EXTREME CARDIAC HYPERTROPHY

REPORT OF TWO CASES WITH AORTIC HYPOPLASIA AND ENDOCRINE DISORDERS

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Cardiac hypertrophy exceeding 1000 grams in weight is rare. Golden and Brams (1937) could only find 37 cases recorded, excluding the 9 that they themselves reported. They did not include in their survey the cases occurring in acromegaly, to which Courville and Mason (1938) drew attention. In the two cases here reported the hearts weighed 1350 and 900 grams respectively and were associated with aortic hypoplasia and disorders of the endocrine system, one having diabetes mellitus, the other an interauricular septal defect and acromegaly.

NOTES OF FIRST CASE

This man had suffered with chronic nasal infection for many years and in 1935 he underwent drainage of the left frontal sinus. In 1936, when 28 years old, he began to lose weight and to be extremely thirsty; diabetes mellitus was diagnosed. He was treated with 60 units of soluble insulin and a diet containing 90 g. of carbohydrate daily.

He first attended the diabetic clinic of the Birmingham United Hospital in November, 1937. The same dietary and insulin regime was continued. Physical examination at that time showed a well-built man, 5 ft. 10 in. tall and 141 lb. in weight. The heart was enlarged and there was a systolic murmur and thrill of moderate intensity, just internal to the apex beat. The rhythm was regular at a rate of 80–85 beats a minute and the blood pressure varied between 100/70 and 120/80. At the diabetic clinic his blood sugar rose to between 300 and 400 mg. per 100 c.c. after lunch, but in spite of this he felt well and was able to do heavy work as a foundry worker. Six months later, however, on the same dosage of insulin and diet he began to have frequent hypoglycæmic attacks and for the next six months he was stabilized with 30 units daily, but then the blood sugar levels again climbed to between 300–400 mg. per 100 c.c. with no obvious change in the patient's well being. In 1938 he was admitted to hospital on account of hypoglycæmic coma, and careful examination at that time suggested a diagnosis of interventricular septal defect. The electrocardiogram showed a normal P–R interval, marked left axis deviation, and inverted T waves in leads I and II. Radioscopy showed the transverse measurement of the heart was 16.5 cm., with a chest diameter of 29.5 cm. (Fig. 1). Physical examination did not show any change and the blood pressure still remained at the same level.

In July, 1940, he was again admitted for investigation. He was then complaining of marked weakness and inability to work over the previous five weeks. He had noted, also, profuse sweating even when at rest and some breathlessness and palpitations on exertion. Again, physical examination was essentially as before, his Wasserman was negative, while his basal metabolic rate was +28 per cent with a basal pulse rate of 88.

At this time he was taking 150 g. of carbohydrate and 25 units of soluble insulin twice a day. He was treated with rest in bed and improved rapidly. After this he gave up his job as a foundry worker and took on that of a bread salesman. In January, 1941, he was admitted with hyperglycæmic coma, which rapidly reacted to treatment, but from this time onwards he began to complain of general weakness, listlessness, profuse sweating, and some swelling of his ankles at nights. His diet had now been increased to 170 g. of carbohydrate daily and his insulin to 25 units twice daily. His symptoms were severe enough to cause him to stop work for 10 weeks and rest at home. This caused a good deal of improvement but a basic metabolic rate, as an out-patient, was shown to be +35 per cent and he was, therefore, admitted again for investigation on 21/1/41. At that time a note was made

FIG. 1.

- (A) 1938. Radiograph showing general enlargement of heart. In 1941 (one month prior to death) a radiograph showed no evidence of any increase in size since 1938.
- (B) 1938. Left (II) oblique view showing left ventricular enlargement.

that his eyes were rather prominent and there was some clubbing of his fingers. Examination of the heart was as before with a blood pressure of 100/70. The thyroid gland was not enlarged or palpable. His basal metabolic rate was +48 per cent with a basal pulse rate of 92. On 17/5/41 he was first seen by us and a note was made: "Main complaint, loss of energy and marked sweating. On questioning, a cough for nearly two years with some sputum (this had been negative for tubercle bacilli in the past), never blood-stained. Weight constant. Some palpitation on exertion, no nervousness, fair appetite, had always had mild exophthalmos."

Examination showed no tremor but much sweating and marked nasal catarrh. No thyroid enlargement and no positive eye signs. Early clubbing of fingers. Heart enlarged. Moderate systolic murmur just internal to apex beat. Spleen not enlarged.

This time his metabolic rate was +60 per cent with a pulse rate of 80. X-ray of chest did not show any pulmonary infection and the heart shadow could be exactly superimposed on that taken in 1938. It was considered that surgery was not indicated at the time and observation was therefore continued and further attempts were made to control his diabetes and his excessive sweating. He was improving and the diabetes becoming more stable so that he was able to be about the ward helping with routine duties. A primary pituitary dysfunction explaining both the unstable diabetic state and thyrotoxic symptoms was considered possible. However, on 4/7/41 following seeing his visitors and being about to have his tea, with no symptoms of any sort, he went unconscious and died a few minutes later.

Post-mortem examination. This was carried out eighteen hours after death by Professor Haswell Wilson. The body was that of a well-developed man, with some lividity of the head, neck, and dependent parts.

The pericardial sac was normal. The heart (Fig. 2) was enormously enlarged, 1350 grams in weight. The left ventricle was hypertrophied, the wall measuring 5 cm. (after fixation in formalin). The right ventricle was also hypertrophied but to a much less extent, measuring 1 cm. in thickness. Both were slightly dilated with relative incompetence of the mitral and tricuspid valves. There was no ante-mortem thrombus. The coronary arteries were healthy in appearance but the solid mass of muscle showed areas of diffuse fibrosis, evidently a degenerative change supervening on extreme hypertrophy. There was no valvular lesion in the heart. The ascending aorta appeared to be of normal diameter at the aortic valves. The diameter gradually narrowed to a point just proximal to the attachment of the remnants of the ductus arteriosus. There did not appear to be any actual coarctation, the circumference at this point in the fixed specimen measured 5 cm. approximately. The distal part of the aorta tapered down gradually so that the circumference of the common iliacs

FIG. 2.—The interior of the left ventricle is shown. The great thickness of the wall and apparently normal aortic valves are seen. The right ventricle has also been opened and also shows hypertrophy (Case 1).

was only 2 cm. respectively. Extensive and severe atheroma was present in the lower part of the aorta and common iliac arteries, contrasting with the ascending aorta.

The lungs were voluminous and overlapped the pericardium. The left was adherent all over by old fibrous adhesions. The right was free. Both showed chronic bronchitis and emphysema, with sticky muco-pus in the bronchi and some œdema at the bases and posteriorly.

The peritoneum was normal. No abnormality was found in the abdominal organs. They were all engorged with blood. The pancreas showed no gross structural change.

The brain and its membranes were congested. The brain itself was rather atrophic with thin convolutions and wide perivascular spaces. The vessels at the base were healthy. No obvious lesion was found in the pituitary, thyroid, or suprarenals.

Histology. The heart muscle fibres were generally greatly hypertrophied although some were atrophic (Fig. 3). All sizes of fibres were present up to a diameter of 23μ . The nuclei were also markedly enlarged, appearing lobulated in many cases. Throughout the whole myocardium the interstitial fibrous tissue was increased and in some areas this was marked. There was no evidence of any inflammatory lesion. The arteries appeared normal though in several areas there seemed to be an increase in the perivascular lymphatic spaces of some arteries. There was no evidence of arteriosclerosis. Special stains did not reveal the presence of either amyloid or glycogen.

Sections from the thyroid and kidneys were entirely normal. Sections from the pituitary were not made.

Comment. This man was able to carry on heavy work as a foundry worker for at least two years with no increase in the radiological size of his heart. Only in the last year of his life did symptoms of diminished cardiac reserve appear. Moreover the measurement of the heart by X-ray examination gave us little indication of the excessive weight. The reason was obvious at autopsy when it was seen that the size of the heart chambers was small when compared with the muscle mass.

For some inexplicable reason the mode of death in gross enlargement of the heart is frequently sudden; and pathological examination, as in this patient, is often unable to elucidate the actual cause.

NOTES OF SECOND CASE

A woman, aged 32, was admitted to the Birmingham United Hospital in August, 1939, for increasing shortness of breath and palpitation on exertion. She had been short of breath all her life, a

FIG. 3.—Photo-micrograph of ventricular wall showing the variation in size of muscle fibres and the increase of fibrous tissue. Magnification $\times 150$ (Case 1).

fact she had attributed to a goitre. Her arms had always been hairy and her menstruation irregular. For ten years she had been taking thyroid tablets which caused her periods to become regular. Her weight had been constant at 165 lb. for many years. Recently her shortness of breath had become so marked that she was unable to do her housework and could only sit out of bed in a chair. Examination then showed a patient of masculine build, 5 ft. 8 in. tall, with a large head and hands and hairy arms and legs. The thyroid was enlarged, extending up from behind the sternum. There was no exophthalmos. The apex beat was outside the midclavicular line (Fig. 4): the heart was fibrillating

FIG. 4.—Radiograph of the chest (Case 2) showing the large retrosternal goitre, the enlarged heart, and the marked pulmonary vascular shadows, especially at the hila.

with a systolic and diastolic murmur at the mitral area heard all over the praecordium. The blood pressure was 130/80. There were no obvious clinical signs of congestive cardiac failure. The lungs, abdomen, and central nervous system did not show any abnormality. A cardiogram showed auricular fibrillation, rate 125, and left axis deviation.

An X-ray of the skull showed enlargement of the pituitary fossa. Her basal metabolic rate taken on five separate occasions varied between +21 and +28 per cent. A diurnal variation blood sugar curve showed values never rising above 100 mg. per 100 c.c. A diagnosis of acromegaly, retrosternal goitre, and rheumatic heart disease with mitral stenosis was made. Following a period of treatment with digitalis and Lugol's iodine, a subtotal thyroidectomy was carried out by Mr. Hugh Donovan in October. She made a satisfactory convalescence and was discharged home on the twelfth day after operation.

Histological report on the gland was as follows: "The gland is divided up by broad dense bands of fibrous tissue into lobules. The epithelium in these areas stains well and is slightly more prominent than usual. Colloid, however, is plentiful and only here and there exhibits a foamy appearance. The histological picture suggests that the thyroid hyperactivity is not a very marked feature."

At home she carried on normally until about one year prior to her final admission when she again became short of breath and unable to do her house duties. She became increasingly dull and disinterested, culminating in a refusal to speak. She was admitted to hospital for the second time in March, 1942. She was then uncooperative, incontinent, and in marked congestive failure (B.P. 105/80). She made no response to therapy. On account of her mental condition she was transferred to a mental hospital, where she died in congestive failure in May.

Post-mortem examination. This was carried out by Dr. Cox twelve hours after death. The body was well-nourished, with very large hands and feet and with marked ascites.

Very thick skull. Brain (1644 g.), normal externally except for small adhesions at tips of frontal and temporal lobes. Pituitary fossa very enlarged. Antra, chronic infected membranes. Frontal sinuses clear. Sphenoids, heavily infected. Teeth, septic and carious.

Lungs, normal in appearance and texture. Sero-sanguinous fluid in both pleural cavities.

Pericardial sac contained 1600 c.c. of straw-coloured fluid. Numerous pericardial adhesions.

Heart covered with thick white fibrinous membrane, the result of old pericarditis.

Heart: weight 900 g. Left ventricular chamber small with greatly hypertrophied walls, maximum thickness 30 mm. (Fig. 5). Right ventricle also hypertrophied but dilated, maximum thickness 8 mm. Left auricle dilated with some increase in the thickness of its wall. Right auricle also hypertrophied and dilated. In the posterior half of the interauricular septum, there was failure of development of the septum secundum, causing a septal defect 22 mm. in diameter. Chordae tendineae of mitral valve hypertrophied. The valve cusps themselves were normal as were those of the tricuspid, aortic, and pulmonary valves.

Pulmonary artery, enlarged. At the pulmonary valves, the circumference was 11 cm. Left pulmonary artery, 1 cm. after bifurcation, measured 9 cm. in circumference.

Aorta, hypoplastic, the circumference at the aortic valves being 8 cm.; at the level of insertion of the fibrous remnant of the ductus arteriosus, 6 cm.; and at a point 12 cm. distal to that, 5 cm. There was no atheroma. The pulmonary veins opened into the left auricle while the superior and inferior vena cava emptied into the right auricle.

Free fluid present in the abdomen. Liver (1990 g.) dark and congested. Spleen (164 g.) unusually firm. Kidneys: right (294 g.) normal; left (420 g.) large number of cysts at the upper pole, otherwise normal. Ovaries, large and fibrotic. Uterus, irregular with fibroids on the posterior surface.

Histology. Sections from the kidneys, liver, and adrenals were normal except for congestion. The heart muscle showed no evidence of inflammation. The individual fibres were large with normal nuclei. The pericardium was thickened with many layers of fibrous tissue, but no area of active inflammation could be detected. The pituitary showed poorly staining cells only. There was no adenoma or obvious increase of eosinophilic cells.

Comment. Enlargement of the heart is frequently noted in interauricular septal defect. For example, Roesler (1934) reported the case of a girl, aged 14, with a heart weighing 800 g., while Bedford, Papp, and Parkinson (1941) included in their series of 52 cases the case of a woman, aged 36, with a heart weighing 930 g., although this was associated with rheumatic heart disease and mitral stenosis. The enlargement and hypertrophy in such cases involves the right side of the heart, the left auricle and ventricle appearing sometimes almost as appendages. Commonly the pulmonary artery is much enlarged while the aorta is smaller than normal. In this case there was marked enlargement of the pulmonary artery and the aorta was small: the ratio between the two circumferences was essentially that given by Roesler, 3:2. The cardiac hypertrophy, however, did not involve the right side, throwing doubt upon the role of the septal defect in the production of such massive enlargement. This finding also suggests that the frequent association of septal defect with a small aorta is not always due to the diminished output of the left ventricle as was suggested by Bedford, Papp, and Parkinson.

FIG. 5.—Photograph of the heart.

- (A) The right ventricle is opened, showing some hypertrophy of its wall, the large pulmonary artery, and the comparatively small aorta.
 (B) The dilated and hypertrophied left auricle is opened showing the interauricular septal defect.

Adhesive pericarditis has been noted in atrial septal defects by many writers, *e.g.* by Cossio and Arana (1937), and by Bedford, Papp, and Parkinson (1941), though usually in association with rheumatic valvular disease. The exact aetiology in this case is obscure though it was probably rheumatic. Auricular fibrillation is also common, occurring in 28 cases out of the 62 collected by Roesler; though Bedford, Papp, and Parkinson did not find any recorded case occurring below the age of fifty except in association with mitral stenosis. Finally, there was no evidence in this case that hypertension had been present to account for the enlargement of the left ventricle.

DISCUSSION

Enlargement of the heart usually takes place for two reasons only, either in response to increased work (*e.g.* high blood pressure, valvular disease, or arteriovenous aneurysm) or to the impairment of the heart's metabolism and reserve by rheumatic fever, the anoxaemia of coronary disease, or lack of thyroid hormone or vitamin B₁, etc. In Case 1, none of these intrinsic factors appeared to play any part. It is difficult to assess the role of diabetes with recurrent hypoglycaemia with subsequent impairment of function. It is not probable, however, that this factor caused such hypertrophy in the short space of two years, from the time of onset of his diabetes in 1936 to the time of the first X-ray in 1938. In Case 2, the role of the septal defect was probably small, seeing that the predominant hypertrophy affected the left ventricle, whilst there was no evidence of the presence of coronary disease, or of vitamin or thyroid deficiency.

Both large and small hearts may be found in aortic hypoplasia, while hypertrophy, usually attributed to the associated high blood pressure, is frequently found in coarctation of the aorta. This last condition occurs in varying degrees, from constriction that is scarcely recognizable to actual atresia, and may be associated with hypoplasia of the distal aorta, again of varying degrees. In Case 1, there did not appear to be any definite coarctation but there was a rapid diminution in the width of the aorta, commencing just proximal to the fibrous remnant of the ductus arteriosus. In Case 2, the aorta appeared to diminish gradually in size from the aortic valves themselves.

The role played by the narrowed aorta in the production of hypertrophy is obscure and there is very little to be gathered from other reports. The first description of aortic hypoplasia was that given by Morgagni in 1788. King (1841) drew attention to the condition in this country. On the continent, Virchow (1872), Spitzer (1897), Burke (1901), and Apelt (1905), all described cases associated with cardiac hypertrophy but none of them had any data on the blood pressure. Spitzer held that hypertrophy was found if the patient attained adult life; otherwise the heart would be smaller than normal. Virchow attributed the hypertrophy to the narrow aorta and increased elasticity of the vessels. In a number of these early cases changes were noted in the kidneys so that it is probable that high blood pressure was present in some. However, as Apelt pointed out, there was no constant feature in any case by which one could say hypertrophy would be present or not. More recently, Whittle (1929) reported the case of a young man, aged 20, who collapsed and died in the street; other than a recent attack of influenza, there was no record of any previous illness. The autopsy revealed a heart weighing 793 g., with a general enlargement chiefly affecting the left ventricle; the descending aorta was hypoplastic, but it was not specifically stated whether the thoracic aorta was of normal calibre; the remaining organs were normal though the heart was not tested for glycogen. Cluver and Jokl (1942) reported the case of an international Rugby football player who suddenly dropped dead. The arch of the aorta were of normal size but the abdominal aorta measured only half an inch, half the normal size; the heart weighed 482 g.; and the left kidney was the seat of advanced hydronephrosis and pyelo-nephritis. They called attention to the large thymus (26 g.) and the possible secondary effects upon the adrenal and pituitary glands.

It is difficult in the two cases here reported to explain the association of gross hypertrophy and normal blood pressure by any of the accepted physiological concepts. Eyster (1927) may provide some clue as to how such hypertrophy takes place. He showed that, by placing a constricting band around the aorta of dogs for a short period, hypertrophy followed some months later, and he suggested that the temporary dilatation provided the stimulus for the subsequent enlargement. This concept might be extended to these cases. The temporary dilatation to cope with the extra output requirements in strenuous work, might act as the stimulus for the hypertrophy and the finding of a normal blood pressure at rest.

While aortic hypoplasia may have played a large part, we find it difficult to believe that this factor alone would account for such massive enlargement. In Case 1, the heart was almost twice the weight of any of the other recorded cases. Case 2, however, was acromegalic and, in view of other recorded examples, *e.g.* Cushing and Davidoff (1927), and the general splanchnomegaly that occurs, it may be assumed that pituitary dysfunction played a large part in the production of the cardiac hypertrophy. Amsler (1912) attributed such hypertrophy to a direct hormonal action on the heart, while Courville and Mason have reported two cases suggesting that enlargement of the heart may precede the development of obvious signs of acromegaly. They stressed the high incidence of hypertrophy and heart failure and the infrequency of high blood pressure in acromegalics, and concluded that the hormonal theory offered the most satisfactory explanation for the cardiac enlargement.

In Case 1, the very variable response of the diabetes and the symptoms suggestive of thyrotoxicosis were clinical features that pointed to a primary pituitary defect. Therefore, if only

for the sake of directing future observations to the possibility in obscure cardiac hypertrophy, we would suggest that excessive action of the anterior lobe of the pituitary gland may have played a part in producing the extreme enlargement found in this patient. Unfortunately, owing to an oversight, no sections were made of the pituitary gland.

Finally, we can only agree with Sir Thomas Lewis (1933) that "There is still much that remains to be explained: it is clear that there must be hidden sources of increased work or the conclusion that increased work is the cause of hypertrophy needs revision."

SUMMARY

Two cases of extreme cardiac hypertrophy are reported.

In the first, a male diabetic, aged 33 years, the heart weighed 1350 grams. There was no associated valvular disease and only moderate increase in the size of the heart chambers. The descending part of the thoracic and abdominal aorta showed moderate hypoplasia. No definite cause for this extreme cardiac hypertrophy could be found, but there was evidence of thyrotoxicosis and it is suggested that pituitary hyperfunction played some part.

In the second, a female acromegalic, aged 35 years, the heart weighed 900 grams. The hypertrophy affected the left ventricle predominantly and was associated with an interauricular septal defect and hypoplasia of the aorta. The pituitary dysfunction was thought to have played the chief part in the production of the enlargement in this case.

We are indebted to Professor Haswell Wilson for the pathological report of Case 1, and we wish to thank Dr. Oscar Brenner for the clinical details, Dr. Pickworth and Dr. Cox for pathological and microscopical reports in Case 2, and Dr. T. C. Graves, Medical Superintendent, Rubery Hill Hospital, for facilities granted.

REFERENCES

- Amsler, C. (1912). *Berl. klin. Wschr.*, **2**, 1600.
 Apelt, F. (1905). *Dtsch. med. Wschr.*, **31**, 1233.
 Bedford, D. E., Papp, C., Parkinson, J. (1941). *Brit. Heart J.*, **3**, 37.
 Burke (1901). *Dtsch. Arch. klin. Med.*, **71**, 189.
 Cluver, E. H., and Jokl, E. (1942). *Amer. Heart J.*, **24**, 405.
 Cossio, R. and Arana, R. S. (1937). *Bull. Acad. Méd. Paris*, **117**, 212.
 Cushing, H. and Davidoff, L. M. (1927). *Monograph 22*, Rockefeller Institute for Medical Research.
 Courville, C., and Mason, V. R. (1938). *Arch. intern. Med.*, **61**, 704.
 Eyster, J. A. E. (1927). *Trans. Ass. Amer. Physicians*, **42**, 15.
 Golden, J. A., and Brams, W. A. (1937). *Amer. Heart J.*, **13**, 207.
 King, F. W. (1841). *Lond. med. Gaz., N.S.*, **1**, 685, 751.
 Lewis, T. (1933). *Diseases of the Heart*, London.
 Morgagni (1789). Quoted by Burke (1901).
 Roesler, H. (1934). *Arch. intern. Med.*, **54**, 339.
 Spitzer (1897). Quoted by Apelt (1905).
 Virchow (1872). Quoted by Apelt (1905).
 Whittle, C. H. (1929). *Lancet*, **1**, 1354.