The Lewis A. Conner Memorial Lecture

The Heart and the Thyroid: with Particular Reference to I\textsuperscript{131} Treatment of Heart Disease

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The physiologic, pathologic, and clinical interrelationships between the thyroid and the cardiovascular system are discussed. The therapeutic effects of hypothyroidism induced by I\textsuperscript{131} to lessen the work of the heart are described in 39 euthyroid patients with intractable advanced angina pectoris or congestive failure. Only patients were treated who were seriously incapacitated despite all conventional forms of therapy for many months or years. The results of two confirmatory series of cases similarly treated by others are reviewed.

We are assembled here at this time to express our respect and esteem for Dr. Lewis Atterbury Conner through this lectureship established in his honor. In reality, all the activities of the American Heart Association are a lasting tribute to him. For he was one of its founders, the creator and first editor of the American Heart Journal. Particularly at this moment, six months after his death on December 4, 1950, it is gratifying to know, that regardless of the time and the place of our meetings, and regardless of the changing program committees, Dr. Lewis A. Conner will always, through this lectureship, participate in the scientific proceedings of our association.

But long before his 83 years had ended, he had become an unforgettable legend. For his was a vibrant and compelling personality. Poise, reserve, dignity, and an almost austere rectitude characterized the immediate impact on meeting him. Sympathy, warmth and wisdom were lavished generously on patient or friend.

His place in the history of medicine is assured by genuine scientific achievement based on bedside experience. His numerous publications cover practically every aspect of the cardiovascular system and repeated reference is made to the effects of the thyroid. The subject of the lecture today, “The Heart and the Thyroid; with Particular Reference to I\textsuperscript{131} Treatment of Chronic Heart Disease” seems, therefore, appropriate.

The interrelationship of the thyroid and the heart has enjoyed a long and honorable tradition. Parry’s original description of exophthalmic goiter in 1786, published in 1825,\textsuperscript{1} is recorded, indeed, as a form of heart disease at the beginning of the chapter entitled “Diseases of the Heart.” Parry thereupon describes the clinical manifestations of exophthalmic goiter and their association with congestive failure and angina pectoris in these patients. With the exacerbation of the signs and symptoms of toxic goiter, evidences of congestive failure and/or angina pectoris became more severe. He also notes the parallel subsidence of both groups of manifestations. With the advent of operative treatment, made possible by the work of Billroth\textsuperscript{2} and the classic contribution of Kocher,\textsuperscript{3} the beneficial effect of thyroidectomy on congestive failure was clearly stated. In the latter part of the nineteenth and the preceding decades of the twentieth century, clinical interest was awakened in various types of thyrotoxicosis, in which several or many

Presented at the scientific session of the Twenty-fourth Annual Meeting of the American Heart Association, Atlantic City, N. J., June 9, 1951.

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This work was carried out under a contract between the Office of Naval Research, the Atomic Energy Commission and the President and Fellows of Harvard College. This investigation was also aided by a grant from the United States Public Health Service and by funds of the Patrons of Research, Beth Israel Hospital, Boston, Mass.
of the characteristic features are absent but in which the manifestations of coexistent heart disease are markedly ameliorated or even abolished after appropriate treatment of the thyrotoxicosis. Interest in the subject in this country may be gaged by the fact that the 1932 meeting of the American Heart Association was devoted entirely to a symposium on "The Thyroid Heart."

The effect of the hyperactive thyroid on the cardiovascular system has been studied extensively. Important insight has been gained into the meaning of the signs and symptoms of hyperthyroidism that are commonly attributed to heart disease.

![Figure 1](image.png)

**Fig. 1.** Relation of the velocity of blood flow through the lungs and basal metabolic rate in patient M. C. Subtotal thyroidectomy was performed during the fourth week of observation.

**Velocity of Blood Flow**

That the speed of blood flow is increased greatly in thyrotoxicosis was shown in 1927 and 1928. We injected the radioactive deposit of radium emanation, that is, radium C, and, by means of Geiger Counters, measured the pulmonary circulation time. The proportionality between the speed of blood flow and the basal metabolic rate is shown in figure 1.

**Minute Volume Output of the Heart**

The patient with hyperthyroidism has a greatly increased cardiac output. Recent studies employing the direct Fick principle by means of catheterization show that with increases in the metabolic rate averaging 35 per cent above normal, cardiac output increases 45 per cent above normal. Under such circumstances the cardiac output in thyrotoxic patients at rest corresponds to that of normal individuals doing light work. This increase in minute volume output is accomplished by increasing the number of heart beats, at times by an increase in the output of blood per beat or by a combination of both. The work of the heart is increased not only at rest but even more on effort. Plummer and Boothby, many years ago, observed that a given amount of effort produces a disproportionate rise in output in patients with hyperthyroidism as compared with normal subjects; the "cost of work" is great.

The increased output of the heart in hyperthyroidism evidently serves two main purposes. More blood is supplied to sustain the increased oxygen consumption of the tissues of the body. Also, the body temperature is held constant by a greatly increased blood flow through the skin, with dissipation of the increased heat generated within the body. The internal environment of the body is maintained thereby at a normal temperature. It recently has been shown by Stead and his associates, indeed, that the increased output of the heart in hyperthyroidism is distributed mainly to the skin, muscles and kidneys; the brain and splanchnic area receiving little or no increased blood supply. The blood and extracellular fluid volume is also increased; the increased pulmonary blood volume leads to a diminished vital capacity and dyspnea.

The cardiovascular manifestations of hyperthyroidism are not to be considered merely as an expression of hypermetabolism. The effects of overactivity of the thyroid on other endocrine organs, on many metabolic processes, and on the central and autonomic nervous systems are of unquestionable importance; their exact nature and influence on the cardiovascular system are still imperfectly understood. The increased sensitivity of the thyrotoxic patient to epinephrine is striking. The susceptibility of the heart in hyperthyroidism to develop auricular fibrillation, auricular flutter, and other arrhythmias is well known, occurring in continuous or paroxysmal forms in about 10 per cent of the patients. The responsible mechanisms for these arrhythmias are not wholly clear despite certain classic contributions including those of Nahum and Hoff.
In regard to the tachycardia of hyperthyroid animals, it has been shown that this will persist after the heart has been isolated from the peripheral vascular tree and from all neural pathways. Markowitz and Yater, moreover, showed that thyroxin causes "tachycardia" to occur in fragments of heart muscle removed from two-day chick embryos before any nerve cells within the heart or neural pathways to the heart have been formed.\textsuperscript{13} Although the available data are not conclusive as to the precise mechanism by which thyroid hormone affects cellular metabolism, some of the critical enzyme systems are evidently implicated.\textsuperscript{14, 15}

The foregoing cardiovascular deviations clarify the meaning of the clinical signs and symptoms of palpitation, tachycardia, increased pulse pressure, and cardiac overactivity with vigorous heart sounds and systolic murmurs. The increased pulmonary blood volume and decreased vital capacity predispose to dyspnea, especially on relatively moderate effort. Slight or moderate cardiac enlargement has been reported in approximately 50 per cent of cases of uncomplicated hyperthyroidism by various observers. In the absence of coexistent organic disease much, if not all, of this enlargement may be due to dilatation. Extreme degrees of cardiac enlargement, rarely if ever occur. When such a finding is encountered, it is usually safe to assume that much of the enlargement has resulted from coexisting non-thyrogenous heart disease.

The fundamental genesis of the exaggerated cardiovascular response in hyperthyroidism presents many gaps in our knowledge. No constant, specific myocardial lesions are found in the hearts of patients who have died of thyrotoxicosis. Varying degrees of lymphocytic infiltrations, spotty degeneration, fibrosis, fragmentation and segmentation of muscle fibers, etc., have been observed, but such changes occur with almost equal regularity in the hearts of patients dying of other causes.

\textbf{Angina Pectoris and Congestive Heart Failure}

Opinions differ as to whether angina pectoris or congestive heart failure ever occur in thyrotoxicosis without coexistent heart disease. Clinically, however, there can be no question but that alleviation of the hyperthyroidism in many instances is accompanied by marked amelioration or even complete disappearance of the angina pectoris and congestive heart failure. Such patients may have a degree of coronary arteriosclerosis or other organic lesions which, by themselves, are insufficient to cause clinical manifestations in the absence of the additional strain imposed by hyperthyroidism. The degree of relief of congestive failure and angina pectoris is so remarkable that "thyroid heart disease" is often classified as one of the "curable" forms of cardiovascular disorders. Congestive failure frequently masks the clinical hallmarks of hyperthyroidism. Particularly in the older age groups, all eye signs, tremor and nervousness may be absent, the thyroid normal in size. The vigorous and roughened first heart sound with apical pre-systolic murmur and thrill, the systolic murmur, cardiac enlargement, or auricular fibrillation and rapid rate in the presence of congestive failure may lead to an erroneous diagnosis of mitral valvular disease.

The diagnosis frequently will be missed and the crippled cardiac patient will be deprived of his only opportunity of recovery unless we suspect the presence of thyrotoxicosis in one of its manifold manifestations in every cardiac patient and assure ourselves of its presence or absence.

We do not believe elaborate studies are indicated in every cardiac patient. The skillful history and physical examination will provide the clues. Unexplained loss of weight, palpitation, emotional instability, weakness, increased fatigability, increased sensitivity to warmth may be elicited from the patient's history of his illness. Inspection may reveal the flush, a slight stare or minimal exophthalmos, infrequent winking, thyroid enlargement, increased pulsation of the peripheral arteries. Moist warm hands, tachycardia, hyperactive heart sounds, widened pulse pressure, unexplained auricular fibrillation or congestive failure responding unsatisfactorily to digitalis and diuretics call for further exploration of the possibility of thyrotoxicosis. Such definitive studies may include measurement of the metabolic rate, serum protein-bound iodine, and thyroid uptake of tracer doses of I\textsuperscript{131}.
The induction of hypometabolism to alleviate intractable heart disease in patients with normal thyroid function is a natural extension of the favorable cardiovascular effects of lowering the high metabolic rate of thyrocardiac patients to normal. Various circulatory studies lent support to this concept. In patients with congestive heart failure and a normal basal metabolic rate, measurements of the velocity of blood flow had shown considerable slowing; the retardation in the velocity of blood flow generally paralleled the degree of circulatory insufficiency. In patients with myxedema but without congestive failure, "the degree of

slowings was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of test. . . . The fact that the myxedematous patients showed no evidence of circulatory insufficiency with a speed of blood flow approximately the same as that of the latter group again emphasizes the fact that the question of whether a given speed of blood flow is adequate can be decided only in relation to the metabolic needs of the tissues."17 It was, therefore, considered that "if the normal metabolic rate of the patient with congestive heart failure (or angina pectoris) was reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of the body."17 The metabolic demands would be reduced to a level to conform to the blood supply (fig. 2).

**Surgical Total Thyroidectomy**

The validity of this hypothesis was confirmed by the results obtained following surgical total thyroidectomy in over 350 patients with intractable angina pectoris or congestive failure operated upon in 26 different clinics.18, 19 More than 50 per cent of the patients obtained distinct relief of angina pectoris or congestive heart failure and a definite correlation was observed between the degree of induced hypothyroidism and clinical improvement. The magnitude of the operation in these patients with advanced heart disease and the occurrence of surgical complications and progression of the underlying disease, which prevented worthwhile results in approximately one half of the patients, precluded adoption of the procedure as a generally applicable practical measure.

**Medical Total Thyroidectomy**

Following the demonstration of the therapeutic benefit of the thiourea derivatives in thyrotoxicosis, these agents, including propylthiouracil have been utilized in euthyroid patients with angina pectoris or congestive failure in order to attain the hypometabolism of total thyroidectomy. Favorable effects have been reported by certain observers.20-25 Unfortunately, however, hypothyroidism can be induced in only some patients. Moreover, to maintain the hypothyroid state, 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.26-32

The availability of radioactive iodine (I131) led us to investigate its possible use to produce hypometabolism in euthyroid cardiac patients. Since the beginning of our investigation, four years ago, in March 1947, our efforts have proceeded in four main directions: (1) the clinical appraisal of the therapeutically value of the procedure; (2) study of possible deleterious radiation effects: (3) establishment of criteria

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**Fig. 2.** Relationship between the basal metabolic rate (black areas) and the velocity of blood flow (stippled areas).
for the proper selection of patients; (4) investigation and control of the secondary consequences of the hypothyroid state.\textsuperscript{35-38}

In the appraisal of therapy of angina pectoris and congestive failure, it is necessary to bear in mind that the clinical course is often irregular and characterized by periods of unexpected remission and improvement. We, therefore, have selected only patients who, despite marked restriction of activities for many months or years, showed evidence of continued incapacity after having received all standard forms of therapy and in whom remissions of the disease were absent or who continued to suffer signs and symptoms even during periods of slight remission. 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 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\textsuperscript{56} and other tests, over a period of many weeks or months before radioactive iodine therapy was instituted. Following the administration of I\textsuperscript{131}, the period of 6 to 26 weeks before the development of definite hypothyroidism served as an additional control period.

Results in 26 Patients with Angina Pectoris Observed 12 to 40 Months After Treatment (Average 24 Months)

The severity of cardiac involvement in these patients is reflected by the fact that 27 attacks of acute myocardial infarction had occurred in these 26 patients prior to treatment (table 1). The etiology of the angina pectoris was coronary arteriosclerosis in all. Arterial hypertension with blood pressures ranging from 160–200/90–120 was present in nine. Three other patients died of probable acute myocardial infarction one to three months after treatment, but before hypothyroidism became evident, and accordingly, have not been included.

In the 26 patients with angina pectoris rendered hypothyroid by I\textsuperscript{131}, the therapeutic result has been decidedly worthwhile in 19. In each instance, the patient has been able to undertake activities which had been impossible for many months or years prior to treatment.

| TABLE 1.—Summary of Results in 26 Cases of Angina Pectoris and Arteriosclerotic Heart Disease |
|-----------------------------------------------|-----------------|
| I. Clinical data                              |                 |
| Ages                                           | 38-72 yrs.      |
| Sex: Male                                      | 20              |
| Female                                         | 6               |
| Duration of angina pectoris                    | 1-18 yrs.       |
| Number of prior myocardial infarctions         | 27              |
| Etiologic basis for angina pectoris            |                 |
| a. all arteriosclerotic heart disease          |                 |
| b. patient with serologie syphilis             | 1               |
| c. diabetes mellitus                           | 3               |
| d. arterial hypertension                       | 9               |
| II. I\textsuperscript{131} therapy            |                 |
| Dose administered—total, each patient         | 26-206 mc.      |
| Average total dose each patient                | 78 mc.          |
| Average single dose                            | 29 mc.          |
| Number of patients with hypometabolism         | 26              |
| Duration of follow-up                          | 12-40 mos.      |
| (av. 24)                                      |                 |
| III. Therapeutic results                       |                 |
| Excellent                                     | 9               |
| (av. follow-up 27 mos.)                       |                 |
| Worth while                                   | 10              |
| Not worth while                               | 7               |

In 9 of these 19 patients, the results have been rather remarkable. Angina pectoris has been abolished or only occasional attacks have occurred despite greatly increased activity. The duration of angina pectoris before I\textsuperscript{131} treatment in these 26 patients was from four months to 15 years and averaged 5.6 years. Four male patients have become gainfully employed whereas prior to treatment they had been largely incapacitated for years because of inability to undertake minimal effort without
symptoms. The following cases are illustrative:

Case 1—Angina pectoris, one year. Status anginosus. Coronary atherosclerosis. Old myocardial infarction. Myxedema induced by four doses of I\textsuperscript{131} totalling 150 mc;\textsuperscript{*} retention by the body 18 mc. Symptoms of myxedema controlled by 30 mg. thyroid daily. Practically complete disappearance of angina pectoris and patient gainfully employed, working eight hours a day as a laboratory assistant for the past 27 months.

J. L., a 41 year old man (B.I.H. \# 69433), was referred through the courtesy of Dr. J. E. F. Rirmian. One year prior to I\textsuperscript{131} therapy, attacks of substernal pressure on exertion and emotion were first noted, and an attack of acute myocardial infarction occurred eight months before treatment. He had been unable to work during the nine months before treatment and had been restricted largely to the house because walking even a hundred feet precipitated an attack. He was awakened from sleep by anginal attacks, often suffering three or four episodes nightly. He noted increasing dyspnea and used two pillows. In the month prior to I\textsuperscript{131} 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.

Physical examination revealed entirely normal findings. The blood pressure was 110/80. The urine and blood were normal. On x-ray examination, the heart was normal in size and shape. The electrocardiogram showed changes consistent with an old posterior infarct.

Post-treatment Course. On April 27, 1948, he received 29 mc. I\textsuperscript{131}; three additional doses of 43, 39 and 39 mc, were administered on July 23, August 13, and November 22, 1948, respectively. Five weeks after the first dose of I\textsuperscript{131}, 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 of hypothyroidism were present. The next few weeks, angina pectoris reverted to the pretreatment severity and frequency; the basal metabolic rate and serum cholesterol values likewise had reverted toward normal. Additional doses led to hypometabolism, marked improvement, and finally, complete disappearance of angina pectoris. In repeated exercise tolerance tests,\textsuperscript{23} 45 to 50 trips were performed without anginal pain; the patient stopped exercise at our request or because of fatigue.

\textbf{Fig. 3.} Case J. L.—The serum cholesterol, basal metabolic rate, and the clinical course following five doses of I\textsuperscript{131} totalling 150 mc.

\textsuperscript{*} The millicurie in these studies conforms to the Bureau of Standards millicurie.

peated pretreatment exercise tolerance tests averaged 30 trips and were invariably halted because of cardiac pain. He has been gainfully employed, working eight hours a day for the past 27 months, experiences no angina except on very strenuous exertion, and is not troubled by symptoms of myxedema. On a daily dosage of 30 mg. of thyroid, the basal metabolic rate is maintained at minus 25 per cent; the serum cholesterol is 900 mg. per 100 cc.

Case 19—Arterial hypertension. Three prior myocardial infarctions. Angina pectoris for 10 years, severe and disabling for the past nine, markedly restricting activity and requiring frequent nitroglycerine and Demerol for relief. Myxedema induced by six doses of I\textsuperscript{131} totalling 150 mc., with 20 mc. retained in the thyroid. Striking relief of angina pectoris for 12 months despite greatly increased activity. Recurrence of angina pectoris during subsequent 12 months but less severe than before treatment, maintenance of increased activity.

L. A., a 67 year old woman, had had angina pectoris for 10 years, and was referred through the courtesy of Dr. Paul D. White, who had observed the patient for five years. She had suffered three myocardial infarctions eight, five, and one year before I\textsuperscript{131}. During the four years before I\textsuperscript{131} treatment
she was largely housebound and suffered attacks daily, not only on effort but on excitement and at night. Despite marked limitation of activity, approximately 60 nitroglycerine tablets and frequent injections of Demerol were required each week.

On physical examination, the heart was enlarged to the left; the rhythm was regular; soft apical and basal systolic murmurs were audible. The blood pressure was 164/92. A small nodule was felt at the right lower pole of the thyroid. The basal metabolic rate was −5 per cent and the serum cholesterol 425 mg. per 100 cc. Electrocardiogram showed left bundle branch block.

I\textsuperscript{131} treatment was begun on April 18, 1949. Four doses totalling 84 mc. were administered. Striking improvement manifested by freedom from angina pectoris despite increased activity was first noted 10 weeks after treatment and was maintained 14 months. Two additional doses totalling 46 mc. were administered when hypometabolism diminished. The basal metabolic rate has been maintained at −20 per cent; the serum cholesterol at approximately 460 mg. per 100 cc. On 12 mg. of thyroid daily, she experiences only slight discomfort from the hypometabolic state. During recent months the clinical course has been uneven. She has experienced no attacks for weeks and at other times, especially when under emotional stress, has had as many as five attacks daily. At no time have the attacks been as severe as before treatment. She has been able to maintain a level of activity considerably above that before I\textsuperscript{131} treatment.

Another patient, R. A., 62 years of age, a bricklayer, had had severe angina pectoris for three years and had been invalided at home since acute myocardial infarction and pulmonary edema 14 months before treatment. He suffered frequent attacks of paroxysmal nocturnal dyspnea. Following three doses of I\textsuperscript{131}, myxedema was produced with complete remission of all cardiac symptoms. He has been maintained on 30 mg. thyroid daily at a basal metabolic rate of −20 per cent, a serum cholesterol level of 350 mg. per 100 cc. and has not been troubled by symptoms of hypometabolism during the post-treatment period of 39 months. He has been gainfully employed as a foreman of bricklayers, work requiring considerable physical activity, for one year. Similar striking results have been obtained in six other patients.

In the remaining 7 of the 26 patients with angina pectoris, the therapeutic result has not been worthwhile. Two of the seven patients died, 12 and 19 months after receiving treatment with I\textsuperscript{131} (cases 10, 11). In one case (case 8), angina pectoris was relieved for six months but has relapsed to pretreatment status. In the other four patients, the results were unsatisfactory.

**The Effect of Hypothyroidism on Congestive Heart Failure, Paroxysmal Nocturnal Dyspnea and Pulmonary Edema**

Thirteen of the 39 patients were incapacitated primarily because of congestive heart failure (table 2). In six patients the results have been worthwhile; in seven they have not been worthwhile. The duration of the worthwhile improvement in the six patients has been 9 to 35 months to date (average 20 months). In four, 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 or disappearance of peripheral edema and of pulmonary congestion. In patient

![Fig. 4. Case L. A.—The serum cholesterol, basal metabolic rate, and the clinical course following administration of I\textsuperscript{131}.](http://circ.ahajournals.org/lookup/fig/10.1161/01.CIR.1.2.228.f1)
M. G., orthopnea and ascites have disappeared, the liver is no longer palpable, cyanosis has disappeared and the vital capacity of the lungs has increased from 2,200 cc. to 3,650 cc. Incapacitated for one and one-half years before treatment, the patient has been able to engage in useful activity during the past 26 months.

Four patients with congestive failure have died, one patient after showing definitely worthwhile improvement for 20 months. The other

Case 15. Hypertensive and arteriosclerotic heart disease. Two previous attacks of acute myocardial infarction seven and five years before 17th. Chronic renal disease with one remaining kidney. Chronic severe congestive heart failure. Auricular fibrillation. Myxedema induced by two doses of 131I totaling 57.5 mc. with marked improvement for 30 months in all manifestations of congestive failure. Amount retained in body 39 mc. A striking therapeutic result.

Pretreatment History. M. G., a 44 year old male and a former automobile mechanic (B.I.H. §17579), had had arterial hypertension for nine years, and had had two prior attacks of acute myocardial infarction. One and a half years before treatment, ankle edema and dyspnea appeared, the blood pressure was 290/120, a nonfunctioning kidney was demonstrated and a left nephrectomy was performed. The blood pressure was reported 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 slightly during seven weeks of hospitalization.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic and slightly cyanotic. The salient findings were as follows: blood pressure of 130/80, distended neck veins, signs of right hydrothorax; with moist rales at both bases, marked enlargement of the heart, grossly irregular rhythm, a grade I apical systolic murmur, protuberant abdomen. The liver was firm, nontender and enlarged five fingerbreadths below the right costal margin. The splenic tip was palpable. Pitting edema over the sacrum was 2 plus, and over the ankles, 1 plus.

Pretreatment Laboratory Examination. The urine specific gravity was 1.019, with 2 to 4 plus albumin; the sediment showed 1 to 10 white cells, occasional erythrocytes and fine granular casts. Blood was normal except for the nonprotein nitrogen which was 54 mg. per 100 cc. Electrocardiograms showed auricular fibrillation and evidence of old posterolateral infarction and left ventricular hypertrophy.

Post-treatment Course. On October 12 and October 23, 1948, the patient received 27 mc. and 30.5 mc. 131I, respectively, and retained 39 mc. in the body (fig. 5). For two months after treatment, he remained seriously ill with no significant change in his congestive failure. At the beginning of the third month post-treatment, the evidences of hypothyroidism, including a rise in the serum cholesterol occurred, and he exhibited progressive improvement.

During the past 30 months, he has been able to

### Table 2. Summary of Results in 18 Cases of Congestive Heart Failure

| I. Clinical data |  
| Ages: Male | 31-70 (av. 49) 
| Sex: Male | 6 
| Female | 7 
| Rheumatic heart disease | 8 
| Hypertension: arteriosclerotic heart disease | 5 
| Prior myocardial infarctions | 3 
| Duration of congestive failure | 6 mos.-17 yrs. (av. 5 yrs.) |

| II. 131I therapy |  
| Dose administered—total, each patient | 25.5-125 mc. 
| Average total dose, each patient | 61 mc. 
| Average single dose | 26 mc. 
| Follow-up | 5-37 mos. (av. 20) |

| III. Therapeutic results |  
| Excellent |  
| (av. follow-up 25 mos.) | 4 
| Worth while | 2 
| Not worth while | 7 |

three patients died, 2, 4, and 18 months after the induction of hypothyroidism without significant improvement.

In addition to the foregoing 13 patients, symptoms and signs of congestive failure were present in many of those incapacitated primarily because of angina pectoris; 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. The following cases are illustrative:
undertake considerable activity, including doing some carpentry and considerable walking, without developing dyspnea. Orthopnea requiring six to eight pillows disappeared and is no longer present. He now sleeps on one pillow. The patient states that he has not felt this well since several years prior to treatment. Venous distention has disappeared 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 electrocardiogram is unchanged. Venous pressure has been 100 mm. of water (compared to 260 mm. before treatment), vital capacity 3,300 cc. (compared to 2,200 cc. before treatment), and the arm-to-tongue circulation time 30 seconds. The nonprotein nitrogen has remained approximately 60 mg. per 100 cc. The period of marked and sustained improvement is now 30 months.

Mrs. R. K., 49 years of age, was referred to us in 1949 for radioactive iodine treatment by Dr. Paul D. White. She had had acute rheumatic fever at 13 with subsequent aortic and mitral valvular involvement. There was progressive loss of functional reserve requiring termination of second pregnancy at 29 years of age, 20 years before the present admission. During the four years before treatment she had had cough, dyspnea, orthopnea, ankle edema, episodes of paroxysmal nocturnal dyspnea, and pulmonary edema despite repeated injections of mercurial diuretics, salt-free diet, digitalis, ammonium chloride. She had been confined to a bed-and-chair existence and required oxygen therapy intermittently. On hospitalization elsewhere under the care of Dr. White, her congestive failure had been refractory to all medical measures.

Physical Examination. The patient was a thin, fairly well-developed woman with moist rales at the right base, heart enlarged to the anterior axillary line, physical signs of mitral and aortic stenosis occasionally, requires mercurial diuretics once a week, and has lost the edema of her legs. The vital capacity has increased to 1,800 cc. She has been able to be up and around outdoors and not infrequently goes to theater or dinners. She takes daily doses of thyroid, alternating between 12 and 18 mg. (3/16 and 3/10 grains). Dr. White has expressed the following opinion: "I believe that Mrs. K. has been a striking success of irradiated iodine therapy in the control of her congestive heart failure. She has survived two years despite a good deal of strain. I am convinced that she would have died at least a year and a half ago if she had not had irradiated iodine therapy."

**DISCUSSION**

*Possible Toxic Radiation Effects*

Throughout our investigation, we have been concerned with possible adverse radiation effects. Before the therapeutic studies of the present communication were undertaken, ob-

![Fig. 5. Case M. G.—The vital capacity, venous pressure, and serum cholesterol following administration of I131.](image-url)
servations were made with gradually increasing doses in euthyroid patients in terminal state. The results of these studies indicated that persistent hypothyroidism could be induced by one or more appropriate doses. Radiation sickness has not been observed in any patient in our series. Similarly, extensive examinations of the blood, urine, liver, and kidney function, have revealed no toxic effects. The distribution of radio-iodine in organs other than the thyroid has been studied and histologic examinations carried out in a smaller series of patients have been in accordance with the above findings and with the data of others.

![Graph](https://via.placeholder.com/150)

**Fig. 6.** Results in 39 euthyroid patients with angina pectoris and congestive failure treated with I$^{131}$.

**General Appraisal of Results**

Each of the patients selected for treatment had received all the conventional medical measures, and, nevertheless, had remained incapacitated for months or years. While unexpected improvement in such patients occasionally occurs, the rather remarkable improvement observed in approximately one third of all patients treated, and the satisfactory improvement experienced by another third of the patients has been impressive (fig. 6).

It was of considerable interest to observe the relation between clinical improvement and the occurrence of hypometabolism. The irregular interval of five weeks to six months after I$^{131}$ treatment, before hypothyroidism becomes evident, is a helpful safeguard against the possible confusing effect of suggestion. Neither physician nor patient can foretell the time at which hypometabolism and clinical improvement will occur. The clinical improvement, first noted by the patient and later found to be coincident with the inception of hypometabolism when the results of the serum cholesterol and basal metabolic determinations are made available, is consequently the more impressive. Conversely, some patients who showed thyroiditis one to two weeks after I$^{131}$, with pain, tenderness, and increased heat over the thyroid area, noted that their condition was definitely worse. In some of these individuals the basal metabolic rate had increased slightly and the serum protein-bound iodine had risen. The correspondence between metabolic levels and clinical cardiac status was observed on 31 occasions in the first 23 patients treated.

**Selection of Cases for Treatment**

This method of treatment is not advised for most patients with angina pectoris and congestive failure. For most patients with angina pectoris and congestive failure, medical treatment successfully alleviates discomfort and provides increased capacity for a satisfactory program of life. In some patients, rapid progression of disease or complications such as acute myocardial infarction or embolic phenomena terminate life after a relatively brief intermediate period of severe discomfort or marked restriction of activity.

There is, however, a relatively small group of patients with angina pectoris or congestive failure, who remain incapacitated and in great discomfort despite all available measures. The disease process is apparently relatively stationary for months or years; the patients enduring great discomfort from congestive failure, or numerous attacks of angina pectoris daily, despite all medical measures. For these patients afflicted with severe angina pectoris, various surgical measures such as sympathectomy, posterior rhizotomy, omentopexy, pericoronary neurectomy, have been advised. For some of these patients radioactive iodine therapy offers the possibility of considerable improvement without the pain and the inevitable hazards of surgery.

Although it is too early to formulate final
indications and contraindications, it is nevertheless desirable to offer a tentative opinion regarding the criteria for the proper selection based on our experience in these 39 patients observed after treatment, on the average, for 23 months.

Unfavorable factors which incline us to advise against treatment may be summarized as follows:

1. Rapidly progressive cardiovascular disease (malignant hypertension, syphilitic cardiovascular disease). There is no reason to believe that hypothyroidism retards the progression of the underlying pathologic process. Even though the patient may experience improvement for a few weeks or months after treatment, a relapse to his former clinical condition is likely to occur if a rapidly advancing pathologic process underlies his difficulties. It is also unwise to treat patients who are in the terminal phases of their disease, particularly since five weeks to six months intervene before the hypometabolic state is attained. However, the presence of moderate or even marked hypertension does not contraindicate the treatment.

2. Hypothyroidism; low basal metabolism. The presence of pre-existing hypothyroidism represents a contraindication to treatment. Patients with a basal metabolic rate of −15 per cent or lower, while they may be relieved of their symptoms when myxedematous at −35 or −40 per cent, often suffer a recurrence of their symptomatology when maintained at the necessary level of −20 to 25 per cent, which is only slightly below their pretreatment level.

3. Associated conditions. The presence of other conditions which may incapacitate the patient and becloud evaluation of this method of treatment constitutes a contraindication. These include active infection such as rheumatic fever, bronchiectasis, emotional instability, cirrhosis of the liver and recent acute myocardial infarction. Intermittent claudication is not benefited by the induction of hypometabolism; on the contrary it may be aggravated and constitutes a definitely unfavorable factor. Similarly, the symptoms of severe painful hypertrophic arthritis may be aggravated.

Favorable Factors. Patients who may be expected to gain the greatest benefit are those in whom the disease has been relatively stationary or only slightly progressive over a period of one or more years. Even though such patients may be seriously incapacitated and may have angina pectoris at rest in bed, if their condition has been quite stable over a period of three months or more, a favorable response to this treatment is likely. Patients with congestive failure should show evidence of some cardiac reserve, such as ability to lose the signs of congestive failure on rest in bed or with the use of diuretics and digitalis. The basal metabolic rate should be above −15 per cent. It is also important that the patient be alert, cooperative and emotionally stable.

When patients are frankly myxedematous with basal metabolic rates of −30 to −40 per cent they are often irritable and nervous. On receiving small doses of thyroid to maintain them at a level of −15 to −25 per cent, they are frequently more stable emotionally than before treatment, and mentally as acute as formerly. In an occasional patient, such as J. K., 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.” The precise mechanisms responsible for these effects are not clear though the adrenal and other endocrine organs may well be involved.

Program of $^{131}$I Treatment

Our present program of treatment entails the following measurements and observations: in every instance tracer doses of 100 to 150 µc. of $^{131}$I are administered. On the basis of uptake measurements an initial dose of 20 to 30 mc. is given, which delivers approximately 40,000 equivalent roentgens.

Following the administration of the therapeutic dose, similar measurements by direct counting are made of the uptake of the therapeutic dose by the thyroid 24, 48, and 72 hours after its administration to ascertain the amount of the therapeutic dose retained in the thyroid. It is, of course, imperative to instruct all patients regarding the safety precautions relative to contamination of clothing and skin, storage of urine immediately following the
therapeutic dose, and other necessary safeguards. Although approximately two-thirds of the patients have exhibited mild to moderate thyroiditis lasting 1 to 10 days after therapy, it has been severe in only one instance. No treatment except the use of analgesics has been indicated. Inasmuch as thyroid hormone is apparently released during the stage of thyroiditis, the activities of the patient should be reduced to a minimum during this time.

In our experience hypometabolism has developed five weeks to six months following an adequate dose of I\(^{131}\). When patients do not develop hypometabolism within several months, it has been our practice to administer additional doses after preliminary tracer dose studies to determine whether residual thyroid tissue capable of taking up I\(^{131}\) exists. In a significant proportion of patients additional doses of I\(^{131}\) are necessary. As many as four and five doses at various periods of time have proved to be necessary, but in each instance myxedema was finally achieved.

A simpler program of treatment has been employed by Wolferth and his associates with apparently successful results.\(^2\) They have administered a single dose of approximately 10 to 20 mc. after preliminary tracer doses. This has resulted in a satisfactory depression of thyroid function in many of their patients. Some of these patients have been maintained without additional doses of I\(^{131}\) and have required no thyroid medication. Others have required additional doses of I\(^{131}\). If troublesome symptoms of hypothyroidism or myxedema ensue, 6 to 30 mg. of thyroid substance are administered daily. Jaffe and his associates\(^4\) at the Cedars of Lebanon Hospital, Los Angeles, have administered a dose of approximately 6 mc. each week for five weeks. Two months after completion of the first course of 30 mc., the patient is re-evaluated. If there has not been sufficient improvement, and if the patient is not hypothyroid, a second course of weekly treatments is given. The patient is re-evaluated after two months and, if necessary, a third course is given. The relative merits of these programs must await the results of extensive experience.

Repeated administration of I\(^{131}\) is particularly indicated when thyroid adenomata are present. In some patients, these adenomata are plainly evident at the time of initial examination. In others they have become apparent only after the normal thyroid has disappeared following the first one or two doses of I\(^{131}\). Presumably these nodules are initially nonfunctioning and do not take up I\(^{131}\) until the normal thyroid tissue has been destroyed. The adenomata apparently then begin to function and may be affected by subsequent doses of I\(^{131}\). Subsequent doses are frequently followed by tenderness of the nodule, its gradual disappearance, and the induction of myxedema with its characteristic clinical manifestations.

It has been our practice to permit marked hypothyroidism or, in some instances, even complete myxedema to develop to assure ourselves that all thyroid tissue has been affected and then to give 6 or 12 mg. of thyroid (\(\frac{1}{2}10\) to \(\frac{3}{10}\) grain) daily. In each patient, thyroid dosage has been adjusted to maintain the patient at the lowest metabolic level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain individuals this may not be possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid is administered to obviate the discomfort of myxedema. Most patients are maintained at a basal metabolic level of approximately \(-20\) to \(-25\) per cent on a daily dosage of 6 to 30 mg. thyroid.

Occasionally patients may suffer a recurrence of their symptoms due to the fact that residual thyroid tissue has regenerated with return of the metabolic rate to pretreatment levels. In such instances, thyroid is withdrawn and if tracer doses show uptake of I\(^{131}\), an additional therapeutic dose is administered.

In addition to these special considerations, the same careful supervision and therapeutic program indicated in all patients with heart disease is essential. The radioactive iodine treatment of heart disease is not to be considered as curative; it is a palliative procedure which is to be considered as an adjunct to the recognized medical measures.
Hypercholesterolemia, Myxedema, and Arteriosclerosis

The question naturally arises as to whether the induced high cholesterol values and hypothyroidism dispose these patients to an increased progression of arteriosclerosis. In our patients, the situation is not strictly analogous to untreated complete myxedema, since our patients receive small doses of thyroid. In this connection we have reviewed the clinical course and postmortem findings of a group of patients who survived 1 to 11 years following surgical total thyroidectomy, and in whom hypometabolism with elevated cholesterol values was present.

We have been interested particularly in the younger patients with rheumatic heart disease. In them, only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed postmortem in such patients, the lesions might well be attributed to the myxedematous state. In all five such patients who survived 1 to 11 years in the hypothyroid state after surgical total thyroidectomy, careful postmortem studies by the Schlesinger technic have revealed only minimal or no coronary arteriosclerosis. Although the number of patients is small, these results demonstrate that progressive arteriosclerosis of the coronary arteries is not a necessary concomitant of the hypercholesterolemia of hypothyroidism or of the hypothyroid state. Because of the above considerations and the uncertain etiological relation of the elevated cholesterol and blood lipids of hypothyroidism to atheromatosis, we have not considered pretreatment elevation of serum cholesterol levels, a contraindication to therapy of these disabled cardiac patients.

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.”

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. On the contrary, with the appearance of such changes, striking clinical improvement has been witnessed. In some patients with congestive failure, the cardiac silhouette becomes smaller, the disappearance of the dilatation of the failing heart offsetting the effect of myxedema on the heart. Our experience is consequently in accordance with that of Willius and Haines, Means, White and Krantz and Christian, who concluded that “myxedema heart” in the sense of causing heart failure occurs rarely, if at all.

Results of Others

The experience of others in the treatment of intractable heart disease is confirmatory of our own results. Wolferth, Chamberlain and Mead have recently reported their observations on 28 euthyroid patients followed for 6 to 24 months after treatment. All had extremely severe angina pectoris and had shown no improvement or become worse despite conventional methods of treatment. In the majority of patients, the most serious problem was nocturnal seizures frequent enough to make adequate rest impossible. Many had suffered one or more attacks of myocardial infarction. Six others had aortic valvular disease with great enlargement of the left ventricle. At least nine had experienced congestive failure and most of these had congestive failure at the time I\(^{131}\) was administered. Nine had fairly severe hypertension. The authors state: “Because the treatment was administered only to patients with far-advanced disease and was denied to none in whom even a remote possibility for relief was thought to exist, it was anticipated we would encounter many cases in which no improvement would result and that a high mortality would be experienced within a short period of time.” As anticipated, 10 patients died, six of them less than a month after treatment before the hypothyroid effect of I\(^{131}\) could be exerted. In the remaining 18 cases, the results were judged to be good in 12, fair in four, and in two, unsatisfactory. A summary of their results is presented in the accompanying table (table 3). The authors express their judgment
as follows: "Although large doses of radioactive isotopes should not be used indiscriminately, our experience during the past two years in deliberately depressing normal thyroid function has convinced us that radioactive iodine has a place in the treatment of severe, otherwise intractable angina pectoris, as well as certain cases with severe congestive failure or abnormal cardiac mechanisms with poorly controlled tachycardia... Radioactive iodine in appropriate dosage is capable of relieving otherwise intractable severe anginal pain."

Table 8.—Summary of Results* in 28 Patients with Angina Pectoris Treated with I\[^{131}\]

<table>
<thead>
<tr>
<th>28 Patients—Angina Pectoris</th>
<th>Follow-up 6-24 months</th>
<th>Cong. fail., 9; art. hypert., 9</th>
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<td>6 d. less than 1 month</td>
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<td>1 d. after sl. imp. one year</td>
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<tr>
<td>18—Follow-up 6-24 Mos.</td>
<td>12 good</td>
<td>4 fair</td>
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<td></td>
<td>2 unsatisfactory</td>
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Table 4.—Results of 95 Patients with Angina Pectoris and Congestive Failure Treated by Jaffe et al., Cedars of Lebanon Hospital, Los Angeles*†

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<td>Good</td>
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<td>Fair</td>
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<td>8</td>
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<td>Poor</td>
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<td>3</td>
<td>1</td>
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<td>Deceased</td>
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<td>34</td>
<td>95</td>
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In a personal communication, Dr. Henry L. Jaffe, Director of the Department of Radiation Therapy at the Cedars of Lebanon Hospital, Los Angeles, has kindly permitted us to state the results obtained by him and his associates in treating their first 95 severely ill cardiac patients. Their results are summarized in the accompanying table (table 4). They have used the divided dose technic and have not attempted to treat all patients to the point of actual clinical myxedema unless they failed to achieve maximum clinical improvement with smaller doses. "Altogether," he states, "we are satisfied that this form of treatment offers something for the severe cardiac which was not available before."

Reports of results in a few cases have been made available to us from several clinics, but while encouraging, the experience is too fragmentary to permit evaluation.

Future Studies

Future experience will clarify many aspects of this new form of therapy.

The criteria for the selection of patients with angina pectoris and congestive failure cannot be definitely established until much more experience in various clinics over an extended period of time becomes available. Additional experience will afford information regarding the durability of the beneficial effects and the question as to whether or not life is prolonged. It is, indeed, possible that the elevation of the serum cholesterol and other lipids may accelerate the progress of atherosclerosis although our evidence to date does not support such a conclusion.

Several different schedules of I\[^{131}\] administration are already being employed; only extensive trial will clarify the advantages and disadvantages of the various programs of treatment.

Although all studies to date have failed to reveal any untoward radiation consequences, long term observations are clearly indicated. Further studies on the mechanisms by which hypothyroidism achieves its beneficial effect on the circulatory system will be of practical as well as of theoretic interest. The reduction in cardiac work, however important, is probably but one factor. Changes in other endocrine organs as well as in the autonomic and central nervous systems may well play significant roles and are the subject of continuing studies.

Summary and Conclusions

1. The physiologic, pathologic, and clinical interrelationships between the thyroid and the cardiovascular system have been discussed.
2. The therapeutic effects of hypothyroidism induced by radioactive iodine in 30 euthyroid patients with intractable advanced angina
pectoris or congestive failure have been described.

3. Only patients were treated who were seriously incapacitated despite all conventional forms of therapy for many months or years.

4. Persistent hypothyroidism can be regularly induced by one or more appropriate doses of radioactive iodine.

5. No radiation sickness and no toxic effects on the blood, kidneys or parathyroids have been observed. Mild or moderate transitory thyroiditis occurred in approximately one-half of the patients.

6. Twenty-six patients with severe angina pectoris have been treated. The average duration of angina pectoris before treatment was 5.6 years. The average follow-up period after treatment is two years and varies from one year to three years. One third of the patients obtained excellent improvement; in another third the improvement, while less, was distinctly worth while. In the remaining one-third the results were not worth while.

7. Among 13 patients severely ill with congestive failure, approximately one-half have shown worth-while improvement; in four it has been striking. The duration of the worthwhile improvement has averaged 20 months with a range of 9 to 35 months.

8. The results of two confirmatory series of cases similarly treated elsewhere have been reviewed.

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Circulation. 1952;6:222-237
doi: 10.1161/01.CIR.6.2.222

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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