Endocrine Pacemaker for Complete Heart Block

By Judah Folkman, M.D., and L. Henry Edmunds, Jr., M.D.

Since electrical stimulation with a myocardial wire has been added to the therapy of complete heart block, longer lived batteries and more sophisticated electrodes have increased the duration of effective control of the heart rate. However, fibrosis around the electrodes and various forms of electrode and equipment failure persist as disadvantages of this technique.

In 1959, experiments were begun to provide a more physiological and permanent pacemaker for chronic heart block by placing an autotransplant of either adrenal medulla or thyroid gland into the ventricular myocardium of dogs with complete heart block. The original concept was that the small area of myocardium surrounding the endocrine transplant would be stimulated by relatively high local concentrations of the respective hormones. Thus, the electrical activity of this area of myocardium might be increased to such a degree that it would become the dominant pacemaker for the ventricle and result in a faster heart rate.

**Methods**

**Creation of Complete Heart Block**

Complete heart block was created in 56 dogs by ligating the bundle of His. Dogs weighed between 18 and 40 Kg. Twelve dogs died and one dog reverted to sinus rhythm. All others remained in complete heart block and were observed for two to six months before any operative procedure was attempted. Pulse rates were recorded at least three times weekly, at rest and after exercise, on all animals to obtain control data. The majority of blocked dogs maintained a fixed rate of approximately 50 beats per minute at rest with not more than ± 2 beats variation from day to day. The highest resting rate was 68/min., the lowest 36. With forced exercise (a run of 100 yards), the heart rate could usually only be driven about 10 or 12 beats per minute above the resting rate.

**Adrenal Medulla Autografts**

In each of three dogs with complete heart block, the left adrenal was removed and thin slices of medulla up to 3 mm. thick were transplanted into the left ventricular myocardium.

**Free Thyroid Autografts**

In four dogs, either one or both thyroid lobes were removed and transplanted as thin slices to the myocardium.

**Thyroid Gland Pedicle Graft**

In eight dogs with complete block, the left thyroid gland was dissected from its bed, leaving its arterial and venous blood supply intact. The left carotid artery was mobilized along its entire length and then ligated and divided above the left superior thyroid artery. The internal jugular vein which collects most of the thyroid venous blood, was then mobilized along its whole length. After the heart had been exposed through the left fourth interspace, the thyroid lobe, accompanied by the attached left carotid artery and left internal jugular vein, was brought down into the chest. This maneuver was prompted by the demonstration of Sabiston et al. that the entire left carotid artery could be mobilized and pulled into the chest for the purpose of inserting it into a myocardial tunnel in dogs, as a method of revascularization. The internal jugular vein was then ligated and divided close to the gland, so that venous blood oozed freely from the surface of the gland. The gland was stripped of its capsule and was then inserted into a wide tunnel made deep in the myocardium of the left ventricle. The gland pulsed with each heart beat, and blood oozed freely from its surface and into the surrounding myocardium. The right thyroid lobe, omitting one parathyroid, was then excised. The chest and neck incisions were closed.

**Tri-Iodothyronine Implantation**

Tablets of 1-tri-iodothyronine (Cytomel*), in doses of 10, 25, and 50 μg., were implanted into myocardial tunnels in the left or right ventricle in 12 dogs with chronic heart block. These tablets, designed for oral use, contained calcium sulfate in addition to the tri-iodothyronine. Although they were not sterilized, no infections occurred after implantation into various locations in the ventricular myocardium.

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ENDOCRINE PACEMAKER

120 -
110 -
90 -
PULSE 80 -
(average)
70 -
60 -
50 -
5 -
LOCK OBSERVED - 6 MONTHS
0 1 2 3 4 5 6 7 8
THYROID TRANSPLANT
WEKS

FIGURE 1
Sustained heart rate elevation after thyroid gland pedicle. In one dog, the resting heart rate remained elevated for over eight weeks. The ventricular pacemaker appeared to originate from the area of the transplant. Since then, the rate has been slowly decreasing toward the control level.

SHAM CONTROLS
Control studies were conducted in four dogs with chronic block. Incisions in the ventricular myocardium were made in two dogs. Autografts of muscle, spleen, and ovary were implanted into the myocardium of two dogs. Dextrose tablets, calcium lactate pellets, and gelfoam pledgets were implanted into the myocardium of two dogs.

Results
ENDOCRINE TRANSPLANTS
Adrenal Medulla Transplants
Within an hour following adrenal medulla transplantation to the myocardium, the heart rate rose 100 to 200 beats/min. above control rates. This sustained tachycardia gradually subsided over a four-day period by which time the rate had returned to control levels. No surviving adrenal medulla could be found on histological sections.

Free Thyroid Autografts
When free thyroid autografts were implanted into the myocardium, the heart rate increased approximately 20 to 40 beats above control levels, and the electrocardiographic site of the pacemaker appeared to shift to the area of the implantation. The sudden increment in rate and the concomitant shift of the pacemaker appeared 8 to 12 hours after transplantation. The rate continued to be moderately elevated for one to three days and then returned to control levels. Autopsies at one, two, and three months demonstrated survival of approximately half of the original transplants.

Implantation of grafts of muscle, ovary, and spleen failed to increase the heart rate or cause a shift in electrocardiographic pattern. Simple incisions in the myocardium did not elevate the heart rate in dogs with chronic block.

Thyroid Gland Pedicle Graft
( Eight Dogs)
Three dogs died shortly after operation because of technical errors. In four dogs, 8 to 10 hours after transplantation, the ventricular rate suddenly increased from an average of 52 beats/min. to 120 to 130 beats/min.
There was a concomitant change in the electrocardiographic pattern which probably represented a shift of the idioventricular pacemaker to the area of implantation. The tachycardia was sustained without interruption for two to three days, but by the fourth day, the rate fell to control levels in three dogs. One dog continued to have an elevated heart rate (20 to 30 additional beats/min.) for eight weeks (fig. 1). In a fifth dog with a control rate of 60/min., the gland was not buried in a myocardial tunnel but was sutured to the surface of the myocardium from which the epicardium had been stripped. The opposing capsule of the thyroid gland was also removed. In this dog, the rate did not rise, and the pacemaker shift did not appear until 48 hours after transplantation. The rate then increased to 110/min. for four days before returning to control levels. A month later when this dog was explored, a thick fibrous capsule was removed to expose a healthy gland with a pulsating carotid artery. The gland was retransplanted into a nearby area, but deeper than before. Eight hours later, the rate was 200/min. and then continued for 24 hours at approximately 250 per minute. During the second postoperative day, the rate varied between 120 and 160; during the third day, between 88 and 100; and during the fourth day, it remained at 88 beats/min. By the fifth day, the rate had returned to control levels. Retransplantation was not attempted in any other dogs, but in two dogs, re-exploration revealed the same thick fibrous capsule surrounding a healthy gland with good arterial supply. An arteriogram in a dog whose rate had returned to control levels showed a patent carotid artery two and one-half months after transplantation. Radioactive iodine uptake studies and photoscans were done by the Radioisotope Laboratory of the National Naval Medical Center on the one dog which achieved a prolonged elevation in rate (fig. 2) and on another dog with only a three-day elevation in rate. Both showed excellent iodine concentration and functioning thyroid gland six weeks after transplantation. No dog demonstrated any change in serum protein-bound iodine levels either before or as long as five months after transplantation.

TRI-IODOTHYRONINE IMPLANTATION

Typical Response to Tri-iodothyronine Tablet Implantation

After implantation of 10, 25, or 50 µg. of tri-iodothyronine as Cytomel, the heart rate did not change for 8 to 12 hours. At the end of this period, the ventricular rate began to increase intermittently to levels 70 to 90 beats/min. above the control rates. Electrocardiograms demonstrated a simultaneous shift of the idioventricular pacemaker to a faster focus which appeared to originate from the area of implantation. At first, the elevated rate persisted only a few minutes, after which the rhythm returned to the control of
Tri-iodothyronine tablet in the myocardium. Change in heart rate after implantation of 10 µg. of Cytomel into the myocardium of an 18-Kg. dog.

the slower pacemaker. Occasionally, this return was punctuated by a Stokes-Adams syncopal attack. After approximately an hour of intermittent tachycardia, the new and faster focus took over entirely, and the heart rate assumed a perfectly regular rhythm at 70 to 90 beats/min. faster than the control rate (fig. 3). Exercise often increased the rate by an additional 20 beats/min. The rate remained elevated for 17 to 30 hours, during which time the dogs were more frisky and active than the usual heart-block dog recovering from a thoracotomy. After this time, the rate began to drop intermittently to control levels. Over a period of two to three hours, the faster focus relinquished its control to the slower pacemaker for longer and longer intervals, until the slower rhythm prevailed, and the rate returned to the slow fixed control levels. Electrocardiograms demonstrated a return to the same idioventricular focus which was active before implantation (fig. 4).

Twenty-five µg. always produced a typical increase in heart rate in all animals. Ten µg. caused an increase in rate in all animals less than 20 Kg., but not in two animals above this weight. However, no dose-weight relationship was established for this small series of animals. In one animal sacrificed an hour after implantation, the tablet was noted to
A. COMPLETE BLOCK, SAME FOCUS 5 MONTHS

B. 8 HOURS AFTER TRI-IODOTHYRONINE IMPLANT

C. 48 HOURS AFTER TRI-IODOTHYRONINE IMPLANT

FIGURE 4
Example of shift of idioventricular pacemaker. (A.) The same pattern was observed in numerous cardiograms recorded over a five-month period. (B.) New focus appears eight hours after 10 µg. tri-iodothyronine had been implanted into high left ventricular myocardium, anterolaterally. (C.) Return to old focus and slower rate after hormone had been expended. Tachycardia had persisted for 22 hours.

have already been macerated by the heart into a fine emulsion. Implantation of as relatively inert materials as dextrose tablets, calcium pellets, and gelfoam squares caused no change in rate.

Local versus Systemic Tri-iodothyronine
A 10- or 25-µg. dose of tri-iodothyronine was implanted into each of three dogs, and the expected 90 to 100 beats/min. elevation was observed. One month later, each dog received 1,000 µg. of tri-iodothyronine as a single dose either by mouth, intramuscularly, or intravenously.* There was no significant increase in heart rate above control levels.

Localization of the New Pacemaker
In all dogs in which the heart rate suddenly rose within 8 to 12 hours after implantation, the electrocardiographic origin of the new pacemaker activity always appeared to correspond to the area of implantation. As supportive evidence for the electrocardiographic method of locating the new pacemaker, 25 µg. of tri-iodothyronine was implanted near the apex, in the anterior left ventricle of one dog. Immediately after implantation, this area was electrically stimulated through the closed chest with bipolar electrodes which had been implanted directly over the tablet. An electrocardiogram was recorded. The electrodes were then removed, and the electrical pattern returned to that of the old idioventricular focus. Ten hours later, when the heart rate suddenly became elevated, another electrocardiogram was taken. This demonstrated a pattern corresponding very closely to that of electrical stimulation of the site of tri-iodothyronine implantation (fig. 5).

Injection of Tri-iodothyronine Emulsion into Myocardium
Five 25-µg. tablets of Cytomel were crushed in 5 cc. of warm saline to make a thin, white emulsion. In an anesthetized dog with a fixed rate of 48, a long 17-gauge needle was inserted through the chest in the left fifth inter-

ENOCRINE PACEMAKER

A SINUS RHYTHM

B COMPLETE BLOCK, SAME FOCUS 3 MONTHS

C ELECTRICAL STIMULATION

D 10 HOURS LATER, TRI-IODOPTHYRONINE ACTIVITY

FIGURE 5
Electrical stimulation of site of tri-iodothyronine implantation. (A.) Sinus rhythm. (B) Complete block created and same focus observed for three months. (C) 25 μg. of tri-iodothyronine implanted in left ventricular myocardium near apex, anteriorly. Bipolar electrodes implanted on top of this site. Electrical stimulation of this area through closed chest, before onset of tri-iodothyronine activity. Then electrodes removed. (D) 10 hours later, appearance of tri-iodothyronine activity produces similar pattern.

STUDIES OF THE MECHANISM OF THE TRI-IODOPTHYRONINE PACEMAKER

Catheter Implantation

A polyethylene catheter (I.D., 0.070 inches) was implanted in the myocardial tunnel beside a 25 μg. tablet of Cytomel in one dog with heart block. The portion of the catheter lying within the tunnel contained five small holes. Both ends of the catheter were brought through the chest incision. The catheter was filled with saline and both ends were sealed. Similar catheters were implanted into the myocardium without Cytomel in two additional animals with complete heart block. In the first dog after 14 hours, when the new pacemaker was well established, 10 cc. of saline was injected into one end of the catheter and into the myocardial tunnel. The 10 cc. was then retrieved by gentle aspiration and was injected into the catheter of a second dog in which no Cytomel had been implanted. No change in heart rate occurred in this dog.
TABLE 1
Summary of Catecholamine Content of Myocardium

<table>
<thead>
<tr>
<th>Dog Sample</th>
<th>µg. Catecholamines/Gm. myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dog Left ventricle (area including tri-iodothyronine)</td>
<td>0.34</td>
</tr>
<tr>
<td>Left ventricle (near apex)</td>
<td>0.29</td>
</tr>
<tr>
<td>Left ventricle (near auricle)</td>
<td>0.20</td>
</tr>
<tr>
<td>Second dog Left ventricle (area of tri-iodothyronine)</td>
<td>0.20</td>
</tr>
<tr>
<td>Left ventricle (near apex)</td>
<td>0.32</td>
</tr>
<tr>
<td>Left ventricle (near auricle)</td>
<td>0.24</td>
</tr>
<tr>
<td>Right ventricle, anterior</td>
<td>0.38</td>
</tr>
<tr>
<td>Right ventricle, lateral</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Usual range = 0.2 — 0.8 µg./Gm.
Per cent recovery = 94 per cent.

Discussion

In the first dog, 5 cc. of saline was again injected into one end of the catheter and then removed from the other end gently by suction. This washing process was repeated until 200 cc. saline had been flushed in and out of the myocardial tunnel. This fluid was blood tinged and contained large amounts of the white Cytomel emulsion. Nevertheless, this irrigation of the area of the new pacemaker did not slow the tachycardia or interrupt its course. The tri-iodothyronine pacemaker maintained a steady tachycardia for the expected 24 hours. Injection of the aspirate into the catheter of the third dog did not change the heart rate.

Reserpine Suppression of the Tri-iodothyronine Pacemaker

In a series of five dogs with chronic heart block, 10 or 25 µg. of Cytomel was implanted in the myocardium, and the expected increase in rate and pacemaker shift was observed 8 to 10 hours later. One month later, each dog was given a single intramuscular dose of reserpine 0.1 mg./Kg. and 24 hours later similar Cytomel tablets were implanted. This time, no change in heart rate or shift in pacemaker occurred.

Myocardial Catecholamine Content after Tri-iodothyronine Implantation

Fifty µg. of Cytomel was implanted in the myocardium of each of two dogs with heart block. In both dogs, the expected tachycardia was observed in 8 hours. The first dog was sacrificed 12 hours after implantation and the second dog 21 hours after implantation. Two Gm. of myocardium at the site of implantation were removed from each dog heart and quickly frozen in dry ice. Pieces of myocardium from other areas of the heart were also removed and similarly frozen. These specimens were assayed for epinephrine and nor-epinephrine content fluorometrically by a modification of the trihydroxyindole method.*

As can be seen in table 1, all samples of myocardium contained equal amounts of catecholamines in the low normal range. There was no significant accumulation of these substances beneath the implanted tablets, nor in any other area of the myocardium.

Discussion

These experiments demonstrate that thyroid autografts or tri-iodothyronine tablets implanted into the ventricular myocardium of dogs with complete heart block cause the surrounding area of myocardium to become the dominant ventricular pacemaker. The heart rate is increased to approximately that of normal animals. Exercise causes a further increase in heart rate. The effect is purely local, and no systemic increase in hormone concentration or undesirable side effects occur. Thus, thyroid autografts or tri-iodothyronine tablets implanted into the myocardium of dogs with complete heart block produce a more rapid pacemaker which approximates the normal heart rate and which is capable of responding to exercise.

Not only do thyroid autografts or tri-iodothyronine tablets implanted into the myocardium raise the heart rate in dogs with complete block, but the new and faster electrical focus which follows implantation appears to originate from the site of the endocrine im-

*Courtesy of Dr. Albert Sjoerdsma, Experimental Therapeutic Branch, National Heart Institute, National Institutes of Health, Bethesda, Maryland.
Another example of shift of idiocentral pacemaker. (A.) Same electrical focus observed for three months. (B.) 12 hours after 50 µg. of tri-iodothyronine implanted in the wall of right ventricle about halfway between base and apex, and slightly anterior (40-Kg. dog). (C.) Return to old focus after hormone had been expanded. Tachycardia had persisted for 26 hours.

The function of the thyroid and its hormones in the role of an endocrine pacemaker in complete heart block was studied briefly. Data from the present work suggest that the elevation of rate is due to a local increase in hormone concentration at the site of the implant. The following observations support this. In all experiments, the electrocardiogram appeared to designate the site of the new pacemaker as corresponding to that of the endocrine implant. Other tissues and tablets were unable to produce a new pacemaker and failed to increase the heart rate. Systemic doses of tri-iodothyronine 100 times that of the locally implanted tablet failed to alter the ventricular rate.

The technique of tri-iodothyronine implantation permitted observations of the action of this hormone in a very small piece of the myocardium without involving other systems of the body. Whatever physical or chemical reactions are going on in this myocardial island during the 8 or 10 silent hours after implantation, the precise time that they are completed is signaled electrically. Since the area of activity remains localized, the cylinder of myocardium may be removed at any time during the reaction for analysis. On the other hand, the intramyocardial catheter technique facilitates study of the endocrine pacemaker in situ, without the necessity of removing it from the animal. Drugs and hormones may be injected or aspirated from the pacemaker area. These techniques may be useful in studying the action of the thyroid hormones on peripheral tissues.
The tri-iodothyronine implantation technique prompted a small investigation of the relationship of tri-iodothyronine and the catecholamines. Brewster et al. demonstrated that the effect of the thyroid hormones depends upon the presence of normal levels of epinephrine and norepinephrine. It is known that these catecholamines can be depleted from the heart by reserpine, and it has been thought that this may be the pathway by which reserpine suppresses the tachycardia of thyrotoxicosis. Roberts and Modell achieved maximal depletion of the catecholamines from the heart in dogs with complete block by a single injection of a 0.1 mg./Kg. dose of reserpine. Our finding that this dose of reserpine prevented the expected increase in heart rate after tri-iodothyronine implantation tends to support the hypothesis that the positive chronotropic action of the thyroid hormones is dependent on the catecholamines. This finding also is consistent with the clinical usefulness of reserpine in patients with thyrotoxicosis.

However, it is unknown whether the positive chronotropic effect of tri-iodothyronine occurs because it allows the accumulation of the catecholamines, or whether it sensitizes the myocardium in some way to the usual level of these hormones. The fact that there was no abnormal accumulation of catecholamines in the myocardium surrounding the tri-iodothyronine emulsions lends weight to the latter theory.

The techniques described above have not consistently produced a permanent endocrine pacemaker. Adrenal medulla transplants never survived, and only a portion of the free thyroid autografts remained viable. Arteriograms, radioactive scans, and retransplantation studies demonstrated that thyroid grafts with a vascular pedicle survived in toto. The major problem limiting sustained pacemaker activity appeared to be fibrous encapsulation of the surviving gland. Experiments are now in progress to control the fibrous reaction in an effort to provide a permanent thyroid pacemaker for patients with complete heart block.

Tablets of tri-iodothyronine as Cytomel elevated the heart rate for only 20 to 30 hours presumably because their supply of hormone was expended in that time. However, because of the feasibility of clinical application of this technique, either at thoracotomy or by needle injection into the heart, investigations are in progress to develop a long-lasting preparation of tri-iodothyronine. Such a preparation would be analogous to pellets of desoxycorticosterone, which after a single implantation, slowly release their hormone for 9 to 15 months. Pilot experiments suggest that the duration of action of tri-iodothyronine may be considerably extended by the use of slow release pellets which contain a soluble binding agent and which may be injected into the heart.

Summary

In dogs with complete heart block, adrenal medulla or thyroid autografts, or tri-iodothyronine tablets implanted into the myocardium produced a sustained elevation in heart rate for 24 to 96 hours. Exercise of the animal caused a further increase in heart rate. Electrocardiographic studies suggested that the faster pacemaker activity originated from the area of implantation of the grafts or the tablets. After implantation of either thyroid grafts or tri-iodothyronine tablets, a latent period of 8 to 12 hours occurred before the new pacemaker became active. Data suggest that the pacemaker shift and the increase in heart rate are due to a local increase in hormones provided by the autografts or by the tri-iodothyronine tablets. There was no effect on the heart rate when similar or higher doses of tri-iodothyronine were given systemically. The method of tri-iodothyronine implantation into the myocardium is valuable in the study of the action of this hormone. The technique has two unique advantages: the reaction remains localized, and the endpoint is signaled electrically. Reserpine suppresses the ability of implanted tri-iodothyronine to increase the heart rate. This suggests that normal catecholamine levels are required for the positive chronotropic action of tri-iodothyronine.

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Myocardial catecholamine concentrations were not increased around the implanted tri-iodothyronine tablets. If catecholamines are necessary for the action of tri-iodothyronine on the myocardium, this suggests that tri-iodothyronine causes sensitization of the myocardium to the catecholamines, rather than causing an accumulation of the catecholamines themselves. Fibrous encapsulation of endocrine transplants appears to prevent permanent pacemaker activity. In lieu of successful thyroid transplants, myocardial implantations of tri-iodothyronine as slow release pellets are potentially applicable for patients with complete heart block.

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