Influence of Thyroidal Function on Vascular Reactivity in Dogs

By Irvine H. Page, M.D., and James W. McCubbin, M.D.

Responsiveness to several vasoactive drugs has been found to be sharply reduced following suppression of thyroidal function with radioactive iodine, propylthiouracil or surgical thyroidectomy in dogs. The exception was tetraethylammonium chloride, its vasodepressor activity being unchanged or increased with the appearance of the athyroid state. Replacement therapy with desiccated thyroid did not restore vascular reactivity towards normal and produced inversion of adrenaline responses. Myxedema occurred in but 1 of 11 chronically athyroid dogs.

VASCULAR reactivity—or responsiveness—of blood vessels may be measured in several ways. Here it is considered in terms of change in arterial pressure following vasoactive chemical stimuli. The relationship between vascular reactivity and thyroidal function has been studied because of: (1) the well known effects of this function on tissue metabolism; (2) the systolic hypertension and increased cardiac output which occur in Grave's disease; (3) the demonstration by Blumgart, Freedberg and Kurland1 that hypothyroidism induced by radioactive iodine lessens the work of the heart and presumably the force of its beat; (4) the demonstration by Sawyer and Brown2 that in hypothyroidism the cardial accelerator response of the heart to adrenaline is diminished; (5) the fact that many of the signs and symptoms of thyrotoxicosis have been explained on the basis of sensitization of sympathetic nerve endings to adrenergic drugs; (6) the fact that in myxedema, reactivity of the whole organism sinks to a low ebb and it is a reasonable presumption that reactivity of the heart and blood vessels is concurrently impaired.

To this end, vascular reactivity has been evaluated in dogs before and after establishment of hypothyroidism (thyroidectomy, radioactive iodine or propylthiouracil) and then again after feeding thyroid powder. The use of the dog as an experimental animal may be unfortunate in that this species seems to be less dependent on thyroidal activity than most laboratory animals. On the other hand, the majority of previous similar studies of vascular reactivity in experimental hypertensive vascular disease have utilized dogs.

METHODS

Twelve normal adult mongrel dogs weighing from 8.6 to 14.2 Kg. were used. Arterial pressure was recorded on a smoked drum from a mercury manometer after cannulation of the femoral artery under sodium pentobarbital anesthesia. Heparin was used in the connecting tubing. Test drugs were adrenaline, noradrenaline, histamine and tetraethylammonium chloride (TEAC) given in this order and, with the exception of tetraethylammonium chloride, each repeated once or several times until nearly identical responses were obtained. Angiotonin (5 cat units) and renin were used in some but not all experiments. Injections were made into a femoral vein. Care was taken that doses of test drugs, again with the exception of tetraethylammonium chloride, were submaximal and the same for each dog for the duration of the experiment. Tetraethylammonium chloride was given in a dose of 5 mg. per kilogram of body weight. Testing was done at intervals of several weeks under standardized conditions so that each dog was tested from four to eight times over periods ranging from 4 to 15 months.

Total surgical thyroidectomy was successful in only three animals. The most frequent cause of failure was that the parathyroid implants often carried residual fragments of thyroid tissue which later regenerated. Regeneration was evidenced by fall in blood cholesterol and by cervical uptake of radioactive iodine (T131)* several weeks or months.

*The radioactive iodine used in this investigation was supplied by Oak Ridge National Laboratory on authorization from the Isotopes Division, U. S. Atomic Energy Commission. We are indebted to Dr. Otto Glasser of the Cleveland Clinic for measuring both therapeutic and tracer doses of radioactive iodine, for his advice on handling the material and for measuring cervical uptake of the tracer doses.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.
after operation. Consequently, therapeutic doses of I\textsuperscript{131} were used in eight dogs, five of which had had previous unsuccessful surgical attempts at removal of all thyroid tissue. Single doses of 15 to 20 milli-
curies, given intravenously, completely suppressed thyroidal function as judged by lack of uptake of tracer doses of I\textsuperscript{131} given at regular intervals throughout the course of each experiment. None of these animals developed tetany. Thyroidal function was suppressed in two dogs by feeding propylthiouracil,† 1.2 Gm. in chopped meat daily for four weeks. One of these subsequently received I\textsuperscript{131} and is included in the group above. Cholesterol determinations were done by the Schoenheimer-Sperry method through the courtesy of Dr. Helen Brown.

RESULTS

1. Hypothyroidism Induced by Thyroidectomy or I\textsuperscript{131}

Suppression of thyroidal activity by surgical thyroidectomy or I\textsuperscript{131} significantly altered vascular reactivity (tables 1 and 2). Adrenaline and noradrenaline responses were uniformly and often strikingly decreased. Reactivity to histamine varied considerably from test to test in both normal and athyreoid dogs; while average responses were decreased in eight dogs, they were unchanged or slightly enhanced in three. Reactivity to tetraethylammonium chloride varied spontaneously from test to test both in normal and athyreoid dogs. In the eight animals treated with I\textsuperscript{131}, average hypotensive responses were consistently greater than in control tests. In the three surgically thyroidectomized dogs, responses to tetraethylammonium chloride were either unchanged or slightly decreased. This was the only significant difference between the two groups.

Responses to repeated doses of tetraethylammonium chloride, initially depressor, diminished and were finally pressor in both normal and athyreoid dogs. Potentiation of adrenaline and noradrenaline responses by tetraethylammonium chloride occurred in both groups, the percentage increase being the same or greater in athyreoid animals.

Responses to angiotonin and renin were greatly depressed in the athyreoid state.

Spontaneous variation in responsiveness to

adrenaline and noradrenaline from test to test is often found in euthyreoid animals. This variability decreased in athyreoid animals. Spontaneous change in reactivity was especially marked in one normal dog in which adrenaline and noradrenaline responses increased progressively over 15 weeks. This sequence was interrupted dramatically by administration of 20

\begin{table}
\centering
\caption{Average Vascular Responsiveness in mm. Hg before and after I\textsuperscript{131}}
\begin{tabular}{|c|c|c|c|c|}
\hline
Dog No. & Condition & Adrenaline & Noradrenaline & Histamine & TEAC \\
\hline
2680 & normal & +41 & +52 & -34 & -59 \\
& 4\frac{1}{2} \text{mos.} & +19 & +20 & -17 & -68 \\
2860 & normal & +25 & +33 & -28 & -24 \\
& 2 \text{mos.} & +19 & +14 & -33 & -33 \\
2431 & normal & +44 & +82 & -30 & -40 \\
& 3 \text{mos.} & +18 & +29 & -13 & -54 \\
2932 & normal & +44 & +39 & -54 & -57 \\
& 1\frac{1}{2} \text{mos.} & +26 & +26 & -38 & -67 \\
2909 & normal & +48 & +41 & -56 & -51 \\
& 4 \text{mos.} & +21 & +30 & -50 & -64 \\
3003 & normal & +38 & +31 & -20 & +6 & -23 \\
& 3\frac{1}{2} \text{mos.} & +15 & +17 & -23 & -48 \\
3133 & normal & +39 & +45 & -26 & -29 \\
& 1\frac{1}{2} \text{mos.} & +18 & +24 & -15 & -37 \\
3150 & normal & +71 & +72 & -24 & -30 \\
& 2 \text{mos.} & +28 & +28 & -9 & -66 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Average Vascular Responsiveness in mm. Hg before and after Total Surgical Thyroidectomy}
\begin{tabular}{|c|c|c|c|c|}
\hline
Dog No. & Condition & Adrenaline & Noradrenaline & Histamine & TEAC \\
\hline
3008 & normal & +36 & +39 & -51 & -64 \\
& 6 \text{mos. after} & +16 & +26 & -27 & -66 \\
2809 & normal & +46 & +50 & -50 & -73 \\
& 1 \text{mo. after} & +28 & +26 & -38 & -25 \\
3167 & normal & +48 & +41 & -44 & -56 \\
& 3 \text{mos. after} & +31 & +30 & -31 & -42 \\
\hline
\end{tabular}
\end{table}

millicuries of I\textsuperscript{131} (fig. 1). Responses to adrenaline and noradrenaline were strikingly decreased, reactivity to histamine diminished and responses to tetraethylammonium chloride were usually larger, though there was considerable variation from test to test.

Definite change in reactivity was observed as soon as four weeks after treatment with I\textsuperscript{131} and as soon as two weeks after surgical thyroidectomy. No attempt was made to determine exactly the latent period preceding change in

† Propylthiouracil powder was generously supplied by Dr. Kenneth Thompson, Organon, Inc., and Dr. S. M. Hardy, Lederle Laboratories.
reactivity after alteration of thyroidal function. Over an average period of six months athyroid dogs showed no tendency to revert to euthyroid reactivity patterns.


Table 3.—Average Vascular Responsiveness in mm. Hg before and after Propylthiouracil

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Condition</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Histamine</th>
<th>TEAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2860</td>
<td>normal</td>
<td>+25</td>
<td>+33</td>
<td>-28</td>
<td>-24</td>
</tr>
<tr>
<td>2766</td>
<td>normal</td>
<td>+6</td>
<td>+4</td>
<td>-27</td>
<td>-58</td>
</tr>
</tbody>
</table>

2. Hypothyroidism Induced by Propylthiouracil

Two normal dogs received propylthiouracil daily for four weeks. At the end of this time, changes in reactivity closely resembled those seen in I\(^{131}\) treated animals (table 3). In one, diminution in reactivity to adrenaline and noradrenaline was more than was later produced by I\(^{131}\) in the same animal. Reactivity to histamine was unchanged in one dog and diminished in the other. Responses to tetraethylammonium chloride were moderately increased in both. Biopsy of the thyroid gland at end of propylthiouracil feeding showed the characteristic changes consistent with the drug-induced hypofunction.

3. Serum Cholesterol in Thyroidectomized and I\(^{131}\) Treated Animals

Vascular reactivity changed before there occurred a significant rise in serum cholesterol. No close correlation was found between cholesterol levels and responsiveness. Cholesterol levels fluctuated widely on the standard kennel diet of Purina dog chow supplemented by 1 pound of ground meat three times weekly, but all animals showed significant hypercholesterolemia. Maximum elevations in I\(^{131}\) treated dogs were 38, 72, 83, 110, 112, 118, 193, and 290 per cent of respective control values. In thyroi-
decomomized animals, maximum elevations were 82, 126 and 150 per cent.

![Figure 2](image.png)

**Fig. 2.** Myxedema in dog No. 3133 and its improvement with thyroid feeding. *Above.* Eight weeks after receiving 20 millicuries of I\(^{131}\). *Below.* After receiving desiccated thyroid 1 Gm. per kilogram for four weeks.

became thick and edematous and body weight increased by 21 per cent. Other changes were common to the whole group. The hair became coarse, dry and thinned and often fell out in patches over the legs and abdomen. Marked apathy and listlessness were characteristic but appetites remained good and slight to moderate weight gain occurred in six of eight animals treated with I\(^{131}\). None of the thyroidectomized group had a gain in weight and one had a moderate weight loss. Neither thyroidectomy nor I\(^{131}\) produced marked change in average arterial pressure.

### Table 4.—Vascular Responsiveness in Athyroid Dogs before and after Being Fed Desiccated Thyroid 1 Gm. per Kg. Daily for Four Weeks.

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Condition</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
<th>Histamine</th>
<th>TEAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3133</td>
<td>athyroid</td>
<td>+18</td>
<td>+24</td>
<td>-15</td>
<td>-37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-10</td>
<td>+10</td>
<td>-25</td>
<td>-50</td>
</tr>
<tr>
<td>3150</td>
<td>athyroid</td>
<td>+28</td>
<td>+28</td>
<td>-9</td>
<td>-66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-7</td>
<td>+35</td>
<td>-20</td>
<td>-54</td>
</tr>
<tr>
<td>3093</td>
<td>athyroid</td>
<td>+15</td>
<td>+17</td>
<td>-23</td>
<td>-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-9</td>
<td>+16</td>
<td>-13</td>
<td>-53</td>
</tr>
</tbody>
</table>

4. Appearance and Behavior of Athyroid Dogs

The complete picture of myxedema appeared in only 1 of 11 thyroidectomized or I\(^{131}\) treated dogs. This animal, eight weeks after receiving 20 millicuries of I\(^{131}\), developed ascites; the skin became thick and edematous and body weight increased by 21 per cent. Other changes were common to the whole group. The hair became coarse, dry and thinned and often fell out in patches over the legs and abdomen. Marked apathy and listlessness were characteristic but appetites remained good and slight to moderate weight gain occurred in six of eight animals treated with I\(^{131}\). None of the thyroidectomized group had a gain in weight and one had a moderate weight loss. Neither thyroidectomy nor I\(^{131}\) produced marked change in average arterial pressure.

Three dogs made athyroid by I\(^{131}\) were fed desiccated thyroid (Parke, Davis USP)* 1 Gm.

* We are grateful to Dr. Harry E. Carnes, Parke, Davis and Co., for a generous supply of desiccated thyroid.
per kilogram of body weight daily and, within three to four weeks, appearance and behavior of all became entirely normal. Recovery was especially characterized by abundant growth of new hair. The one animal showing signs of myxedema was included in this group (fig. 2). Weight returned to normal in all. Subsequent weight loss or other signs of thyrotoxicosis failed to appear, although one dog was fed 1.5 Gm. desiccated thyroid per kilogram of body weight daily for two months.

5. Influence of Thyroid Feeding on Reactivity in Athyroid Dogs

Paradoxically, though these dogs were entirely normal in appearance and behavior after treatment with desiccated thyroid, adrenaline responses were further decreased, becoming entirely depressor in all. Reactivity to noradrenaline, histamine and tetraethylammonium chloride was largely unchanged with no consistent trend towards a return to euthyroid reactivity patterns (table 4; fig. 3).

Discussion

The athyroid state in dogs is associated with consistent and striking diminution of vascular responsiveness to adrenaline and noradrenaline. When animals were restored to normal appearance and behavior with large doses of desiccated thyroid, reactivity to noradrenaline remained unchanged. Adrenaline responses, however, became inverted. This seemingly anomalous effect of replacement therapy in athyroid dogs is in accord with a recent report of Riggs, Stanbury and Carr4 who found that feeding large amounts of desiccated thyroid to normal dogs decreased vasopressor activity of adrenaline.

It is puzzling why the administration of large amounts of thyroid powder failed to restore vascular reactivity to normal. Enough time would appear to have elapsed for the thyroid to exert its full effect. It seems as if the long athyroid period may have caused changes in the heart and blood vessels which were irreversible. Alternatively, there is the possibility that destruction of the thyroid causes the loss of functions not alone replaced by oral thyroid powder. The latter possibility is the more appealing one to us.

The hypotensive action of tetraethylammonium chloride was found to be slightly increased in animals treated with I131 or propylthiouracil but was unchanged by surgical thyroidectomy. There were no other significant differences in reactivity patterns between the three groups and the reasons for this slight discrepancy are not now apparent. Replacement therapy with desiccated thyroid in I131 treated dogs failed to restore responses to tetraethylammonium chloride to normal.

As concerns tetraethylammonium chloride, the more interesting problem is not the slight increase in depressor responses caused by athyroidism, but rather the fact that, at a time when responses to other drugs are severely depressed, tetraethylammonium chloride exerts full or increased activity. Evidently, transmission of autonomic impulses is independent of thyroidal function, while the response of the peripheral vessels and heart show such dependence. In normal animals, tetraethylammonium chloride causes marked augmentation of the response to many vasoactive drugs.5,6 Athyroid dogs exhibit the same phenomenon but to a somewhat increased degree, suggesting that their sluggish reactivity may depend in part at least on increased autonomic inhibition. This must be a minor factor, however, for tetraethylammonium chloride blockade does not usually increase the absolute responses of athyroid dogs to values found in control periods.

Responsiveness to renin and angiotension was markedly decreased with the appearance of the athyroid state. Reactivity to histamine was generally reduced in all three groups of athyroid dogs but not as consistently or as impressively as adrenaline, noradrenaline and angiotensin. Again, replacement therapy with desiccated thyroid failed to restore responses to euthyroid values.

We had not been aware that myxedema was so difficult to produce in dogs. While there were some changes, such as loss and coarsening of the hair and apathy, only 1 of 11 animals showed the full syndrome. All dogs were tested
for I$^{131}$ uptake and none found, so it does not appear that residual thyroid tissue was responsible. This disposes of the opinion that abundant accessory thyroid tissue accounts for the infrequent appearance of myxedema in the dog after surgical thyroidectomy. These experiments confirm that, unlike man and most animals, the dog is not dependent to a great degree on thyroid hormone and that thyrotoxicosis is produced with great difficulty in the dog by feeding large doses of thyroid powder.$^7$-$^9$

It is important that these facts be emphasized, for reports often appear concerning animal experiments in which hyper- or hypothyroidism is assumed without stating exactly the condition of the animals that justified this conclusion.

**Summary**

Vascular responsiveness to adrenaline, noradrenaline, angiotonin, renin, histamine and tetraethylammonium chloride has been measured before and after suppression of thyroidal function by surgical thyroidectomy, I$^{131}$ or propylthiouracil. Attention was called to the difficulty of accomplishing complete surgical thyroidectomy in dogs. Responsiveness to adrenaline, noradrenaline, angiotonin and renin was consistently and markedly reduced in all three groups of athyroid animals. Reactivity to histamine varied widely from test to test in both euthyroid and athyroid dogs but the majority of animals showed a moderate decrease in responsiveness. Average hypotensive responses to tetraethylammonium chloride were slightly greater following treatment with I$^{131}$ or propylthiouracil but were not regularly altered by surgical thyroidectomy. Reactivity patterns in the three groups of athyroid animals were otherwise the same. Blockade of autonomic ganglia with tetraethylammonium chloride in athyroid dogs augmented the response to vasoactive drugs as in normal dogs but to a slightly greater degree. Absolute responses after tetraethylammonium chloride remained less than they had been before suppression of thyroid function. There was no tendency for athyroid dogs to revert to euthyroid reactivity patterns over an average period of six months and for as long as 12 months. No correlation was found between degree of vascular responsiveness and serum cholesterol level. The latter was significantly elevated in all thyroidectomized and I$^{131}$ treated animals.

The full-blown syndrome of myxedema appeared in only one of eight animals treated with I$^{131}$ and in none of the surgically thyroidectomized group. All showed marked apathy and listlessness, lost hair over the legs and abdomen and moderate weight gain occurred in six of eight dogs receiving I$^{131}$. Thyroidectomized dogs did not gain weight, one having moderate weight loss, but otherwise resembled I$^{131}$ treated animals. Three dogs treated with I$^{131}$, the one myxedematous animal included, were fed desiccated thyroid. The appearance and behavior of all became entirely normal within three to four weeks. Vascular reactivity was not similarly modified, however. Adrenaline responses were further decreased in all, becoming entirely depressor. Reactivity to noradrenaline, histamine and tetraethylammonium chloride was largely unchanged, there being no definite tendency toward a return to euthyroid reactivity patterns with replacement therapy. Thyroid replacement therapy did not elicit hyperthyroidism.

**Conclusions**

Vascular responsiveness to a variety of pressor and depressor drugs in dogs is, in some degree, dependent on activity of the thyroid gland. Failure of this glandular function leads to depression of vascular reactivity to several vasoactive drugs, but not to tetraethylammonium chloride, the effect of which is even enhanced. The conductance of vasomotor impulses by sympathetic ganglia seems largely independent of thyroidal function. Responses to vasoactive drugs are not restored by feeding desiccated thyroid.

Minor degree of clinical hypothyroidism can be produced readily in dogs but myxedema is infrequent. The dog is unusual in that it is relatively insensitive to both excess and deficit of thyroidal hormone.

A possible mechanism explaining the beneficial effects of suppression of thyroidal activity
in man is that, as in dogs, vascular reactivity is sharply reduced and the vascular tree no longer over-reacts to the normal impacts of life.

REFERENCES
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