td>
<td>Therapeutic Result: 0</td>
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<td>15. M. G. M, 44</td>
<td>Hypertensive and arteriosclerotic h.d. 2 prior myocardial infarcts, chronic renal disease</td>
<td>1.5</td>
<td>Before</td>
<td>+0</td>
<td>255</td>
<td>35</td>
<td>2200</td>
<td>260</td>
<td>Yes</td>
<td>Cyanosis, ascites, orthopnea 6-8 pillows, ++ peripheral edema, rales, liver enlarged 5 fingers</td>
<td>Therapeutic Result: 0</td>
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<tr>
<td>16. E. M. F, 46</td>
<td>Rheum. heart disease, mitral and aortic sten. and insuff.</td>
<td>7</td>
<td>Before</td>
<td>+5</td>
<td>220</td>
<td>42</td>
<td>1700</td>
<td>140</td>
<td>Yes</td>
<td>Frequent parox. noct. dysp.; pleural effusion; ascites; cyanosis</td>
<td>Therapeutic Result: 0</td>
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<tr>
<td>17. E. D. F, 47</td>
<td>Rheum. heart disease, mitral sten. and insuff.</td>
<td>17</td>
<td>Before</td>
<td>-4</td>
<td>210</td>
<td>19</td>
<td>1350</td>
<td>230 to 300</td>
<td>Yes</td>
<td>Pulm. emboli; parox. noct. dysp.; probable rheumatoid arthritis; slight peripheral edema</td>
<td>Therapeutic Result: 0</td>
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<td>18. N. A. F, 43</td>
<td>Rheum. heart disease, mitral and aortic sten. and insuff., multiple pulmonary emboli.</td>
<td>6</td>
<td>Before</td>
<td>+7</td>
<td>205 to 280</td>
<td>29</td>
<td>2000</td>
<td>140</td>
<td>Yes</td>
<td>Occ. parox. noct. dysp.</td>
<td>Thyroid 15 mg. No dramatic change in cong. failure</td>
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*++++* striking; +++ excellent; ++ good; + fair; 0 not worthwhile.
Case 15.—Hypertensive and arteriosclerotic heart disease. Two previous attacks of acute myocardial infarction seven and five years before \(1^{st}\). Chronic renal disease with one remaining kidney. Chronic severe congestive heart failure. Auricular fibrillation. Myxedema induced by two doses of \(1^{st}\) with marked improvement in all manifestations of congestive failure. A striking therapeutic result.

Pretreatment History. A male, M. G., 44 years of age, a former automobile mechanic, B.I.H. 
M1759, received 27 mc. \(1^{st}\) on October 12, 1948. Hypertension had been noted nine years before treatment. He suffered an attack of acute posterior myocardial infarction seven years before treatment. Three days after getting out of bed a second attack, lasting one hour, occurred. Two years later a similar episode was treated by some weeks of bed rest following the taking of an electrocardiogram. The patient then changed to a more sedentary type of work and was fairly well until one and one-half years before \(1^{st}\) therapy, when he noted the onset of ankle edema. The blood pressure was 230/120. A nonfunctioning kidney was demonstrated and a left nephrectomy was performed. The blood pressure was said to have dropped to 114/70. Five months before entry he noted recurrence of ankle edema, increased weight and dyspnea. Despite a low-salt diet, digitoxin and mercurial diuretics, the dyspnea, orthopnea and intermittent edema became worse and he was hospitalized. On vigorous treatment with bed rest, low salt diet, a period on a rice diet, digitoxin, supplementary vitamins and frequent injections of mercurial diuretics as well as thoracenteses, the patient improved only slowly during seven weeks of hospitalization. At the time of maximum improvement, however, there was \(1^{+}\) pitting of the ankles and \(2^{+}\) pitting over the sacrum.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic and slightly cyanotic. The blood pressure was 130/80. The neck veins were distended. The thyroid was barely palpable and non-nodular. There were dullness and diminished breath sounds at the right lung base posteriorly with moist rales at both bases. The heart was enlarged to the anterior axillary line; the rhythm grossly irregular. There was a Grade I apical systolic murmur. The abdomen was protuberant. The liver was firm, nontender and palpable, five fingers below the right costal margin. The splenic tip was palpable. Pitting edema over the sacrum was \(2^{+}\), and over the ankles, \(1^{+}\).

Pretreatment Laboratory Examinations. (See table 3.) The urine specific gravity was 1.019, plus 2 to plus 4 albumin; the sediment showed 1 to 10 white cells, occasional erythrocytes and fine granular casts. Blood was normal. The nonprotein nitrogen was 54 mg. per cent. On x-ray examination, the heart was dilated to the left and the right. Electrocardiograms showed auricular fibrillation and evidence of old posterolateral infarction and left ventricular hypertrophy. The seventy-two-hour urinary excretion of a tracer dose of \(1^{st}\) was 29 per cent, evidently due to the presence of severe congestive failure.

Post-treatment Course. On October 12 and October 23, 1948 the patient received 27 mc. and 30.5 mc. \(1^{st}\), respectively (table 1). In the immediate posttreatment period, he continued to show 4 to 5 pillow orthopnea, dyspnea, markedly distended neck veins, auricular fibrillation with a pulse deficit of approximately 60, flatness and diminished breath sounds at the right base, the liver edge at the level of the umbilicus, + + + edema of the left leg, and + edema of the right leg. The dose of digitalis was increased, ammonium chloride and mercurial diuretics were again given and some improvement was noted. During the first two months after \(1^{st}\) treatment, the cholesterol decreased slightly from 278 to about 238 mg. per cent, and then began to rise, reaching and remaining at a level of 500 mg. per cent. The patient's face became puffy, his hands cool and dry, but he experienced no symptoms of hypothyroidism. During this period of hypometabolism he demonstrated progressive improvement.

At the present time, six months after induction of myxedema, he is able to undertake considerable increased activity, including doing some carpentry and considerable walking, without developing dyspnea. Orthopnea has decreased from 6 to 8 pillows and is no longer present. He sleeps on one pillow. The patient states that he has not felt this well in the last two years. Venous distention has diminished and there is no peripheral edema. Lungs are clear to percussion and auscultation. Ascites, present at the time of treatment, did not recur after one paracentesis. Neither spleen nor liver is now palpable. The transverse diameter of the heart, as measured by physical examination and as checked by x-ray examination, has diminished 4.8 cm. The electrocardiogram is unchanged. Venous pressure is 65 mm. of water, vital capacity is 3650 cc. (2350 complementary air and 1300 supplemental air), and the arm-to-tongue circulation time is thirty seconds. The nonprotein nitrogen has remained approximately 60 mg. per cent.

Comment: A 44 year old male with hypertensive and arteriosclerotic heart disease, two previous myocardial infarctions and severe intractable congestive failure, complicated by chronic renal disease in the one remaining kidney, was treated with two doses of \(1^{st}\). Myxedema was induced and concomitantly there was striking improvement in congestive failure, despite greatly increased activity. There was decreased dyspnea, no orthopnea, no edema. The vital capacity
increased from 2200 to 3650 cc. and the venous pressure decreased from 260 to 60 mm. He has experienced no discomfort from hypometabolism and at present is on 6 mg. thyroid daily. A striking therapeutic result.

Case 16.—Rheumatic heart disease with auricular fibrillation, mitral and aortic stenosis and insufficiency, chronic congestive heart failure for seven years. Severe exacerbation with general anasarca one year before I$^{131}$ treatment, recurrent paroxysmal nocturnal dyspnea. Myxedema induced with two doses of I$^{131}$. A good therapeutic result.

Pretreatment History. E. M., a 46 year old housewife, B.I.H. $\#$ M177, received 8.5 mc. I$^{131}$ on July 5, 1947. She entered the hospital in 1941 because of progressive ankle edema, dyspnea and orthopnea during the previous year. She had had chorea at the age of 10. Physical examination revealed marked cardiac enlargement, mitral and aortic stenosis and insufficiency, auricular fibrillation, congestion of the lungs and liver, ankle edema and orthopnea. She improved after one week in the hospital. In 1942, symptoms and signs of thyrotoxicosis appeared; the basal metabolic rate was approximately plus 33 per cent. A maximal subtotal thyroidectomy was done in 1943. Myxedema followed and the signs and symptoms of congestive heart failure markedly improved and she returned to work. Thyroid extract, 65 mg., was administered daily until January 1947, when for the fifth time the patient entered the hospital with orthopnea, pleural effusion, ascites, and peripheral edema. Thyroid medication was omitted. Despite adequate digitalization, frequent mercurial diuretics, and salt restriction, little improvement resulted. Following discharge from the hospital, the above signs and symptoms became progressively worse, paroxysmal nocturnal dyspnea appeared, and she re-entered on June 14, 1947. Only slight improvement resulted from the above regime of treatment.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic, and deeply cyanotic. There was marked engorgement of the neck veins. The blood pressure was 160/80. The heart was greatly enlarged, and the characteristic murmurs of aortic and mitral stenosis and insufficiency were audible. Auricular fibrillation and, at times, a bigeminal rhythm were present. The firm, non-tender edge of the liver was felt four fingers breadth below the right costal margin. Ascites was present. There was 3+ edema of the lower legs and slight edema over the sacrum.

Pretreatment Laboratory Data. (See table 3.) The urine specific gravity was 1.010 with intermittent albuminuria. The nonprotein nitrogen was 40 mg. per cent. The blood was normal. The electrocardiogram revealed auricular fibrillation, ventricular premature beats and left ventricular hypertrophy. By x-ray examination the cardiac transverse diameter was 18.3 cm. with marked left and right dilatation.

Post-treatment Clinical Course. On July 5, 1947, 8.5 mc. of I$^{131}$ were administered (table 1). Approximately ten weeks later the basal metabolic rate was $-14$ per cent and the serum cholesterol 400 mg. per cent. On November 1, 1947 24 mc. of I$^{131}$ were administered (table 1). A tracer study on December 4, 1947 showed 84 per cent excretion in three days. On December 10, 1947, six weeks after the second dose, the basal metabolic rate was $-26$ per cent and the serum cholesterol was 440 mg. per cent. Clinical evidences of myxedema were present. Her cardiac status improved. She was able to sleep flat in bed and undertake considerably more effort without dyspnea. Peripheral edema reaccumulated more slowly and, therefore, mercurial diuretics were required less frequently. Thyroid, 6 mg. per day, mitigated the symptoms of myxedema and enabled the patient to maintain clinical improvement. In the following nineteen months, the patient has been maintained in a hypometabolic state (table 3). She has had two additional hospital admissions, four months and twelve months after the induction of hypometabolism, for further regulation of congestive failure. The first was occasioned by cessation of mercurial diuretics, because of temporary intolerance to these compounds, and the second was precipitated by a period in which she was refractory to mercurial compounds. This, too, was temporary. At all other times the patient was ambulatory, able to do her own housework and run her own home, leading a restricted but otherwise normal existence.

During recent hot humid weather immediately preceding an injection of a mercurial diuretic, she has had intermittent paroxysmal dyspnea. There is some but less dyspnea on exertion particularly on bending, orthopnea requiring the use of two pillows and swelling of the ankles. She has been on a regimen of digitoxin, ammonium chloride, and biweekly injections of mercurial diuretics. On thyroid 12 mg. daily; she has had no symptoms referable to her hypometabolism.

Physical examination reveals signs of moderate hypometabolism. The lungs are clear. The liver is palpable and occasionally tender, two to four fingers breadth below the right costal margin. There is little sacral edema but marked edema of the ankles.

Comment: This 46 year old woman with a past history of rheumatic heart disease and chronic congestive failure for seven years was completely incapacitated at the time of the inception of hypometabolism nineteen months ago. Congestive failure previously uncontrolled was markedly improved in that dyspnea, orthopnea, paroxysmal nocturnal dyspnea were ameliorated with the occurrence of hypometabolism following
I^{131}, She has been able to do her own housework, visit friends, and lead a generally more active though still restricted regimen. At the present time, two years after I^{131} treatment, there has been an exacerbation of the symptoms of congestive heart failure, and paroxysmal nocturnal dyspnea has been troublesome. The period of nineteen months of definite clinical improvement despite a more active life constitutes a good therapeutic result.

**Case 17.**—Rheumatic heart disease with auricular fibrillation, mitral stenosis and insufficiency. Recurrent congestive failure, requiring seventeen hospital admissions in seventeen years. Multiple attacks of pulmonary embolism, paroxysmal nocturnal dyspnea. Myxedema induced by a single dose of 27 mc. of I^{131}. Congestive failure improved after treatment, but the change could be due to concomitant improvement in associated disease, probably rheumatoid arthritis and erythema nodosum, rendering estimate of therapeutic effect of I^{131} equivocal.

**Pretreatment History.** E. D., 47 year old receptionist, B.I.H. *M2717, received 27 mc. of I^{131} on February 12, 1948. Seventeen years before treatment, rheumatic heart disease with mitral stenosis and insufficiency was diagnosed. In the nine years before her first entry to the Beth Israel Hospital, while under the care of Dr. Samuel L. Gargill, she was hospitalized elsewhere twelve times because of severe dyspnea, orthopnea, fatigue, chest pain, cough and ankle swelling. When admitted to the Beth Israel Hospital, eight years before I^{131} treatment, congestive failure, pulmonary edema, mitral stenosis and insufficiency, paroxysmal auricular fibrillation and paroxysmal nocturnal dyspnea were noted.

Seventeen months before I^{131}, a second admission, because of an acute upper respiratory infection, chronic congestive heart failure with auricular fibrillation, was complicated by phlebitis and pulmonary infarction. Early in 1948, repair of an inguinal hernia was complicated by pulmonary infarction. Throughout this pretreatment period, despite the presence of exertional dyspnea, four-pillow orthopnea, palpitation and edema of the legs, the patient continued to work as receptionist in a department store. Therapy consisted of digitoxin, low salt diet and occasional injections of mercurial diuretics.

**Pretreatment Physical Examination:** The patient was dyspneic and orthopneic. The heart was markedly enlarged and showed murmurs characteristic of mitral stenosis and insufficiency; the rhythm was grossly irregular; the rate 76. There was dullness at the right lung base posteriorly, with inconstant raies. A tender liver edge palpable four to five fingersbreadth below the right costal margin and minimal peripheral edema were noted.

**Pretreatment Laboratory Examinations.** (See table 3.) The blood, urine and stool were normal. Serology was negative. X-ray examination revealed a markedly enlarged heart, increased hilar shadows and markings, and small amount of fluid in the right costophrenic angle. The electrocardiogram revealed auricular fibrillation.

**Post-treatment Course.** On February 12, 1948, she received 27 mc. of I^{131} (table 1). The post-I^{131} course was complicated by the occurrence of thrush with a severe sore throat, purulent sinusitis, leg and joint pain and erythema nodosum and, later, acute cholecystitis and cholelithiasis. Seven weeks after I^{131}, the basal metabolic rate was −20 per cent. The excretion of successive tracer doses of I^{131} rose from 42 to 87 per cent. There was no evident change in the cardiovascular status. Four months after I^{131}, two months after the onset of myxedema, the patient noticed a decrease in exertional dyspnea and fewer episodes of paroxysmal nocturnal dyspnea. This improvement was temporary.

In the late spring of 1949, fifteen months after treatment, the patient began to improve with some remission of the joint symptoms, decrease in dyspnea and less frequent paroxysmal nocturnal dyspnea. In June 1949, acute cholecystitis and cholelithiasis required cholecystectomy. The patient withstood operation well and returned to work in four weeks.

**Comment:** This patient, with a seventeen-year history of rheumatic heart disease and recurrent congestive heart failure, received one dose of 27 mc. of I^{131}. It has been extremely difficult to evaluate the effect of the hypometabolic state in this patient, owing to the overlay of psychogenic factors and the continued presence of stiff, swollen and painful joints of the hands and feet, tender, blotchy, erythematous areas and exquisite tenderness of the lower extremities. There is less dyspnea and more infrequent paroxysmal nocturnal dyspnea. Orthopnea and chest pain persist. The vital capacity is unchanged. The venous pressure is 120 mm. of water as compared to 230 to 300 mm. prior to treatment. The basal metabolic rate is −27 per cent. The serum cholesterol is 350 mg. per cent. There are no symptoms referable to the hypometabolic state. She has continued to work and has been maintained on a regimen of desiccated thyroid 15 mg., digitoxin 0.1 mg., vitamins and intermittent injections of mercurial diuretics. While her cardiac condition has unquestionably improved, this cannot be confidently attributed to I^{131} because of concomitant improvement in the arthritis.

**Case 18.**—Rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and
insufficiency, dyspnea on exertion for twenty years, auricular fibrillation for fifteen years, progressive congestive heart failure for six years with two admissions in the three months before treatment for marked congestive heart failure despite optimal therapy. Myxedema induced with one dose of I\textsuperscript{131}. Temporary but no lasting worthwhile improvement of congestive failure.

Pretreatment History. N. A., a 43 year old woman, B.I.H. #71514, received 39 mc. I\textsuperscript{131} on November 9, 1948. Twenty-five years previously polyarthritis occurred and there was intermittent recurrence during the next ten years. Twenty-one years ago she noted dyspnea on marked exertion with occasional ankle edema, and for the past fifteen years irregularity of the pulse. Twelve years prior to I\textsuperscript{131} treatment, acute paroxysmal dyspnea was experienced, and the diagnosis of rheumatic heart disease was made. Six years ago exacerbation of rheumatic fever, and again later that same year, mild congestive failure subsequent to a respiratory infection required hospitalization. She was subsequently followed in the Cardiac Clinic, and maintained on digitalis and ammonium chloride. She had moderate dyspnea, orthopnea, occasional paroxysmal nocturnal dyspnea and mild ankle swelling. Three years ago she was hospitalized for increasingly severe congestive failure and hydrothorax and again three months before treatment because of congestive heart failure, polycythemia vera and multiple cerebral episodes with transient hemiparesis and aphasia.

Following discharge she experienced episodes of paroxysmal dyspnea, severe orthopnea, suffered marked dyspnea on minimal effort and gained 16 pounds despite a salt-free diet, digoxin and a weekly injection of a mercurial diuretic. She was only barely able to do light housework. One month before treatment she was again admitted to the hospital with severe congestive failure, accompanied by persistent abdominal swelling. An enlarged liver, abdominal ascites, right hydrothorax, evidence of hepatic insufficiency with serum bilirubin of 0.8 mg. per cent, icteric index of 13 to 19 and sulfobromophthalein sodium retention of 26 per cent in forty-five minutes were noted. The patient responded to vigorous treatment with bed rest, diuretics and digitalis.

Pretreatment Physical Examination. The patient was mildly dyspneic, cyanotic and orthopneic. The thyroid was palpable. The lungs were clear. The heart was markedly enlarged to the left. The rhythm was grossly irregular, and with bigeminy, trigeminy and quadrigeminy. The characteristic signs of advanced mitral stenosis and insufficiency were heard. The nontender liver was palpable three to four fingersbreadth below the right costal margin. There was ascites and no ankle edema.

Pretreatment Laboratory Examinations. (See table 3.) Most urine specimens revealed a specific gravity of 1.017 with 2 to 3 plus albumin, 10 to 12 white blood cells and occasional red blood cells. The hemoglobin was 13.9 grams, red blood count 4.5 million, white blood count 6,850 with a normal differential count. The nonprotein nitrogen was 38 mg. per cent, the icteric index 13-19, total protein 7.8 Gm. per cent; normal albumin/globulin ratio. On x-ray examination the heart was markedly enlarged to the right and to the left, the transverse diameter being 17 cm.

The electrocardiogram showed auricular fibrillation, multiple ventricular extrasystoles, right axis deviation and was consistent with left and right ventricular hypertrophy. In the seventy-two hours following a tracer dose of I\textsuperscript{131}, 58 per cent was excreted in the urine.

Post-treatment Clinical Course. On November 9 1948, 39 mc. of I\textsuperscript{131} were administered (table 1). Four weeks later, she suffered an embolus to the left popliteal artery and left kidney. She recovered gradually without sequelae.

Ten weeks after I\textsuperscript{131}, the basal metabolic rate was \(-25\) per cent and there was slight improvement in congestive failure, manifested by some decrease in dyspnea and orthopnea. In the following weeks further improvement occurred. She was able to undertake more housework and could sleep almost flat, had no cough and much less abdominal swelling than previously. At this time she achieved the peak of her improvement. She stated that her breathing had not been so good in two years. With the administration of thyroid, 20 mg. daily, the basal metabolic rate gradually rose to \(-15\) per cent and congestive failure recurred (table 3); compensation was maintained on by the use of weekly injections of mercurial diuretics. She continued to show an enlarged liver, right pleural effusion and evidence of ascites. The rhythm continued to be irregular with bigeminy and trigeminy.

Comment: A 43 year old woman with rheumatic heart disease, progressive congestive heart failure, complicated by multiple embolic phenomena, and probably cardiac cirrhosis was treated with one dose of I\textsuperscript{131}. Myxedema was induced and was associated with temporary clinical improvement. At the present time, six months after induction of myxedema, congestive heart failure is controlled with difficulty on a rigid medical regimen, and weekly injection of diuretics. On 12 mg. of thyroid daily, she suffers no discomfort from hypometabolism. Her cardiac condition is approximately the same as before I\textsuperscript{131} and the therapeutic result is not considered worthwhile.

Discussion of Results

The accurate evaluation of every clinical therapeutic measure is beset by the possibly
favorable effect of suggestion and spontaneous improvement due to changes in the natural history of the condition. Throughout this investigation we have tried to reduce such errors to a minimum. Practically all patients were treated on an ambulatory basis, obviating the possible effect of prolonged bed rest and hospitalization. Following administration of I\textsuperscript{131}, hypothyroidism appeared only after five weeks to five months, and could not be anticipated by either the patient or the observers. It was particularly impressive to have the patient report, after receiving I\textsuperscript{131}, that for the first time in months or years he felt definitely improved, and then to find definite improvement on physical examination. Concomitantly, the laboratory reports of the basal metabolic rate measurements and serum cholesterol determinations indicated the inception of hypothyroidism (fig. 1, Case 3). Conversely, some patients, during the period in which they gave evidences of thyroiditis as manifested by pain and tenderness with increased heat over the thyroid area, noted their condition was definitely worse. In some of these individuals the basal metabolic rate was slightly elevated (figs. 1 and 2, Cases 3 and 5). We have observed in such instances an elevation of the serum protein-bound iodine measurement. Several patients during this time also exhibited slight tachycardia and increased nervousness and sweating indicative of mild hyperthyroidism. As clinical improvement became evident, the degree of improvement generally was proportional to the degree of hypothyroidism. This correspondence between metabolic levels and clinical status was manifested in twenty-six episodes in the 18 patients.

The observed relation between the metabolic rate and clinical improvement is a clear verification of the rationale of this procedure which has been elucidated in previous communications\textsuperscript{1, 2, 28, 29} and, therefore, will be described only briefly. Circulation and metabolism are two closely related fundamental characteristics for, clearly, metabolic activity of the tissues would be impossible without adequate blood supply. The normal metabolic level of the body is maintained by the normal thyroid. With decreased function of the thyroid, the metabolic level is decreased until, in the absence of thyroid function, the basal metabolic rate is approximately 40 per cent below normal. At these levels the cardiac work, as indicated by the diminished output and the slower speed of blood flow\textsuperscript{1, 20} is decreased; the decrease in circulation is, indeed, even more than the metabolic rate would indicate, for the arteriovenous oxygen difference is widened. It was thought, therefore, that the diseased heart, while unable to meet the demands of normal metabolic and circulatory requirements, nevertheless might be able to meet the reduced needs in hypothyroidism.

Clinically, it has long been known that subtotal thyroidectomy in thyrocardiac patients usually accomplishes permanent lowering of the basal metabolic rate from abnormally high levels to a normal level, with coincident improvement in angina pectoris and congestive failure as the demands on the heart are lessened\textsuperscript{31-33}. Conversely, when thyroid is administered to patients with spontaneous myxedema, angina pectoris\textsuperscript{34-36} and the signs and symptoms of congestive failure\textsuperscript{36-38} not infrequently develop because of the increased demands on the heart\textsuperscript{39-41}. It is well recognized that exercise, emotion and other factors which increase cardiac work tend to aggravate angina pectoris and congestive failure. The enforcement of diminished activity or complete bed rest benefits patients by reducing the demands on the heart. The use of sedatives and the action of digitalis in reducing the ventricular rate in auricular fibrillation have a similar effect.

The induction of hypothyroidism for the treatment of angina pectoris and congestive failure is an extension of this therapeutic principle. In lessening the demands on the heart in patients with intractable heart disease by purposefully inducing myxedema, a diminution in cardiac work is accomplished. Since the heart in hypothyroidism performs less work and starts at a lower level of oxygen consumption, it can withstand a greater increment of work before reaching the upper limit of its work capacity. This upper limit of work capacity in patients with congestive failure is imposed by the presence of valvular disease, hypertension, or injury because of rheumatic myocarditis or prior myocardial infarction. In angina pectoris,
many of these factors, as well as the limitation of blood supply by the relatively fixed arteriosclerotic coronary vessels, are operative; the coronary circulation cannot increase in accordance with the increased needs of the heart. Relative anoxemia results, and angina pectoris occurs.

The hypothyroid state also possibly exerts a favorable effect in several other directions. When patients are frankly myxedematous with basal metabolic rates of $-30$ to $-40$ per cent they are often irritable and nervous but, on receiving small doses of thyroid to maintain them at a level of $-15$ to $-25$ per cent, they are frequently more placid and even-tempered emotionally than before treatment, though mentally as acute as formerly. In an occasional patient, such as J. K. (Case 3), this factor may be significant; the patient stating that all his life prior to treatment he was prone "to fly off the handle whereas now I am more even-tempered." Accordingly, after the induction of myxedema, small doses of 6 to 100 milligrams of thyroid are administered daily to maintain all patients at a level, usually of $-15$ to $-25$ per cent, at which they experience the least discomfort from myxedema and the maximum relief from their cardiac symptoms.

The question naturally arises whether the increased emotional stability in some of our patients is due to a lessened sensitivity to epinephrine. Previous studies of the effects of known concentrations of epinephrine administered intravenously before total thyroidectomy and at various metabolic levels after operation demonstrated that the response of blood pressure, cardiac rate, oxygen consumption and respiration remained unchanged as long as the basal metabolic rate was not lower than $-30$ per cent and the patient was free from the distressing symptoms of myxedema. At levels below that at which our patients are maintained, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances. These observations on the unaltered sensitivity to epinephrine at the metabolic levels maintained in our patients do not preclude the possibility, however, that a decreased secretion occurs in the hypothyroid state.

**The Effect of Hypothyroidism on Angina Pectoris**

Angina pectoris has been strikingly lessened or abolished in 8 of the 13 patients with intractable cardiac pain (table 2). The duration of angina pectoris in these 8 patients was from one to ten years and averaged three years, eight months. All of these patients had experienced cardiac pain on exertion and many had attacks on emotion; several had pain which came on at rest and even during sleep. The improvement has been particularly striking in five patients (Cases 1 to 5). These patients are able to undertake considerably more exertion than formerly with only occasional or no attacks of angina pectoris. Cases 1 and 2 are gainfully employed, whereas prior to treatment they had been completely incapacitated for years because of angina which was precipitated by the slightest effort. In the other 3 of the 8 patients, the result has been definitely worthwhile according to the appraisal by the patient and by us. In addition to the foregoing 8 patients, Case 14, incapacitated primarily because of congestive failure, also suffered angina pectoris on moderate exertion. With improvement in the congestive failure, angina pectoris no longer occurs.

In the remaining 5 of the 13 patients with angina pectoris, the therapeutic result has not been striking. In Case 9, angina pectoris was relieved for nine months but has since relapsed to pretreatment status. In the 4 patients (Cases 10, 11, 12 and 13) in whom the therapeutic result was not considered worthwhile, angina pectoris was either strikingly lessened or abolished when the patients exhibited the clinical and laboratory evidences of myxedema. It was impossible, however, to maintain these patients at such metabolic levels because of the discomfort of myxedema. When thyroid was administered to ameliorate the discomfort of myxedema, attacks of angina pectoris occurred with sufficient frequency and severity to make us consider the result not worthwhile. Some of these patients have been restored to their pretreatment euthyroid status by thyroid with return of their cardiac pain to its pretreatment characteristics.
THE EFFECT OF HYPOTHYROIDISM ON CONGESTIVE HEART FAILURE, PAROXYSMAL NOCTURNAL DYSPNEA AND PULMONARY EDEMA

Five of the 18 patients were incapacitated primarily because of congestive heart failure (table 3). Three of the 5 patients (Cases 14, 15 and 16) showed worthwhile improvement; in the first 2 the improvement has been striking. The relief from dyspnea, attacks of pulmonary edema and paroxysmal nocturnal dyspnea has been associated with objective evidences of diminution (Case 16) or disappearance (Cases 14 and 15) of peripheral edema and of pulmonary congestion. In Patient 15, orthopnea is no longer present, ascites has remained absent, the liver is no longer palpable, cyanosis has disappeared and the vital capacity of the lungs has increased from 2200 cc. to 3650 cc. The patient is able to engage in useful activity for the first time in one and one-half years.

In the 2 patients in whom a worthwhile therapeutic effect could not be ascribed to I$^{131}$ therapy, definite improvement of congestive failure occurred in one (Case 17) but this may have been due to improvement in the concomitant rheumatoid arthritis. In the other patient (Case 18), definite temporary improvement was evident for approximately one month followed by relapse to her pretreatment status consequent to small doses of thyroid.

In addition to these 5 patients, symptoms and signs of congestive failure were present in many of those incapacitated primarily because of angina pectoris. Congestive failure had been noted for ten years in Patient 4, for five years in Patient 6 with episodes of peripheral edema, pulmonary congestion, recurrent paroxysmal nocturnal dyspnea and orthopnea. Paroxysmal dyspnea and attacks of acute pulmonary edema had also occurred in Cases 2 and 3. In all of these patients the significant improvement in angina pectoris was associated with comparable improvement in the manifestations of congestive failure, the signs and symptoms being impressively relieved or entirely dissipated.

Effect on Associated Diseases

Diabetes mellitus was present in 2 patients (Cases 8 and 12). In one patient, the disease was mild and required no insulin; no change could be discerned after treatment. In the other patient, 56 units of protamine and 20 units of regular insulin were required daily before treatment, compared to 50 and 12 units after treatment; the control of glycosuria was better after treatment. While not as striking a reduction in insulin requirement as observed in some cases after total thyroidectomy, the amelioration of diabetes mellitus is in accordance with our previous experience.

Advanced chronic nephritis was present in one patient (Case 15). The striking improvement in congestive failure in this patient was not followed by any striking change in the blood nonprotein nitrogen.

Changes in Objective Clinical Measurements after Induction of Hypothyroidism

The basal metabolic rate has been significantly lowered in every patient thus far treated. The decrease in metabolic rate has become evident five weeks to five months after treatment. In some instances, no effect has been noted after the initial dose of I$^{131}$ and one or more additional doses were necessary. In most patients, a state of frank myxedema was permitted to become manifest before thyroid medication was administered, but in certain patients an optimal hypothyroid state has been induced and thyroid medication was not necessary. When patients are in marked myxedema, the discomfort not infrequently prevents attainment of a true basal state. Administration of small doses of thyroid makes them more comfortable and consequently in such patients one may occasionally witness an initial decrease in metabolic rate from higher levels to $-25$ per cent or $-30$ per cent when thyroid is administered.

The serum cholesterol measurements provide an invaluable guide in the estimation of the presence and degree of hypothyroidism. They are of particular importance in those individuals, such as Cases 4, 8 and 15 in whom reliable basal metabolic measurements cannot be obtained. Definite increases in serum cholesterol, coincident with clinical improvement, were at times noted a week or two before a significant decrease in basal metabolic rate became manifest. This was observed particularly in patients
in whom some variation in metabolic rate determinations could not be obviated.

The velocity of blood flow also shows significant changes. Previous studies demonstrated that the speed of blood flow is slowed in myxedema. In the usual euthyroid patient with congestive failure, the blood flow is also slowed but becomes more rapid as compensation is regained. In accordance with these studies, we have observed that patients with angina pectoris but no congestive failure (Cases 3, 5, 7) showed a slowing in velocity of blood flow as hypothyroidism was induced. In patients with congestive failure who showed clinical improvement as hypothyroidism developed, two opposing influences were operative; the clinical improvement and regaining of compensation tend to cause an increased blood flow; the hypothyroidism, a decreased flow. Measurements of the arm to tongue circulation times under such circumstances represent the resultant of these two opposing influences. Thus in Case 15 there was an increased speed of blood flow because of the preponderant influence of striking clinical improvement, whereas in Case 16 the arm to tongue circulation remained approximately the same; the two opposing influences tending to offset each other. In Cases 14 and 17 the velocity of blood flow was decreased.

Arterial hypertension had been experienced by 7 patients (Cases 2, 6, 7, 10, 12, 14, 15). No effect on blood pressure levels was discerned.

The vital capacity of the lungs and its subdivisions underwent a decided increase in the one patient with striking improvement in whom the measurement was feasible (Case 15). In myxedema, the vital capacity of the lungs is abnormally low even in the absence of symptoms or signs of congestive failure. In patients with improvement in congestive failure induced by hypothyroidism, vital capacity measurements are evidently the resultant of two opposing factors: (1) improvement in congestive failure tending to increase the vital capacity of the lungs and (2) development of the low metabolic rate of myxedema tending to lower the vital capacity of the lungs.

Exercise tolerance tests were considered hazardous in most of the patients with angina pectoris in whom attacks occurred on very slight exertion or even at rest and in whom episodes of paroxysmal dyspnea and acute pulmonary edema frequently had been observed. In Patient 1, the increased ability to undertake effort during the test was in accordance with his striking improvement manifest in daily activities; in Patient 9, the results of the exercise tolerance test were also in accordance with the clinical appraisal.

The Development of the Signs and Symptoms of Clinical Myxedema, Including Electrocardiographic and Heart Size Changes

After the administration of therapeutic doses of 131I, no discernible evidences of hypothyroidism were noted for five weeks to five months. In approximately one-third of the cases receiving single doses of 8.5 to 56 millicuries, tenderness and occasionally slight pain have been observed over the thyroid (table 1) persisting usually several days, but occasionally, seven or ten days. Concomitant with these manifestations of probable thyroiditis, slight elevations in the metabolic rate, slight tachycardia, elevation of the serum protein-bound iodine have been noted. With these evidences of mild hyperthyroidism, the symptoms and signs of angina pectoris sometimes became slightly but definitely worse during this brief period (Cases 3 and 5).

The first intimation of incipient hypothyroidism may consist of one or more of the following: rise in serum cholesterol, decreased basal metabolic rate, slight fullness or puffiness of the face, a report by the patient that the attacks of angina are milder or less frequent, improvement in the dyspnea of congestive failure or lessening of orthopnea.

During the next weeks or months the clinical evidences of myxedema become more definite. In a few patients, such as Case 15, an optimal level of hypometabolism is reached and maintained for a considerable period during which no thyroid medication or further 131I dosage is indicated.

Most patients experience discomfort at basal metabolic levels below −25 per cent but considerable individual variations have been ob-
served. Some patients tolerate levels as low as —23 per cent (Case 5) or —24 per cent (Case 3) without any significant discomfort; others must be maintained at relatively high levels such as —15 per cent (Case 14). Patients 1, 2, 3, 5 and 15 are maintained in the hypometabolic state with little or no discomfort, whereas others (Cases 11, 12 and 13) are uncomfortable at similarly decreased levels. The explanation of the considerable individual differences is not clear. The distress of myxedema which requires thyroid therapy includes the following: lethargy and sleepiness, stuffiness of the nose and ears, stiffness and ache of the muscles and joints, paresthesias, weakness of the legs, irritability and depression, puffiness of the eyes and face.

In each instance, thyroid dosage must be adjusted to maintain the patient at the lowest level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain patients (Cases 11, 12 and 13), this has not been possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid was administered to obviate the discomfort. In general, a pretreatment basal metabolic level of —10 per cent or higher permits a greater leeway.

Each of the present authors has been impressed with the fact that at comfortable levels of hypometabolism, usually —15 to —25 per cent, the patients are bright and alert rather than mentally lethargic.

The Question of "the Myxedema Heart"

As in previous studies, particular attention has been devoted to the appearance of evidence of the signs or symptoms of the so-called "myxedema heart." Observations of the heart in spontaneous myxedema demonstrated that (1) the cardiac silhouette on x-ray examination and the area of percussion dullness on physical examination are usually increased; (2) the voltage of the P and T waves and the QRS complex in the three standard leads is frequently diminished and the P-R interval is increased; and (3) cardiac contractions are less forceful. Opinions differ concerning the clinical significance of these alterations. Zondek and Fahr maintained that cardiac function is often impaired in patients with myxedema having such changes. Willius and Haines, Case, and Means, White and Krantz, however, studied a total of three hundred patients with myxedema and concluded that heart function is rarely, if ever, impaired. From a review of the literature and a comprehensive study of 30 additional cases at the Massachusetts General Hospital, Lerman, Clark and Means concluded that "myxedema heart" in the sense of heart failure occurs rarely, if at all—an opinion likewise expressed by Christian.

Our own observations are in accordance with the latter findings; an increased cardiac silhouette or area of percussion dullness, decreased voltage of the electrocardiogram and less forceful pulsations on fluoroscopy have been observed in some of our subjects. But "myxedema heart" in the sense of a condition aggravating or precipitating attacks of angina pectoris or congestive failure did not develop in our cardiac patients. On the contrary, with the appearance of such changes, striking clinical improvement has been witnessed. In some patients with congestive failure, the cardiac silhouette became smaller, the disappearance of the dilatation of the failing heart offsetting the effect of myxedema on the heart. We believe that the designation, "the heart in myxedema," is more accurate than the term "myxedema heart" as employed by Zondek and Fahr. A detailed report of our findings will be presented subsequently.

Hypercholesterolemia, Myxedema and Arteriosclerosis

The question naturally arises as to whether the hypercholesterolemia in hypothyroidism predisposes the patient to an increased progression of arteriosclerosis. Despite the common statement that arteriosclerosis is conspicuous in myxedema, the evidence is not conclusive. In our own patients, the situation is, moreover, not strictly analogous to untreated or complete myxedema, since our patients are maintained at basal metabolic levels of —15 to —25 per cent and almost always receive small doses of thyroid.
In this connection we have reviewed the clinical course and postmortem findings of patients who survived three to eleven years following surgical total thyroidectomy and in whom hypometabolism with elevated cholesterol values was present. Cases with angina pectoris in the fifth decade or beyond shed no light on this question, for pathologic studies have clearly demonstrated that such patients have extensive coronary arteriosclerosis in the absence of myxedema. We have, therefore, studied the findings in the younger patients with rheumatic heart disease who survived one or more years after total thyroidectomy and in whom basal metabolic readings, hypercholesterolemia or clinical manifestations of hypothyroidism was evident. Only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were disclosed after total thyroidectomy, they might well be attributed to the hypercholesterolemia of hypothyroidism. In all 5 such patients who survived three to eleven years after total thyroidectomy in the hypothyroid state, careful postmortem studies by the Schlesinger technic revealed, however, only minimal or no coronary arteriosclerosis. Similar findings were disclosed in 3 additional cases of the Peter Bent Brigham Hospital made available to us through the courtesy of Dr. George W. Thorn and Dr. Samuel A. Levine. In one ambulatory patient, aged 39, with rheumatic heart disease, mitral stenosis and insufficiency, sixteen years after surgical total thyroidectomy, x-ray studies by Dr. Felix G. Fleischner, Roentgenologist to the Beth Israel Hospital, failed to reveal any evidence of calcification of the leg vessels, of the abdominal or thoracic aorta, coronary artery calcification or other similar abnormalities.

The Relative Advantages and Disadvantages of I\textsuperscript{131} Therapy to Induce Hypothyroidism Compared to Total Thyroidectomy

The many advantages of inducing hypothyroidism by radioactive iodine rather than total thyroidectomy may be summarized as follows: Surgical interference with its inevitable mortality, pain and discomfort is obviated. Prolonged hospitalization is not necessary. Some of our patients have been studied in the hospital for brief periods to facilitate our research; others, however, have been treated wholly on an ambulatory basis. In the evaluation of therapeutic benefit, the possible effect of bed rest in hospital need not be considered after radioactive iodine therapy. Total thyroidectomy, like subtotal thyroidectomy, entails possible damage to the parathyroids and recurrent laryngeal nerves, and the possibility of aberrant or residual thyroid tissue not readily seen or removed at operation. Immediately following total thyroidectomy, amelioration or disappearance of the pain of angina pectoris was observed due to the severance of sensory nerve pathways. This early relief is not enjoyed after I\textsuperscript{131} therapy, but on the other hand, the therapeutic effect of hypothyroidism per se can be more accurately observed, uncomplicated by this early relief, by the period of hospital bed rest, and by the possible effect of suggestion. The irregular interval of five weeks to five months after I\textsuperscript{131} treatment, before hypothyroidism becomes evident, is an additional safeguard against the possible effect of suggestion. The time at which hypometabolism and clinical improvement occurs cannot be foretold by the patient or the physician; the clinical improvement, first noted by the patient and later found to be coincident to the inception of hypometabolism when the results of the serum cholesterol and basal metabolic determinations are made available, is consequently the more impressive.

In the doses needed to induce myxedema, radioactive iodine therapy is not attended by any symptoms of radiation sickness or any other serious discomfort; in approximately two-thirds of the patients receiving 8.5 to 42.5 millicuries as the first dose, local tenderness and slight pain on swallowing roughly equivalent to the discomfort of an acute, mild to moderate sore throat has been noted for several days and up to a week. More recently, we have administered two to four doses of approximately 20 millicuries each to obviate these symptoms.

In 1933, it was stated: "It is hoped that ultimately operation will be unnecessary to produce a low metabolic rate. Many studies
have been made on antithyroidal substances, and comparatively recent reports give hope that the administration of such substances may cause lowering of the metabolic rate. Radioactive iodine fulfills this hope but possesses certain disadvantages. Its use entails highly specialized skills and extensive apparatus of considerable cost. Patients require observation for an extended period of weeks or months to determine whether additional doses are required to produce hypothyroidism. Studies regarding dosage schedules, uptake by the thyroid, and the determination of the roentgens delivered are in progress, however, and are expected to be helpful in the future clinical management of these patients.68

In general it may be stated that radioactive iodine therapy imposes no pain or discomfort except temporarily in the instances of thyroiditis noted above. If the patient cannot tolerate the hypothyroid state, it may always be abolished by appropriate doses of thyroid.

COMPARISON OF PROPYLTHIOURACIL WITH $^{131}$ I THERAPY IN EUTHYROID CARDIAC PATIENTS

The thiourea derivatives, including propylthiouracil, also have been used to attain the hypometabolism of total thyroidectomy by medical instead of surgical means. These drugs are readily available, comparatively inexpensive, and, like $^{131}$ I, are administered by mouth. Unfortunately, however, hypothyroidism can be induced in only some patients. Moreover, to maintain hypothyroidism in the patients in which it is effective, administration of the drug must be continued for the remainder of the patient’s life. At any time during such administration, dangerous drug reactions, including granulocytopenia, agranulocytosis and death, may suddenly occur.69-73

SELECTION OF PATIENTS

The criteria for the proper selection of patients can be established only after the results of this therapy have been observed by various investigators over a period of many years in numerous patients representing the various forms and degrees of severity of cardiovascular disease. Although the results in these 18 patients during the past two years are informative, the duration of hypothyroidism is too short and the number of cases too small to permit the deduction of final conclusions. It may be of value, however, to state our tentative opinion at the present time.

We believe this procedure should still be considered in the investigative stage and, therefore, should be reserved for those patients who in spite of all available therapeutic medical measures remain cardiac invalids. Before radioactive iodine is administered, the patient’s condition should be improved to the fullest possible extent by prolonged and adequate treatment in order that the effect of $^{131}$ I therapy may be evaluated as clearly and as accurately as possible.

Patients whose incapacity is due in significant measure to other conditions which will not be helped by the hypometabolic state and which may even be adversely affected should not be accepted for treatment. Included in this category are patients with emotional instability, particularly with depressions (see Cases 7, 10 and 17), patients with intermittent claudication of the legs (Case 11), patients with rheumatoid arthritis (Case 17) or active rheumatic fever, and patients prone to embolic phenomena which may dominate the clinical situation at any time (Case 18).

Patients with a rapidly progressive clinical course should not be treated. There is no reason to believe that the induction of hypothyroidism will retard the development of arteriosclerosis or impede the narrowing of the valvular orifices or retard active syphilitic aortitis. One should expect that although patients who show a rapidly progressive pretreatment clinical course may experience temporary and perhaps considerable improvement, they will probably succumb to the underlying disease process sooner than other patients with a less rapidly progressing condition. Patients with malignant hypertension and with syphilitic heart disease having a short but progressive history of failure are unfavorable candidates.

Since this form of treatment is based on a fall in metabolic rate and since most patients experience discomfort from myxedema at levels of −25 per cent or less, regardless of the pretreatment level, it is evident that patients with
initial basal metabolic rates of $-15$ per cent or less, can experience but relatively slight change before requiring thyroid. We have, therefore, with but one exception, not undertaken $I^{131}$ therapy in any patient with initial metabolic levels below $-15$ per cent. The one patient (Case 10) who constitutes the exception was relieved of angina pectoris when the basal metabolic rate was $-42$ per cent but experienced no worthwhile improvement when maintained at $-25$ per cent, which was practically identical with that before treatment.

In general, our results with patients with angina pectoris have been more striking than in those with congestive failure. In angina pectoris one is dealing with a solitary symptom which, when relieved or abolished, frees the patient from disability. In patients with congestive failure one usually can anticipate only partial relief from disability. If bedridden continuously with congestive failure, they may enjoy freedom from failure when up and about. If congestive failure develops on only mild exertion, they may enjoy a moderate increase in activity. With such increased activity, relief of dyspnea, paroxysmal nocturnal dyspnea, pulmonary edema and diminished frequency or abolition of injections of mercurial diuretics may be observed.

It may be helpful to state our present concept of a favorable candidate for $I^{131}$ therapy. The patient is between 40 and 60 years of age with angina pectoris due to coronary arteriosclerosis. He is alert, intelligent, cooperative, and emotionally stable. He has suffered from frequent attacks daily on slight to moderate exertion, such as walking short distances or a flight of stairs. He has night attacks, or attacks at rest or after meals, despite all available medical measures and despite curtailing his activities. Although his angina pectoris is severe, it has remained essentially unchanged for several years. The patient is not suffering from any concomitant disease. Although he has had one or more attacks of acute myocardial infarction, his economic status and occupation are such that, if relieved of some or all of his cardiac pain, he will not feel compelled to engage in arduous physical work. Physical examination discloses no significant abnormalities.

The blood pressure is normal or slightly elevated. The basal metabolic rate is above $-10$ per cent. Examinations of the blood, urine and stools reveal normal findings. Although a good therapeutic result is not invariable, our experience demonstrates that well over half of such patients will experience worthwhile improvement.

**Pre- and Post-Treatment Management**

Radioactive iodine therapy for euthyroid cardiac patients, as previously stated, is to be regarded as an adjunct; the patient's cardiac condition must continue to be treated with the same painstaking care previously exercised. Before administering $I^{131}$, we have placed the patients on a low iodine diet and have assured ourselves that stable iodine has not been received by the patient. The most common sources of iodine are in cough or other medicines, gall-bladder dye, antiluetic drugs or iodized salt. We have explained the present investigative nature of this form of therapy to our patients and have administered tracer doses of 100 or 150 microcuries. A dose of approximately 40 millicuries in our experience is usually effective in producing myxedema. To obviate the discomfort of possible thyroiditis, we recently have increased the total dose slightly and administered it in three divided doses at ten- to fourteen-day intervals. Twenty-four hourly collections of urine for three days following the tracer dose and again following each therapeutic dose have been measured for $I^{131}$ content. In some patients, the amount of $I^{131}$ uptake by the thyroid has been measured directly by the method devised by one of us.12

If the patient has a thyroid nodule, the possibility exists that $I^{131}$ will destroy the normal thyroid tissue, following which the adenoma may take on function. In at least one instance, however, the single initial therapeutic dose affected the nodule as well as the normal tissue with resultant hypothyroidism. In other patients, additional doses may be required to effect destruction of the adenoma.13

With the appearance of hypothyroidism, it has been our practice to permit frank myxedema to develop in order to learn the effects of $I^{131}$ uncomplicated by other medication. It is possi-
ble that patients may be safeguarded from some of the unpleasant symptoms of myxedema by administering small doses of thyroid before they reach markedly lowered levels of metabolic rates below −30 per cent. In a patient recently treated, but not included in this series, we have administered 6 mg. of thyroid daily after the basal metabolic rate had declined from −5 per cent to −20 per cent, at which latter level the patient was conspicuously relieved of attacks of angina pectoris but showed no discomfort from hypothyroidism.

Patients with myxedema are remarkably responsive to small doses of thyroid. The optimum metabolic rate level for each patient varies somewhat but is usually between −15 and −25 per cent. Fifteen milligrams of thyroid is usually sufficient to maintain this level, but in some patients only 6 mg. is necessary. Depending on the metabolic rate level and the severity of the symptoms of myxedema, if present, it has been our practice to initiate thyroid medication in doses of either 6 or 12 mg. daily (1/10 to 2/10 grain). In some patients, higher doses of thyroid are necessary, as in Case 14 who was maintained by daily thyroid doses of 90 mg. at a level of −15 per cent, compared to a pretreatment level of +20 per cent. In general, it has been our practice to begin with small doses and to raise the amount administered in accordance with the patient's symptomatology, basal metabolic rate measurements, and at times determination of the serum cholesterol concentration. All patients should be seen at least once a month, since it is entirely unnecessary for a patient to suffer from the distressing symptoms of myxedema.

Most patients feel so much better that they must be warned against overexertion. This procedure does not alter the underlying pathological process, and so it is important that they should not overtax themselves. Three of our patients, because of economic necessity, are working eight to twelve hours a day. While this is not advisable under ideal circumstances, 2 of the patients are highly intelligent and although performing manual labor, one as a foreman of bricklayers, and the other as a laboratory assistant, they are careful to avoid intense effort.

The social-economic problems in our patients have been many. While some patients must be warned not to overdo, others have their previous suffering so vividly before them that they must be encouraged to develop self-confidence and undertake moderate exercise. Fear of recurrence of angina pectoris or congestive failure in some patients presents a serious psychologic problem. Some patients, supported by other members of the family for years, are faced with the necessity of becoming self-reliant and independent on being relieved of their angina pectoris or congestive failure.

Problems Requiring Further Study

The final appraisal of this new therapeutic procedure awaits the results attained in numerous patients with various types of cardiovascular disease. Whether the duration of life is actually prolonged by this treatment can only be ascertained by studying the subsequent history of these patients over their entire clinical course. From our previous experience with total thyroidectomy, it would appear that in any case, duration of life is not shortened, and that undoubtedly many months of a worthwhile and comfortable existence already have been added to these invalided cardiac patients, many of whom have suffered greatly from recurrent attacks of angina pectoris, paroxysmal dyspnea, acute pulmonary edema, and the distressing symptoms of congestive failure.

Our previous experience with total thyroidectomy, as well as the results in Case 8, indicate that concomitant diabetes mellitus is ameliorated as judged by the lessened insulin requirement.

The hypothyroid state involves complex relationships between the thyroid, pituitary, adrenals, gonads and other endocrines. In accordance with our previous experience with total thyroidectomy, we have observed in the hypothyroid state that some of our patients became less irritable and more stable emotionally, a fact which suggests that induction of myxedema may be helpful in the care of unmanageable, disturbed psychotic patients who require forcible feeding and constant restraint.

The marked variation displayed by different patients in the symptomatology of myxedema suggests that the effects of the hypothyroid
HYPOTHYROIDISM PRODUCED BY RADIOACTIVE IODINE

state on the other endocrine glands may be responsible for some of these symptoms. If this proves to be the case, and if substitution therapy for the hypofunction of other endocrine organs can be given without raising the metabolic rate, some patients might be maintained in comfort at a lower and more beneficial metabolic rate. This problem is receiving further study by us and it is hoped that other investigators may also bend their efforts in this direction.

SUMMARY AND CONCLUSIONS

1. The therapeutic results of hypothyroidism induced by radioactive iodine in 18 euthyroid patients with intractable advanced angina pectoris or congestive heart failure are reported. The duration of post-treatment observation was seven to twenty-four months and averaged thirteen months.

2. Persistent hypothyroidism can be regularly induced by one or more appropriate doses of radioactive iodine (1131).

3. No radiation sickness and no toxic effects on the blood or kidneys have been observed. Mild or moderate transitory thyroiditis occurred in ten patients, was severe in only one, and was absent in seven. Temporary mild hyperthyroidism occurred in 2 patients.

4. Each patient received orally a total of 25.5 to 150 millicuries in single or divided doses, of which a total of 7.3 to 39 millicuries was retained within the body during the following seventy-two hours. The largest single dose was 56 millicuries.

5. The average total dose was 54.4 millicuries; the average three day retention, 17.9 millicuries.

6. Only patients were treated who were seriously incapacitated despite all standard forms of therapy and marked restriction of activities for many months or years.

7. Angina pectoris has been strikingly lessened or abolished in 8 of the 13 patients with intractable cardiac pain. Several patients have been rehabilitated and are gainfully employed. Concomitant congestive failure present in several of these patients was likewise improved. In the other 5 of the 13 patients, angina pectoris was greatly relieved when the patients were myxedematous but recurred when thyroid was administered to ameliorate the discomfort of myxedema.

8. Three of 5 patients incapacitated primarily because of congestive heart failure have shown worthwhile improvement; in 2 of these the improvement has been striking.

9. Tentative criteria for the selection of patients are presented, and the pre- and post-treatment management of the clinical course is described.

10. In the clinical management of these patients, we have attempted to maintain the lowest metabolic rate consistent with the comfort of the patient and have administered small doses of thyroid after the induction of myxedema.

11. This group represents the intractable cardiac cripples who are ordinarily considered for surgery. Hypothyroidism induced by radioactive iodine promises to accomplish worthwhile improvement through medical means without the inevitable risk and complications of surgical intervention.

12. This procedure is therefore proposed as a means of treating angina pectoris and congestive failure refractory to the standard medical measures and is submitted for further investigation by other workers in this field.

13. Final evaluation of this therapy must await prolonged study. At present it can be said that many months of worthwhile existence already have been added to the lives of these disabled cardiac patients who were refractory to all standard forms of medical therapy.

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Hypothyroidism Produced by Radioactive Iodine (\( ^{131}I \)) in the Treatment of Euthyroid Patients with Angina Pectoris and Congestive Heart Failure: Early Results in Various Types of Cardiovascular Diseases and Associated Pathologic States

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