

CARDIAC GLYCOGENOSIS

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Cardiomegaly due to excessive glycogen deposition in cardiac muscle as part of a generalised glycogenosis often presents diagnostic problems which can only be resolved at autopsy. More generally known as cardiac glycogenosis, this is apparently not a common condition and somewhat less than fifty cases have so far been recognised in literature (Kringelbach, 1960). Related to von Gierke's disease only by the fact that the abnormal storage material is glycogen, it was first described by Pompe in 1932. Since then, the sporadic and sometimes confusing reports have contributed to the obscurity of this disease entity until the careful description of di San't Agnese et al. (1950a, 1950b) and the biochemical evidence of Cori (1954) have helped to elucidate the subject of glycogenosis in general and cardiac glycogenosis in particular.

CASES

Case 1: T.E.B. (9755/61), a nine months old male Chinese baby was admitted to the Penang General Hospital on 15-7-61 with a history of cough and fever of four days' duration. The parents had also noticed the child being somewhat "breathless" and having a weak cry two days before admission. He was a normal full term baby and the only child.

On examination, the child was found to be dyspnoeic, with cold extremities and peripheral cyanosis. There were some feeble attempts at coughing. Percussion was impaired over the whole of the left chest, anteriorly and posteriorly and air entry was absent over the same area. There were no adventitious lung sounds. The heart was rapid—160 beats per minute—and the cardiac dullness was increased to the right side. Auscultation revealed a triple rhythm but no murmurs were heard. The other significant finding was the liver which was enlarged 2 finger-breadths below the right costal margin.

A provisional diagnosis of left pleural effusion and cardiac failure was made and a chest aspiration done. One and a half ounces of clear serous fluid was obtained. The radiograph showed an enlarged heart shadow continuous with a uniform opacity in the left chest (Fig. 1). The electrocardiogram showed a regular heart rate of 150 per minute; P-R interval of 0.16 sec.; left ventricular preponderance; QRS of high voltage in all standard limb and chest leads and

a duration of 0.12 sec., S-T depression in leads I, II, AVL, AVF and V₆; inverted T wave in leads I, II, III, AVF, V₄ and V₆.

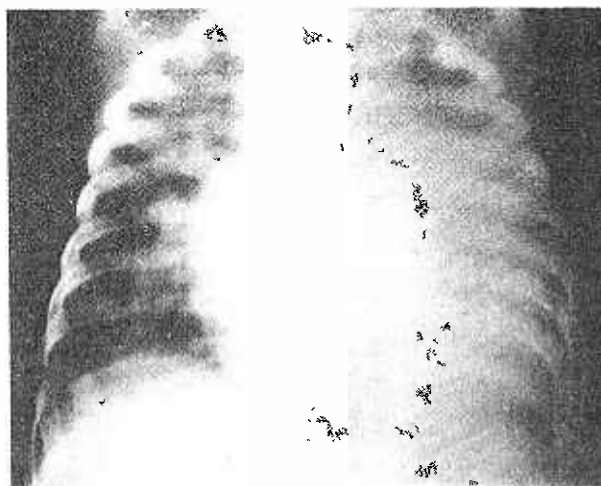


Fig. 1. Chest radiograph of Case 1.

He was treated with Lanoxin 0.15 mgm. stat and 0.05 mgm. b.d. and crystalline penicillin 0.5 mega units b.d.

No improvement in the clinical condition was observed and he died 10 days later after steady deterioration.

The autopsy was performed 12 hours after death. The body was that of an apparently normally developed child for that age. There were no external malformations. The heart was greatly enlarged and filled the whole of the left hemithorax, collapsing and displacing the left lung upwards. This enlargement was mainly due to the left ventricle whose wall measured 30 mm. thick. The right ventricle was also uniformly thickened to 15 mm. There was no valvular abnormality or septal defect and the coronary as well as the great vessels were normal. The atria were not thickened. The other viscera did not show any gross abnormality except for the slightly enlarged and pale-looking liver.

Portions of the heart, liver, spleen and kidneys were taken and fixed in 10% formal saline. Routine H. & E. sections showed characteristic vacuolation of all cardiac fibres—the so-called "lace-work" appearance (Figs. 2 and 3). The media of the coronary vessels were also diffusely affected (Fig. 4). The liver cells were swollen and "foamy" (Fig. 5). The spleen showed no changes except for vacuolation of the media of

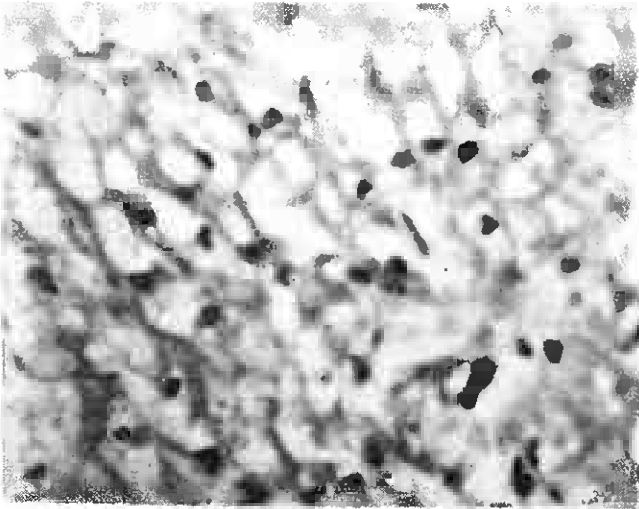


Fig. 2. Transverse section of heart muscle showing the "lace-work" appearance. H. & E. X 440.

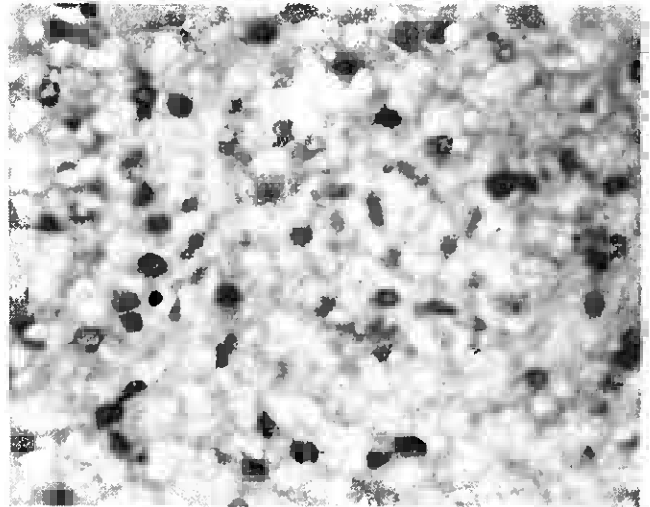


Fig. 5. Swollen "foamy" liver parenchymal cells. H. & E. X 440.

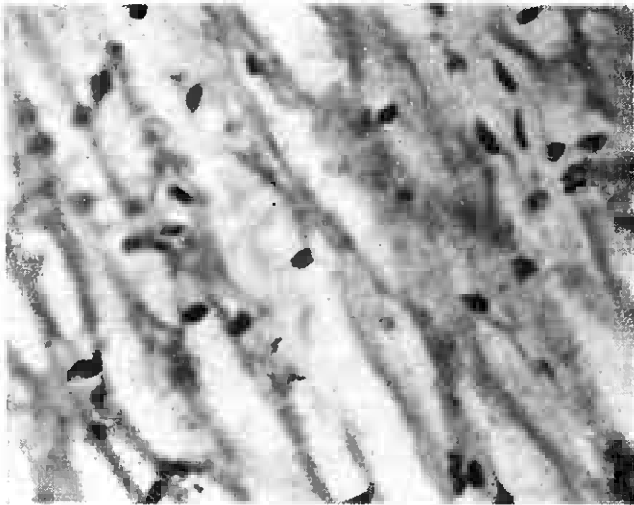


Fig. 3. Longitudinal section of cardiac muscle, showing vacuolation through the length of the fibre due to glycogen infiltration. H. & E. X 470.

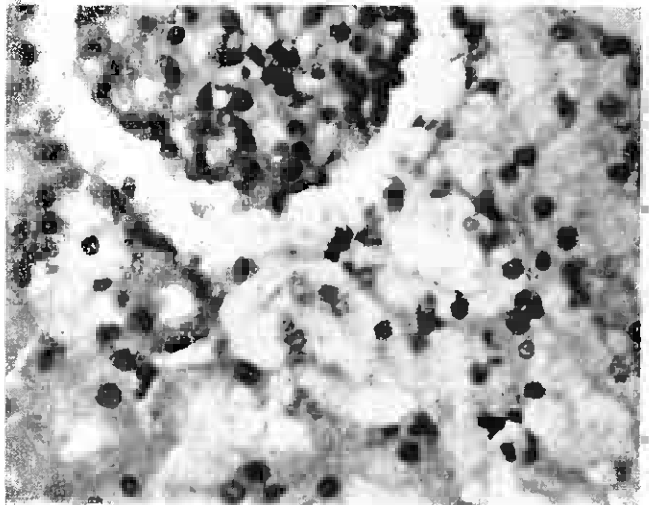


Fig. 6. "Foamy" infiltration of the distal convoluted tubule cells of kidney. Compare with normal adjacent proximal tubules. H. & E. X 440.

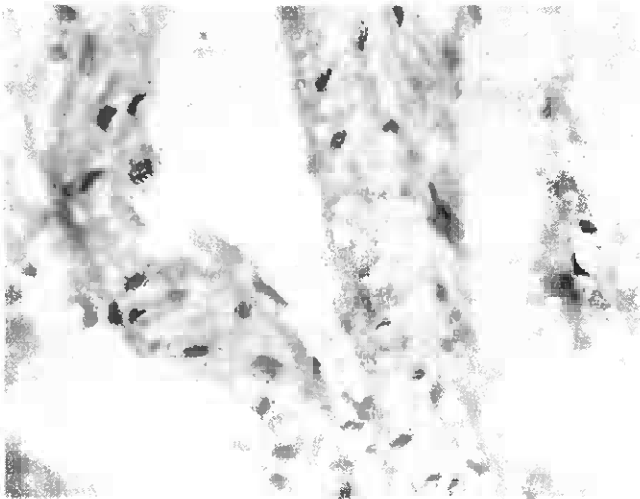


Fig. 4. Media of coronary artery infiltrated with glycogen. H. & E. X 440.

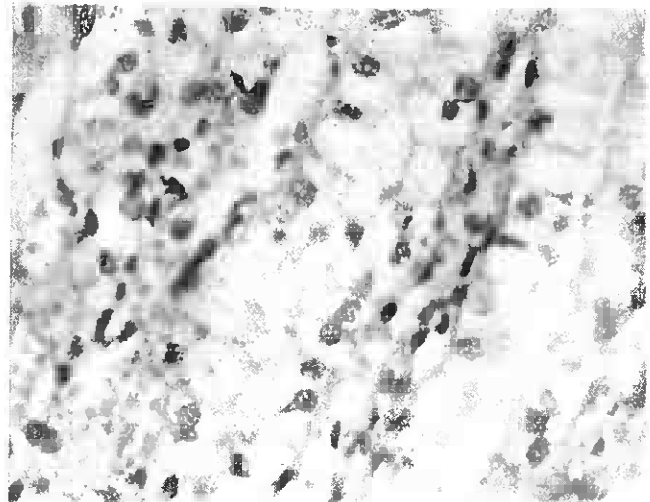


Fig. 7. Water-clear appearance of collecting tubules of kidney. H. & E. X 440.

the vessels. In the kidney sections there was vacuolation of the vascular media, "foamy" infiltration of the distal convoluted tubules (Fig. 6) and a water-clear appearance of the collecting tubules (Fig. 7). Histochemical studies revealed partial fatty infiltration of the liver. Tiny discrete globular periodic acid Schiff (P.A.S.) positive and diastase-labile bodies were seen diffusely and irregularly distributed in the vacuolated areas of the heart, blood vessels, renal tubules and in the foamy cells of the liver. Best's carmine stained these areas somewhat irregularly. The spleen showed a diffuse uniform dusting of P.A.S. positive particles.

The diagnosis of generalised or cardiac glycogenosis was made.

Case II: Y.L.K. (5690/62) a female Chinese infant 50 days old, was admitted on 4-5-62 with "rapid breathing" and fever for the previous 3 days. She was the 6th in a family of apparently healthy children and was normally delivered at full term.

On examination the child was found to be mildly cyanosed and dyspnoeic but the neck veins were not engorged. She had a temperature of 99°F and a weak cry. There was impaired percussion over the right hemithorax anteriorly with diminished breath sounds and rales at the right lung base. The heart sounds were distinct and regular. There were no murmurs. The liver was 2 finger-breadths enlarged below the right costal margin.

A provisional diagnosis of lobar pneumonia was made and this was confirmed radiologically when a picture consistent with right upper lobe consolidation was obtained. In addition globular cardiomegaly was also noticed (Fig. 8).

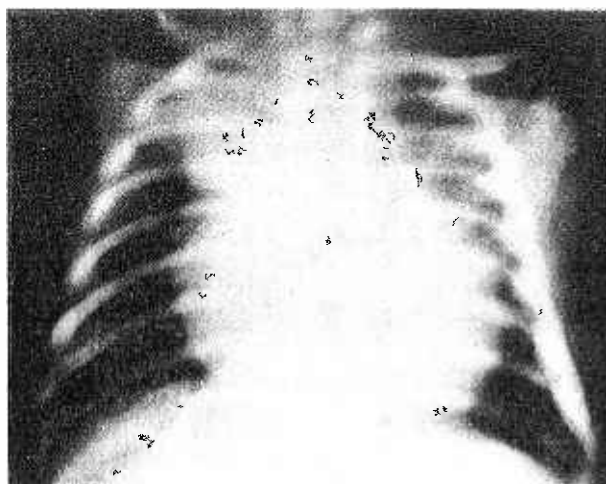


Fig. 8. Chest radiograph of Case II. Note the globular heart configuration.

The child was treated with crystalline penicillin injections and Lanoxin to which she responded gradually and after 20 days was deemed to have recovered. An E.C.G. done during this time showed a regular heart rate of 150 per min.; a P-R interval of 0.12 secs.; narrow QRS complexes (0.04 sec.) of high voltage in all the leads. There was evidence of right as well as left ventricular predominance. The P wave was peaked and more than 3 mm. in lead II. Depression of the S-T segment and pointed T-wave invasion were seen in V_1R , V_1 , V_2 , and V_1 .

On the evening of 24-5-62, the child suddenly became severely dyspnoeic. On examination the neck veins were engorged but there was no cyanosis. The heart was regular. There was no impaired percussion but moist sounds were heard over both lungs. The liver was 3 finger-breadths enlarged below the right costal margin.

The diagnosis of acute heart failure was made and intramuscular digoxin 0.1 mgm. was given. The child did not respond to treatment and died early the following day.

An autopsy was done on the same day of death. The body was that of a normally developed child. The heart was enlarged, this being due to uniform thickening of both ventricles whose walls were 10 mm. thick. There were no valvular or septal defects nor abnormalities of the coronary or great vessels. Both basal lobes of the lung were congested. The liver was enlarged and pale. There were no other gross abnormalities.

Sections from the heart showed a "lace-work" pattern similar to that of Case I (Figs. 9 & 10). The liver architecture was preserved but the parenchymal cells had a "foamy" appearance.

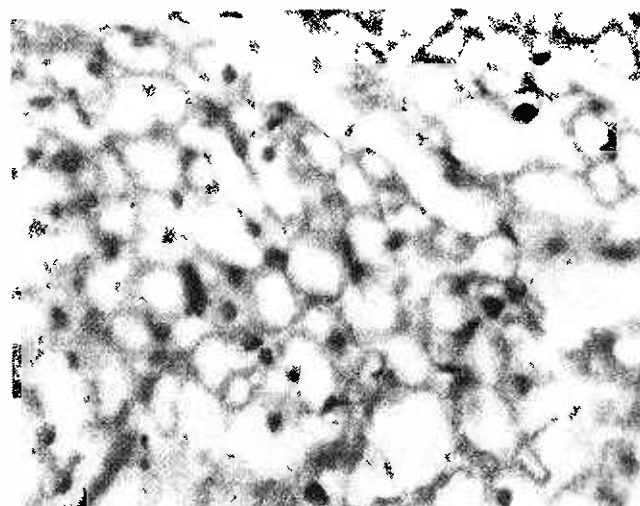


Fig. 9. Frozen section—transverse—of cardiac muscle of Case II. H. & E. X 440.

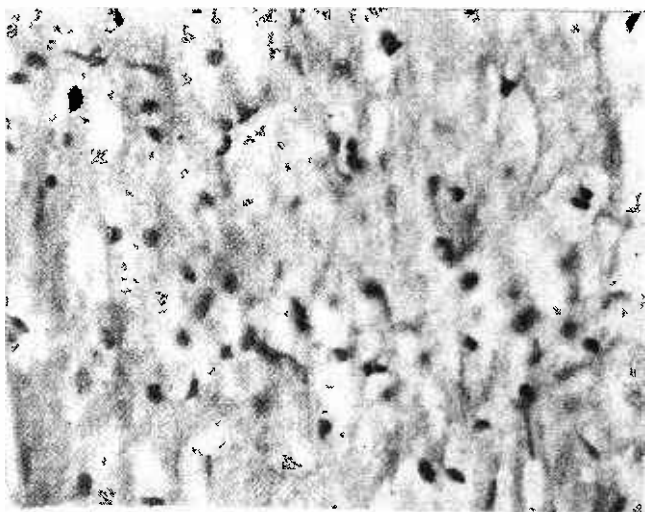


Fig. 10. Frozen section—longitudinal—of cardiac muscle. Note thin hazy film over vacuolated areas. This is due to a thin layer of intact myofibrils. H. & E. X 440.

Except for mild vacuolation of the media of the renal and splenic vessels, no striking changes were seen in these organs. There was partial fatty infiltration of the liver, but histochemical tests for glycogen were negative. (These organs were fixed in 10% formal saline). In spite of this failure to demonstrate glycogen, the characteristic histological picture and the clinical presentation of the case, was sufficient to warrant the diagnosis of cardiac glycogenosis.

DISCUSSION

Cardiac glycogenosis is one of the better known of the group of diseases of abnormal accumulation of glycogen, the best known entity being von Gierke's disease. The work of Cori (1954) on the few cases of glycogenosis has given us a provisional biochemical basis of classification. (di San't Agnese, 1959), viz.,

- Type I — Hepato-renal, von Gierke's
- Type II — Cardiac or generalised
- Type III — Limit dextrinosis
- Type IV — Hepatic type with cirrhosis
- Type V — Muscular type.

Whilst the other types are commonly characterised by a well-established enzyme defect and varying biochemical abnormalities, cardiac glycogenosis is distinguished by the absence of any of these. This increases the difficulty of diagnosis during life unless there is awareness of the possibility of this condition and muscle biopsy or tissue glycogen analysis is carried out. In the cardiac form, all the affected organs show a variable increased glycogen content but the characteristic histological changes occur mainly in

cardiac and skeletal muscles. Recently Kringelbach (1960) reporting the first case in Scandinavia found a raised serum glutamic oxaloacetic transaminase in his case. The actual significance of this finding is difficult to interpret but it is possibly due to damage to the muscular tissue by the infiltrating glycogen.

In common with von Gierke's disease, a familial incidence has been found in some instances (di San't Agnese, 1950a; Hinerman, 1955) but the invariably fatal course of the disease in infancy and its rarity has precluded direct analysis of heredity (McPhie, 1960). Clinically there are no pathognomonic features which point to its immediate recognition. Radiologically there is the globular enlargement of the cardiac shadow which was so extreme as to mimic a pleural effusion in Case I. The E.C.G. changes are variable, the most consistent being QRS complexes of great amplitude, depressed ST segments and inverted T waves in the same affected leads (di San't Agnese et al., 1950a, Kringelbach, 1960). In this report, the depression of the ST segments and the corresponding T wave inversions were more obvious in standard limb leads of one case (Case I) and in chest leads of the other (Case II).

The autopsy findings in such cases are striking. The heart is uniformly and greatly enlarged, this being due to the *uniform* thickening of the ventricular walls. The valves are normal and the great vessels as they emerge from the base of the heart are dwarfed in comparison to the big bulging ventricles. In Case I the cardiac enlargement was so gross that it almost occupied the whole of the left hemithorax. An important feature is the *uniform* thickening of the ventricle and the absence of other structural defects. Glycogen containing tumours—the rhabdomyomas—sometimes occur and might be mistaken as examples of cardiac glycogen storage disease. Such cases often show multiple tumours in otherwise normal ventricular musculature. The distinction between these and true cases of cardiac glycogenosis has been stressed (Landing and Farber, 1956) and the excellent review by Batchelor and Maun (1945) leaves us in no doubt as to the entirely different nature of these "congenital glycogenic tumours" of the heart. In certain other cardiac malformations e.g., anomalous origin of the coronary artery, abnormally large foramen ovale and pulmonary artery, and endocardial fibroelastosis, circumscribed areas of degenerate muscle with abnormal amounts of glycogen have been described (di San't Agnese, 1950; Caplan, 1958). These are mentioned to stress their difference from true cardiac glycogenosis which is a de-

finitely diffuse infiltration of the ventricular myocardium of an otherwise normal heart. The other viscera usually show no gross macroscopic abnormalities although this condition is histologically a generalised glycogenosis. The liver was slightly enlarged in both cases described here. This was partly due to a concomitant mild degree of fatty infiltration.

Histologically, changes in the cardiac muscle are striking and characteristic. The centre of the cardiac muscle fibre is vacuolated and the sarcoplasm is displaced peripherally. This is due to the infiltrating glycogen which is not stained in H. & E. sections. On transverse section the myofibrillae are especially prominent in frozen sections, having a granular appearance. Suitable longitudinal sections show intact striations. This widespread vacuolation uniformly affects all the ventricular muscle fibres giving it the so-called lace-work appearance (Figs. 3, 4, 9, 10). Similar changes are said to occur in skeletal muscles. The generalised nature of this condition is seen in the widespread vacuolation of the media of the blood vessels. The liver is also affected and the parenchymal cells show a "foamy" appearance (Fig. 5). The kidneys are affected according, apparently, to the severity of the glycogenosis. In Case I, vacuolation was seen in the distal convoluted tubules and the collecting tubular cells, giving the latter an appearance of so-called "water-clear" cytoplasm. No significant changes of this nature were seen in Case II who died at the age of two months. Although di San't Agnese et al. (1950) described glycogen in acinar, duct and several islet cells of the pancreas, it was Hinnerman (1955) who in his report on generalised glycogenosis associated with maternal diabetes, paid particular attention to the islet cells. He found marked hypertrophy and hyperplasia of the beta- and gamma-cells and marked diminution of alpha-cells and postulated that glucagon, a potent glycogenolytic factor, which was manufactured by the alpha-cells might be deficient in these cases. This observation based on morphologic data has not been substantiated biochemically.

Direct histochemical demonstration of glycogen in the affected tissues might be desirable as in the first case, but not an indispensable primary requisite in the diagnosis of glycogenosis. The pitfalls of histochemical methods in such cases should be realised. Glycogen is a normal storage substance in the body and the demonstration of glycogen by itself does not prove the presence of glycogenosis. As has been pointed out, certain other cardiac conditions can give rise to glycogen in the heart but these conditions

are by no means the same as cardiac glycogenosis. From the practical point of view, it has perhaps been insufficiently stressed that the glycogen in the affected tissues of these cases behaves normally as far as autoglycogenolysis is concerned. At 37°C. this occurs at variable but appreciable rates which vary from 15-83% for cardiac glycogen and nearly 100% for hepatic glycogen in 24 hours. This also occurs in the other affected tissues (di San't Agnese et al., 1950a, 1950b). Therefore, unless adequate precautions are taken to collect the specimens soon after death, the amount of histochemically detectable glycogen might be markedly diminished if not absent. Glycogen is also freely soluble in aqueous solutions giving it an opalescence (Beattie and Dickson, 1948). This phenomenon was observed personally during the fixation of the heart muscle prior to the frozen section in Case II. As soon as the tissue was placed in the hot formal saline, the fixative became cloudy. It is obvious then, that tissues which are fixed in aqueous formalin would lose an appreciable amount of histochemically demonstrable glycogen and alcohol is the fixative of choice. In Case I, although histochemical glycogen was demonstrated, this was not homogeneously present as would be expected if all the glycogen was present, but rather it was found as irregularly sized and distributed P.A.S. positive, diastase-labile globules in the vacuolated cells. This is indicative that a great proportion of the glycogen had been lost. This is seen much more in Case II where apart from the negative histochemical evidence, the findings are typical of cardiac glycogenosis. Pearse (1960) is of the view that the solubility of glycogen in aqueous solutions is probably exaggerated. This does not appear to be so in the cases of cardiac glycogenosis dealt with here. Possibly this reflects the peculiar difference in the tissue glycogen binding capacity between normal tissue and cases of glycogenosis. di San't Agnese (1959) advocates not only analysis of the organs for the markedly increased glycogen content but also biochemical studies to prove the normal glycogen structure and preserved glycogenosis in liver and striated muscle to support the diagnosis of glycogenosis. This is ideal but facilities are seldom available for these investigations except perhaps in a highly specialised laboratory. It is perhaps because disproportionate stress is placed on histochemical and biochemical data that aspersions have been cast by McPhie (1960) on the validity of certain diagnoses of glycogenosis.

It is interesting to note that in spite of the gross generalised infiltration of glycogen, car-

diac glycogenosis is associated with paucity of biochemical disturbance detectable by presently available tests. This contrasts sharply with the more well-known von Gierke's disease where there is gross disturbance of carbohydrate and fat metabolism. In the few cases of cardiac glycogenosis so far studied, no enzymic defect has been demonstrated in the affected tissues. Recently Sokal et al. (1960) in a study of the disordered carbohydrate metabolism in liver glycogenosis (von Gierke's disease) reported one case in which the liver showed no enzyme deficiency and yet exhibited disordered metabolism. Why this should be is perplexing.

Cori (1954) has found in cardiac glycogenosis a normal response to epinephrine in the blood sugar and accumulation of fermentable sugar and lactic acid the liver and muscle following death—this showing that the glycogen is readily available. He in fact postulates that "moderate decrease in rate of glycogen breakdown with normal rate of synthesis might lead to storage; a reduction of phosphohexoisomerase or phosphofruktokinase content, for example, would be difficult to find and evaluate; reduction in one of these enzyme activities might lead to storage, particularly in heart and muscle". But from the biochemical point of view, if the connotation "glycogen storage disease" is applied to mean that somehow the glycogen is unavailable and as a result, accumulation or storage occurs in an organ, then this idea is contradicted by the available evidence and the term glycogenosis is a more appropriate one (Sokal et al., 1962).

The criteria advanced by di San't Agnese (1959) for the diagnosis of cardiac glycogenosis viz marked enlargement of the heart, death within the first year due to heart failure, and typical "lace-work" appearance of the myocardium resulting from massive deposition of stored material in all cardiac muscle fibres were fulfilled in the two cases presented. Although post-mortem biochemical analysis was not performed owing to restricted facilities, the existing evidence is sufficient to support the validity of the diagnosis. It is perhaps interesting to note that in di San't Agnese's paper (1950b) he came across only 3 cases in 37 years in more than 3000 autopsies, Kringelbach and Yamamoto et al. reported the first case from Scandinavia and Japan respectively in 1960. This report covers two different cases seen within a year—probably the first ones recorded in Malaya—and should draw our attention to the possibility of cardiac glycogenosis as a cause of infantile cardiomegaly.

SUMMARY

Two cases of cardiac glycogenosis are described. The concept of cardiac glycogenosis and the problems of diagnosis are discussed.

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