Interrelated Hormonal Factors in Cardiac Hypertrophy

Experiments in Nonhypertensive Hypophysectomized Rats

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WITH THE TECHNICAL ASSISTANCE OF MISS JACQUELINE MERRILL

Evidence is presented that cardiac hypertrophy may ultimately be due to metabolic influences of hormones among which the pituitary growth hormone (somatotrophic hormone, STH) is the most important. In hypophysectomized rats, marked cardiac hypertrophy was elicited by administration of STH in the presence of subnormal blood pressure levels. Other hormones, especially the thyroid hormone and the adrenal mineralocorticoids—the latter through their action on myocardial electrolyte balance—seem to play subsidiary roles. Cortisone inhibited the cardiotropic effect of STH and by itself decreased cardiac mass.

The widespread notion that cardiac hypertrophy can be ascribed solely to mechanical factors, such as increased peripheral resistance (hypertension) or other forms of augmented myocardial work, appears incompatible with the fact that high degrees of myocardial hypertrophy occur in the absence of any exaggerated mechanical cardiac strain, for example, in cases of so-called "idiopathic" cardiac hypertrophy and of normotensive acromegaly. The latter feature suggests a possible role of the somatotropic or growth hormone (STH) of the pituitary in the process of myocardial hypertrophy. This assumption has been indirectly supported by Beznák and Hajdu who showed that the hearts of hypophysectomized rats decreased in size and, in contrast to those of nonhypophysectomized animals, failed to gain in weight when the aorta was constricted by a clamp. On the other hand, administration of STH partially prevented the hypophysectomy-induced atrophy of the hearts and restored their ability to respond to constriction of the aorta with an increase in myocardial mass. The weight of normal hearts was not significantly altered by STH administration (five days), unless exposed to the strain of a clamped aorta. In unilaterally nephrectomized rats fed a sodium-rich diet, STH was found by Selye to elicit cardiac hypertrophy similar to that induced by desoxycorticosterone acetate (DCA). Since maximal effects were achieved by the administration of both hormones, Selye believed that STH sensitizes the myocardial tissue to the hypertrophy-producing action of DCA.

Two sets of observations seem to support this concept: von Metzler reported that DCA does not affect the heart size of normally-fed resting animals but causes cardiac hypertrophy in hypophysectomized rats. It also accentuates the cardiac hypertrophy induced by exercise and induces a concomitant enlargement of the adrenals. Rather observed that adrenalectomy interferes to some extent with the hypertrophy of the heart in rats with experimental hypertension. However, Beznák found that adrenalectomy did not abolish the cardiac hypertrophy following aortic constriction; also, cortical extracts (Eucortone) and adrenocorticotropic hormone (ACTH) failed to influence the cardiac atrophy following hypophysectomy and the hypertrophic response to aortic constriction. Beznák therefore concluded that these latter phenomena are not
mediated by secondary adrenal hypofunction due to hypophysectomy but by absence of growth hormone itself.

It has also been reported that cortisone does not alter heart size in normally fed rats even when it induces hypertension, but that lipo-adrenal cortical extract inhibits both the hypertension and cardiac hypertrophy otherwise elicited by DCA. According to Selye cardiac hypertrophy induced by STH can be prevented by cortisol in doses "adequate to produce adrenocortical atrophy." Friedman and colleagues, however, failed to confirm this and also found that "Compound A" does not prevent cardiac hypertrophy induced by DCA. Von Metzler's observations differ from those of Beznák in that hypophysectomy was not followed by an atrophy of the heart, while ACTH produced an increase of the heart weight in trained rats.

It has long been known that thyroid hormone induces cardiac hypertrophy which may be very marked. Thyroidectomy, on the other hand, is followed by a diminution of the heart size, unless the heart becomes enlarged by myxedematous swelling. It was reported by Salmon, Evans and co-workers, and Laqueur and associates, that the growth-promoting effect of the pituitary hormone on the body is abolished or diminished in thyroidectomized animals. It could, however, be restored by the administration of thyroid hormone. From these observations and from their own finding that the cardiac hypertrophy after aortic constriction is diminished by thyroidectomy, Beznák and Hajdu concluded that the thyroid hormone is essential in maintaining a normal response of the myocardial tissue to the growth-stimulating effect of the somatotropic hormone. According to Selye and co-workers the cardiac hypertrophy-producing effect of DCA is augmented by the administration of thyroid hormone.

The following experiments were carried out on hypophysectomized rats in order to study the interrelated influences of the pituitary growth hormone, adrenal corticoids and thyroxine upon the mass of the heart muscle with the least possible interference on the part of the test animal's intrinsic hormone production and as independently as possible of blood pressure changes. The weights of other tissues (kidney, liver, spleen, thymus, adrenals) and total body weight were also examined to evaluate the degree of organ specificity of the cardiac weight changes observed.

**MATERIALS AND METHODS**

Observations were made on 142 young, male, Sprague-Dawley rats which had been hypophysectomized by Hormone Assay Laboratories, Inc., in Chicago, five to six weeks prior to the beginning of our experiments (to permit the development of adrenal and thyroid atrophy). Some were used as controls, others were injected with hormones in various combinations described below. The completeness of the hypophysectomy was checked at necropsy; a few animals in which it proved incomplete were excluded from our records.

The rats were fed powdered "Purina Fox Chow" with a supplement of oranges and carrots and were allowed tap water ad libitum. The sodium chloride content of the diet was kept within normal limits in order to avoid nephrosclerotic changes after administration of DCA. The four first experimental groups (numbers 1-4) lasted 35 days; the others were terminated after 27 days so as to prevent the loss of too many animals. The rats were killed by exsanguination, and the organs were immediately placed in Zenker's fluid plus formalin for 12 to 15 hours. They were then washed for 24 hours under running tap water and stored in 70 per cent alcohol before weighing.

Somatotropic hormone (STH) was obtained from Frank W. Horner, Ltd., Montreal, in three different lots. According to Dr. L. Mitchell, Director of Research, this material showed "a very good growth-promoting activity" and, compared by the tibia test with the electrophoretically pure hormone of C. H. Li, had an "almost identical potency." Contaminations with thyrrotropin, ACTH, gonadotrophins, prolactin, pressor and oxytocic principles were negligible. The STH was dissolved in 1 per cent sodium chloride solution and administered subcutaneously in a dosage of 3 mg. a day (three injections of 1 mg. each at eight-hour intervals).

Thyroxine ("Thyroxinesodium," British Drug Houses, Ltd.) was dissolved in distilled water and injected subcutaneously once daily (50 ug per dose). Cortisone acetate microcrystals (Merck and Co.) dissolved in saline solution (25 mg. per milliliter) was administered subcutaneously once daily in the following doses of the hormone: 10 mg., first seven days; 5 mg., next five days; 2.5 mg., the remaining fifteen days. The toxicity of cortisone made such diminishing doses necessary.

Desoxycorticosterone acetate (DCA; "Percorten" Ciba in sesame oil, containing 0.5 per cent chloro-
### Table 1: Blood Pressure and Heart Weight

<table>
<thead>
<tr>
<th>GROUP No.</th>
<th>ANIMALS</th>
<th>BLOOD PR. (MM Hg)</th>
<th>HEART WEIGHT (MG PER 100 GRAM INITIAL BODY WT.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>CONTROLS</td>
<td>±37</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>THYROXINE</td>
<td>±40</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>STH</td>
<td>±35</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>STH + THYROXINE</td>
<td>±66</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>CORTISONE</td>
<td>±31</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>CORT. + THYROXINE</td>
<td>±35</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>CORT. + STH</td>
<td>±32</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>CORT. + STH + THYROXINE</td>
<td>±41</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>DCA</td>
<td>±16</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>DCA + THYROXINE</td>
<td>±31</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>DCA + STH</td>
<td>±35</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>DCA + STH + THYROXINE</td>
<td>±36</td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>CORT. + DCA</td>
<td>±18</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>CORT. + DCA + THYROXINE</td>
<td>±34</td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>CORT. + DCA + STH</td>
<td>±25</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>CORT. + DCA + STH + THYR.</td>
<td>±43</td>
</tr>
</tbody>
</table>

**Fig. 1.**

### Table 2: Kidney and Liver Weight

<table>
<thead>
<tr>
<th>GROUP No.</th>
<th>ANIMALS</th>
<th>KIDNEY WEIGHT (MG PER 100 GRAM INITIAL BODY WT.)</th>
<th>LIVER WEIGHT (MG PER 100 GRAM INITIAL BODY WT.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>CONTROLS</td>
<td>±231</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>THYROXINE</td>
<td>±232</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>STH</td>
<td>±232</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>STH + THYROXINE</td>
<td>±823</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>CORTISONE</td>
<td>±250</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>CORT. + THYROXINE</td>
<td>±583</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>CORT. + STH</td>
<td>±733</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>CORT. + STH + THYROXINE</td>
<td>±452</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>DCA</td>
<td>±264</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>DCA + THYROXINE</td>
<td>±642</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>DCA + STH</td>
<td>±442</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>DCA + STH + THYROXINE</td>
<td>±160</td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>CORT. + DCA</td>
<td>±260</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>CORT. + DCA + THYROXINE</td>
<td>±260</td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>CORT. + DCA + STH</td>
<td>±246</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>CORT. + DCA + STH + THYR.</td>
<td>±184</td>
</tr>
</tbody>
</table>

**Fig. 2.**

Kidney: *P* (1-2), (3-7), (4-8), (3-15), (4-15), (4-16) < 0.01 — *P* (1-5), (1-7) < 0.05.
Liver: *P* (1-5), (1-6), (1-7), (1-8), (1-9), (3-15), (7-11) < 0.01 — *P* (3-11) = 0.05 — *P* (11-15) = 0.1 — *P* (1-2), (3-4) > 0.1.
butanol) was injected subcutaneously in a dosage of 1 mg. per day. The different types and combinations of hormone treatment and the numbers of animals used in each experimental group are indicated in figures 1, 2, 3 and table 1.

Blood pressure was determined by the "tail-
cuff" method under light nembutal anesthesia before the beginning of the experiments, after 15 days of hormone treatment, and at the end of the experimental periods.

**Results**

**Blood Pressure.** As shown in the left section of figure 1, no significant elevation of the mean blood pressure above the normotensive level (about 120 mm. Hg) was observed in any of the experimental groups. Most of our hypophysectomized animals were hypotensive, but in those treated with STH combined with cortisone (groups 7-8), or with STH plus cortisone and DCA (groups 15-16), the blood pressure was near normal. It never reached the "hypertensive" level of 140 mm. Hg.

**Body Weight (Table 1).** STH produced a pronounced increase of body weight (groups 1, 3; 1, 4; 1, 11; 1, 12). Thyroxine enhanced body weight slightly (groups 1, 2). Cortisone reduced it markedly in the absence of STH (groups 1, 5; 1, 6; 1, 13; 1, 14) and antagonized the growth-promoting effects of STH and thyroxine (groups 3, 7; 2, 6; 4, 8), while DCA had no such effect (groups 3, 11; 2, 10; 4, 12). Neither did thyroxine interfere with the individual or combined effects of STH and cortisone (groups 3, 4; 5, 6; 7, 8; 11, 12; 13, 14; 15, 16).

**Organ Weights (General).** The weights of the individual organs were expressed in relation to 100 Gm. of initial body weight, that is, of the weights taken at the beginning of our experiments. This procedure, rather than expression of the organ weights in terms of terminal body weight, was deemed necessary because changes of organ weights and total body weight, although usually tending in the same direction, proved quantitatively quite disproportionate in some instances. For example, the marked loss of total body mass under treatment with cortisone in which the heart participates only to a minor extent, if used as the basis for calculation of the change of cardiac mass, will create the misleading impression of an increase of heart weight, while in reality the opposite is the case (see below).

**Heart Weight (Fig. 1).** Increases of the heart weights above the controls were observed under the influence of STH alone or in combination with other hormones in the following descending order of magnitude: STH + thyroxine (+74 per cent, group 4); STH (+59 per cent, group 3); STH + DCA (+53 per cent, group 11); STH + DCA + thyroxine (+41 per cent, group 12); STH + DCA + cortisone + thyroxine (+36 per cent, group 16); STH + cortisone (+22 per cent, group 7); STH + DCA + cortisone (+16 per cent, group 15); STH + cortisone + thyroxine (+13 per cent, group 8). All of these values are significant (P < 0.01). The STH-induced increases of cardiac mass were unaccompanied by any abnormal elevations of the blood pressure; indeed the latter was subnormal in most instances.

The catabolic property of cortisone was manifested by the significant decreases in heart weight [groups 1-5; P (1-5) < 0.01], as well as by its inhibitory interference with the cardiotrophic action of STH (groups 3, 7). However, in no instance of combined administration of cortisone and STH, (without or with additional DCA and thyroxine) (groups 7, 8, 15, 16) was the cardiotrophic action of STH entirely abolished. It remained significant in all these groups.

In the absence of extra sodium, DCA diminished the cardiac weight significantly [groups 1, 9; P (1-9) < 0.01] and showed this moderate anticardiotrophic tendency also in combination with thyroxine (groups 2, 10), and with STH + thyroxine (groups 4, 12).

Thyroxine, per se, produced a slight but significant enlargement of the cardiac mass [groups 1, 2; P (1-2) = 0.02]. It did not significantly potentiate the cardiotrophic effect of STH [groups 3, 4; P (3-4) > 0.10], nor did it significantly alter the effects of cortisone (groups 5, 6), DCA (groups 9, 10), or other hormone combinations (groups 7, 8; 11, 12; 13, 14). Only the cardiotrophic effect of STH + cortisone + DCA seemed increased by thyroxine (groups 15, 16).

**Kidney Weight (Fig. 2).** The trend of alterations of the kidney weight was in general the same as that observed on the heart. The combination of STH with thyroxine produced a slight but significant additive augmentation of the renotropic effect of STH [groups 3, 4; P
Neither cortisone nor DCA displayed a significant catabolic effect by themselves, and the inhibition of the growth-promoting action of STH by cortisone was less marked than on the heart.

Liver Weight (Fig. 2). The hormonal effects on the liver differed from those on the heart only in that thyroxine did not produce any increase in tissue mass.

Spleen Weight (Fig. 3). The main difference between the reactions of the spleen on the one hand and those of heart, kidney and liver on the other was the practically complete abolition of STH action by cortisone [P (1-7), (1-8), (1-15), (1-16) > 0.1], while in the other organs mentioned cortisone exerted only a weakening influence on the STH effect. Thyroxine and DCA per se left the spleen weight unaltered, but both combined produced a slight weight increase [P (1-10) < 0.05].

Thymus Weight (Fig. 3). The response of the thymus weight to hormonal influences resembled that of the other organs, except that cortisone brought the thymus tissue in all instances to virtually complete disappearance, even in combination with STH. The thymotropic action of STH was significantly diminished by DCA, both without and with thyroxine [P (3-11), (4-12) < 0.01].

Adrenal Weight (Table 1). Neither STH nor thyroxine caused any significant change of weight of the partly atrophic adrenal glands, while it was further markedly reduced by both cortisone and DCA and by their combination with each other or with STH and thyroxine.

**Discussion**

Several salient points emerge from the above described observations:

1. In hypophysectomized rats STH produced a marked cardiac hypertrophy, as compared with the heart mass of 30 normal rats of the same weight, despite subnormal blood pressure levels (fig. 1).

2. Thyroxine, in the relatively small doses applied, did not significantly intensify the cardiac hypertrophy-producing action of STH, but displayed a slight cardiotropic effect by itself. This does not necessarily disprove the contention that an adequate amount of thyroid hormone is essential in guaranteeing a full response of cardiac tissue to the cardiotropic action of STH, as indirectly suggested by observations on total body growth.7,12,22

3. In agreement with observations of v. Metzler,13b cortisone diminished the size of the heart significantly and inhibited the cardiotropic effects of both STH and thyroxine. The concept of Selye6 that the anti-STH action of cortisone is due to the concomitant adrenal cortical atrophy appears open to question in view of our observations that (a) DCA which, like cortisone, caused a marked atrophy of the adrenals, did not significantly interfere with the cardiotropic action of STH, and (b) cortisone inhibited the effect of STH on the heart weight maximally even in the presence of adequate doses of administered DCA. We feel rather inclined to attribute the antcardiotropic effect of cortisone to its specific protein-catabolic properties, which were also strikingly manifested on other organs (kidney, liver, spleen, thymus) and on total body weight.

4. DCA reduced the weight of the hearts of our hypophysectomized rats significantly in contrast to its cardiac hypertrophy-producing action in unilaterally nephrectomized and extra sodium-fed animals,26 and in those exposed to the stress of physical exertion.13 The unexpected discrepancy which, by the way, did not appear in v. Metzler’s hypophysectomized rats,13b may find some explanation in the observations of Vaccari20 and Michelazzi.14 They reported that DCA augments myocardial glycogen in vivo and in vitro, which suggests a loss of myocardial protein as the source of glycogenogenesis.

It seems that the different effects of DCA on heart size in salt-fed rats and in our normally fed but hypoadrenal, hypophysectomized animals can be attributed to differences in electrolyte balance. DCA tends to accumulate available sodium intracellularly in the myocardium,6,20 and surplus sodium enhances the hypertensive effect of DCA.15 The cardiotropic effect of DCA in exercising animals16a may be attributable in part to the potentiating action of DCA upon the pressor effect of the adrenosympathogenic neurohormones,16 which
disappears as a result of induced sodium lack.\textsuperscript{17}

In our series, DCA inhibited the cardio-trophic effect of thyroxine but not that of STH. The fact that the cardiotropic action of STH was not accentuated by DCA does not seem to support Selye's assumption that STH enlarges the heart through the mediation of DCA, but neither does it suffice, in itself, to disprove this concept. The absence of extra sodium and hypertension may have prevented such a hypothetical mechanism from becoming manifest. Furthermore, the adrenal atrophy of our hypophysectomized animals was not complete enough to exclude the presence of mineralocorticoids, which might have permitted the injected STH to exert its effect through them. However, even total adrenalectomy does not abolish the cardiotropic action of STH\textsuperscript{8} so that mediation through DCA cannot be considered an indispensable prerequisite for cardiotropic STH action.

(5) Our findings make it obvious that an increased cardiac work is not a necessary prerequisite for the development of myocardial hypertrophy under the influence of STH. Nevertheless, we cannot ignore the fact that increased peripheral or intracardiac (valvular) resistance and other conditions, which impose an abnormal work load on one or more chambers of the heart, are usually followed by a regional myocardial hypertrophy which is limited to the respective chamber or chambers. Under the assumption that STH action is indispensable for the development of work-induced cardiac hypertrophy, as indicated by the experiments of Bezğer and Hajdu,\textsuperscript{2,4} one may speculate whether the metabolic myocardial changes following contraction against abnormal tension may facilitate the hypertrophy-producing action of even normal amounts of circulating STH. Schumann\textsuperscript{22} has advanced the hypothesis that hypertrophy of the heart muscle develops whenever its oxidative metabolism is constantly increased, and an augmentation of myocardial metabolism under the influence of increased peripheral resistance has been shown experimentally.\textsuperscript{8, 21, 29} Observations in humans by means of coronary sinus catheterization and indirect approximation of the left ventricular myocardial mass were interpreted by Bing and associates\textsuperscript{8} as suggesting a normal myocardial consumption by that section of the heart in patients with hypertension and other forms of increased resistance, but the validity of such calculations remains to be established beyond doubt.

(6) The behavior of the total body weight, kidney, liver, spleen, and thymus under the hormone treatments used in our experiments followed in general the same pattern as that of the heart weight, except for certain quantitative differences and some minor qualitative variations. Spleen and thymus were distinguished by a maximal catabolic effectiveness of cortisone which totally abolished the growth-promoting effect of STH, and which brought the thymus to practically complete disappearance. In contrast to findings reported by v. Metzler,\textsuperscript{16} the size of the adrenal glands was reduced to a minimum by both cortisone and DCA.

(7) Our observations furnish a clue for a better understanding of "idiopathic" cardiac hypertrophy, as well as that which is found in normotensive individuals with acromegaly or coronary sclerosis. The incomplete and irregular causal linkage between so-called "hypertensive heart disease" and arterial hypertension has been critically discussed by one of us elsewhere.\textsuperscript{15, 16} We agree with the opinion of v. Metzler\textsuperscript{16} that cardiac hypertrophy may be caused either by increased cardiac work in the presence of a normal cardiotropic hormone production or by an excessive quantity of such hormones under normal cardiac dynamic conditions. It appears conceivable that hypertrophy of the human heart is dominated by the pituitary growth hormone, regardless of whether an excessive production occurs, as in acromegaly, or whether other factors, especially of increased myocardial work, sensitize the myocardium to normal hormonal concentrations in the blood stream. The complexity of the interrelated hormonal and hemodynamic factors (for example, STH-inhibitory but sometimes pressor action of cortisone) makes certain failures of correlation between cardiac
hypertrophy and arterial hypertension more readily intelligible.

**SUMMARY AND CONCLUSIONS**

Experimental studies on hypophysectomized rats indicate that cardiac hypertrophy is a complex phenomenon of essentially hormonal origin in which the pituitary growth hormone (STH) plays the leading part.

Increased mechanical work of the myocardium, although an important contributory factor conceivably through metabolic sensitization of the myocardium to STH, was not found to be a necessary prerequisite for the development of STH-induced cardiac hypertrophy. Marked increases of the myocardial mass were elicited by the administration of STH in hypophysectomized hypotensive rats without elevation of the blood pressure level.

Thyroxine possesses cardiotrophic properties of a lesser degree. It appears probable that the presence of a certain quantity of thyroid hormone is essential for a full tissue response to the growth-promoting action of STH.

Electrolytes appear to be involved in cardiac hypertrophy, for DCA, which increases intracellular myocardial sodium, and whose pressor action depends on the availability of sodium, did not induce cardiac hypertrophy in our hypophysectomized hypotensive rats without elevation of the blood pressure level.

Cortisone, apparently by virtue of its protein-catabolic properties, reduced the cardiac muscular mass and largely inhibited the cardiotrophic effect of STH.

The hormone-induced alterations of the heart weight, in the absence of arterial hypertension, were paralleled by similarly directed changes in the mass of other organs (kidney, liver, spleen, thymus) and in total body weight, but the degrees of these changes varied from organ to organ. The growth-promoting effect of STH on the spleen and thymus was completely abolished by cortisone while in other tissues it was only weakened by this hormone.

Applications of the above outlined conclusions to the understanding of "idiopathic" cardiac hypertrophy, as well as that found in normotensive individuals with acromegaly, etc., and the frequent disproportion between heart size and blood pressure level in "hypertensive" heart disease are briefly discussed.

**REFERENCES**

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