Alcoholic Cardiomyopathy

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ABSTRACT

Three white men, who died of a condition clinically diagnosed as alcoholic heart disease, showed virtually identical autopsy findings. These consisted of g l o b a l cardiomegaly and absence of stigmata of arteriosclerotic, hypertensive, rheumatic or congenital heart disease. Histological examination revealed degenerative and occlusive changes in small branches of coronary arteries, associated with microscopic foci of heart muscle necrosis and scarring. In two of the cases the degenerative changes were severe and extensive in the atria. Edema of the arterioles in the early stages was followed by disorganization of the vessel wall and subintimal accumulation of homogeneous, smudgy, PAS (periodic acid–Schiff)-positive material. This sequence of events, which suggests increased vascular permeability, is believed to be related directly or indirectly to chronic alcohol intake.

SOMMAIRE

Chez trois hommes blancs morts d'une pathologie qui avait été diagnostiquée comme étant une cardiopathie alcoolique, les constatations faites à la nécropsie étaient virtuellement identiques. Elles consistaient en une cardiomégalie globale et l'absence de stigmates d'artériosclérose, d'hypertension, de cardiopathies d'origine rhumatismale ou congénitale. L'examen histologique a révélé de la dégénérescence et de l'occlusion des petites branches des coronaires, accompagnées de foyers microscopiques de nécrose du myocarde et de tissu cicatriciel. Ces modifications de dégénérescene étaient graves et étendues dans les oreillettes, dans deux des cas. L'œdème des artérioles, aux phases primaires, était suivi d'une modification profonde de la paroi vasculaire et de l'accumulation sous-intimale d'une substance homogène, estompée, positive à l'épreuve de l'acide périodique de Schiff. Cette succession de faits permet de croire à l'augmentation de la perméabilité vasculaire et peut être reliée directement ou indirectement à l'ingestion chronique d'alcool.

THE clinical and pathological effects of alcoholism on the central nervous system and gastrointestinal tract have been amply described in the literature, but relatively little is known about the effect of chronic alcoholism on the cardiovascular system.

Although death due to cardiac failure in chronic alcoholics is a well-known clinical entity,[24] its pathological counterparts have not, in our opinion, received the attention that they merit.

As early as 1873, Walshe[25] described "localized cirrhosis in the ventricles and columnae carneae" in alcoholics; Evans[8, 9] in 1959 and 1961 described in detail the clinical picture of alcoholic heart disease; but Coutu[5] in a relatively recent article did not list the heart among the organs damaged in chronic alcohol addiction.

The purpose of this report is to describe the gross and histological changes in the hearts of three men, chronic alcoholics, who died of heart failure. In the discussion an attempt will be made to correlate clinical and pathological findings and some suggestions will be advanced regarding possible pathogenesis.

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CASE REPORTS

CASE 1.—W.M., a 54-year-old white man, was admitted to hospital in November 1959, three days before he died. He had a history of paroxysmal auricular fibrillation since June 1959. Jaundice had been noted on and off since July 1959. The clinical picture did not suggest coronary arteriosclerosis.

On admission, gross cardiomegaly was apparent. The clinical picture was that of mitral and tricuspid regurgitation with gross jugular vein distension, hepatomegaly, pulmonary congestion and massive peripheral edema involving the legs, scrotum and abdominal wall. Moderate jaundice was noted, pertinent laboratory findings in this respect were: serum glutamic oxaloacetic acid transaminase (SGOT), 142 units; serum bilirubin, total: 4.5 mg. %, direct: 1.1 mg. %. His blood pressure was within normal limits. Hemoglobin and plasma proteins were normal and clinical features of avitaminosis were not present. On the electrocardiogram, auricular fibrillation was noted and the presence of an anteroseptal scar was suggested.

The differential diagnosis entertained in this case included rheumatic heart disease and cardiomyopathy due to a disorder such as hemochromatosis. The use of vitamin supplements was suggested. After this patient died, enquiry revealed that he had been a chronic alcoholic and had consumed large quantities of beer over a long period of time. A delayed clinical diagnosis

of alcoholic heart disease was then submitted to the pathologist.

Autopsy revealed a slightly icteric and moderately emaciated white man, with marked pitting peripheral edema and engorgement of neck veins. There were no skin changes suggestive of pellagra.

The heart weighed 680 g.; the pericardium was normal. The right ventricle measured 8 mm. and the left 2.4 cm. in thickness. The tricuspid valve measured 15.5 cm. and the mitral valve 17 cm. in circumference. The endocardium was smooth but there were a few greyish-white areas subendocardially. There was mural thrombosis in the appendage of the right atrium. The myocardium showed no gross scars but was markedly flabby. The coronary arteries showed no significant atheromatous or other pathological changes. The posterior leaflet of the mitral valve was slightly sclerosed and thickened; otherwise all the valves were normal.

There was bilateral hydrothorax, ascites and marked chronic passive congestion of the viscera, with a pronounced "nutmeg" appearance of the liver. There was acute pulmonary edema and a few, probably terminal, peripheral emboli were noted in the lower lobe of the right lung.

CASE 2.—E.E., a 54-year-old white man, was admitted to hospital in August 1961. He died the same day in heart failure with a supraventricular tachycardia of about 220/min. He had discontinued his digitalis therapy about two weeks earlier on his own initiative.

His history was well documented because he had had several hospital admissions in 1960 and 1961. In 1960 it was recorded that he was a heavy consumer of alcohol and had recently been on an inadequate diet. Auricular fibrillation had been present for several years. Gross global cardiomegaly was complicated (on and off) by marked edema, ascites and jaundice. His maximum total bilirubin was 14 mg. %, approximately one-half of which was direct-reacting bilirubin. Relative tricuspid regurgitation was suggested by an appropriate, variable systolic murmur. His blood pressure was normal. The history did not suggest coronary arteriosclerosis. The electrocardiogram showed left-axis deviation and right bundle-branch block. Vitamin deficiency was not clinically apparent (his hemoglobin was 16.5 g. %), and vitamin supplements were of no value in his treatment. A clinical diagnosis of alcoholic myocardiopathy was made.

At autopsy this well-nourished middle-aged white man showed marked pitting peripheral edema, and cyanosis of the ear lobes and nail beds. There were no skin manifestations suggestive of pellagra.

The heart weighed 750 g. The right ventricle measured 1.8 cm. and the left ventricle 4.0 mm. in thickness. The tricuspid valve measured 16 cm. and the mitral valve 11 cm. in circumference; otherwise all of the valves were grossly normal. The myocardium was flabby and brown in colour, and showed no grossly obvious scarring. The pericardium and endocardium were grossly normal. The coronary arteries showed mild patchy eccentric atheroma without significant stenosis, or recent or old occlusion. There were acute pulmonary edema, hydrothorax and mild ascites (6 oz.). Both auricles showed a small amount of attached mural thrombus.

The viscera showed marked chronic passive congestion with a pronounced nutmeg appearance of the liver and apparent early fibrosis, without external nodularity.

CASE 3.—A.K., a white man, was 63 years of age at the time of his death in 1963. He had been drinking a pint of whisky per day for some 15 years but had been eating well. He had been in heart failure on and off since 1961 with progressive dyspnea and edema. His terminal illness was a complex affair involving hepatorenal and cardiac failure. His total bilirubin reached the astonishing level of 29 mg. %, with a direct fraction of 17 mg. %. The blood urea nitrogen reached a peak of 158 mg. %; the serum creatinine was 5.1 mg. %; and the hemoglobin 14.4 g. %. His blood pressure was normal. Coma, shock, electrolyte disturbance, acidosis, Kussmaul breathing and potassium retention were corrected but the patient died in pulmonary edema. The clinical picture did not suggest a diagnosis of coronary arteriosclerosis. Clinical evidence of vitamin deficiency was not apparent and vitamin supplements were of no value in his treatment. The heart was enlarged. Significant murmurs were not present. Auricular fibrillation was noted before he died. A clinical diagnosis of alcoholic cardiomyopathy was made.

Autopsy revealed a somewhat undernourished, markedly jaundiced white man, weighing an estimated 145 lb. There was peripheral and pulmonary edema, and extreme passive congestion of the liver and, to a lesser extent, of other viscera.

The heart weighed 500 g. The right ventricle measured 5 mm. and the left ventricle 1.4 cm. in thickness. The tricuspid and mitral valve rings were moderately dilated but there was no evidence of valvular disease. The myocardium was flabby but showed no grossly recognizable lesions. The pericardium and the endocardium were grossly normal. Mural thrombi were seen in the right auricle.

The aorta and the major coronary artery branches showed surprisingly little atheroma.[17]

Microscopic Findings

The microscopic changes in all three cases were so similar that they will be summarized together and slight differences pointed out where indicated.

The myocardium showed patchy perivascular fibrosis or interstitial fibrous scars in areas where one might otherwise expect to see a small branch of a coronary artery (Fig. 1). Changes of this type were observed in both ventricles and were more pronounced subendocardially. The endocardial patches described grossly in Case 1 were composed of dense, poorly cellular, collagenous connective tissue. Sections from the slightly thickened mitral valve cusp (Case 1) showed no evidence of rheumatic involvement. In Case 3 a few foci of recent myocardial necrosis were seen in the left ventricle and its papillary muscle. These foci were associated with edema, fibrosis and spotty calcification, but no significant cellular inflammatory reaction (Fig. 2). Very little recent necrosis in the ventricular muscle was seen in Cases 1 and 2. On the other hand, the atria of these two patients showed pronounced and extensive degenerative changes. There was interstitial edema, notably around small vascular channels, associated with hydropic vacuolization of the adjacent

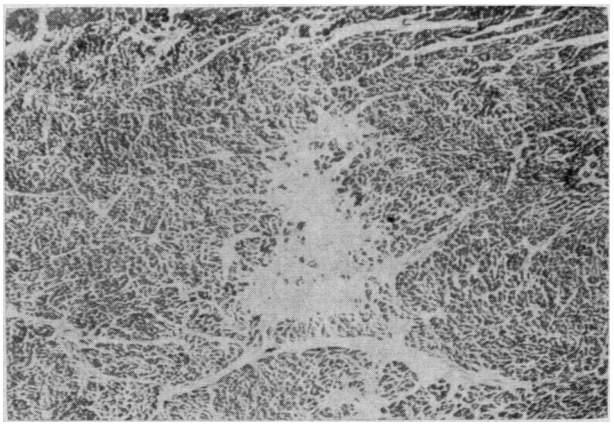

Fig. 1.—One of the many small foci of scarring in the myocardium of the left ventricle. (Hematoxylin and eosin, × 40.)

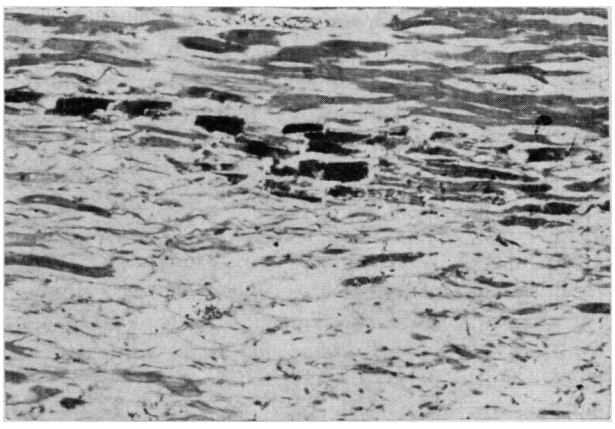

Fig. 2.—Recent necrosis in the papillary muscle showing dystrophic calcification. Note paucity of cellular inflammatory reaction. (Hemalum-phloxine-saffron, × 200.)

myofibrils. The latter showed loss of striation, smudginess of sarcoplasm, pyknosis, macronucleosis and loss of nuclei. One or two small round-cell collections were seen in relation to the most advanced degenerative changes. The subendocardial portions showed transition into fibrosis, and mural thrombi were present in both auricles.

The aorta and the major branches of the coronary arteries disclosed only minimal atheromatous changes, particularly in Cases 1 and 3. Case 2, a well-nourished man, showed mild patchy atheroma without significant stenosis. In contrast to the large and medium-sized branches, the walls of the small branches of the coronary arteries were arranged in loose, disorganized layers with an increase of collagen in the adventitia (Fig. 3). In some of the smaller arteries, subintimal

The liver in all three cases showed marked to extreme chronic passive congestion, associated with centrilobular necrosis and early centrilobular (cardiac) cirrhosis in Cases 2 and 3. In addition there was mild periportal fibrosis in Case 2. In none of these cases were there any findings suggestive of toxic or infectious hepatitis.

The lungs in all cases showed acute edema, and there was early hemorrhagic infarction in the lower lobe of the right lung in Case 1. The kidneys showed passive congestion in Cases 1 and 2, and edema and interstitial fibrosis in Case 3, without any significant abnormality in the glomeruli or tubules.

No capillary "thrombi" were seen in any of the organs examined.

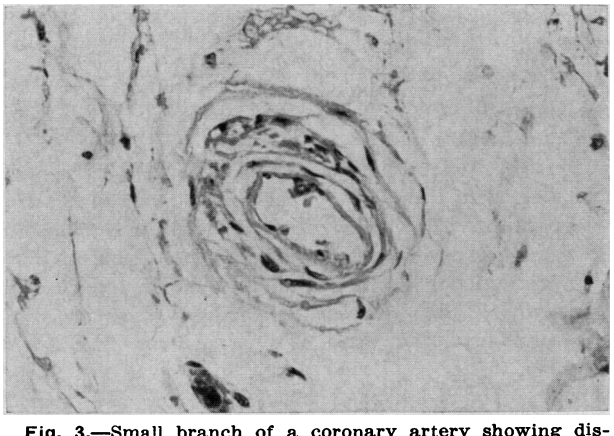

Fig. 3.—Small branch of a coronary artery showing disorganization of its wall by edema and degeneration, as well as increase of collagen in adventitia. (Hemalum-phloxine-saffron, × 400.)

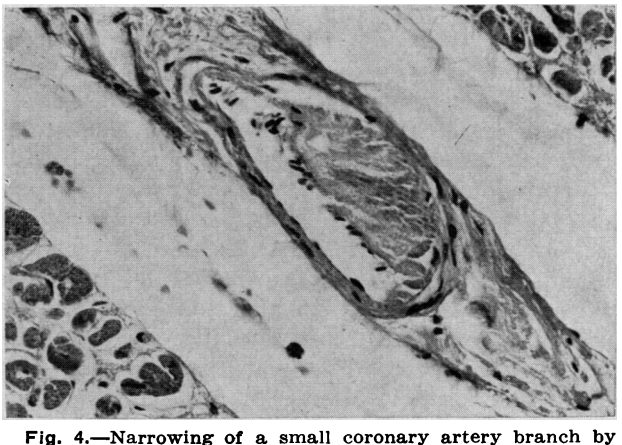

Fig. 4.—Narrowing of a small coronary artery branch by homogeneous, smudgy, PAS-positive material. (Hemalum-phloxine-saffron, × 400.)

plaques of homogeneous, reddish, smudgy material were observed (Fig. 4). This material stained faintly positive with periodic acid–Schiff (PAS) reagent and was negative for fibrin with the Mallory's phosphotungstic acid–hematoxylin stain. In some of these small vascular channels there was considerable narrowing of the lumen, estimated at 60% or more. This was due to subintimal accumulation of the PAS-positive material which produced inward bulging of intima, suggesting possible leakage of blood constituents through the intima and into the vessel wall.

DISCUSSION

The syndrome that has been described, clinically and pathologically, in this communication can conveniently be designated as alcoholic cardiomyopathy. To refer to this syndrome as occidental beriberi would be to imply thiamine deficiency, an assumption that is not proved. Our experience confirms earlier reports that vitamin B supplements are valueless in therapy of such patients, as might be expected from the irreversible pathology demon-

strated at autopsy. Extensive degenerative and fibrotic changes in the atria were in keeping with the antemortem finding of auricular fibrillation. The progressive myocardial failure due to scarring leads to dilatation of valve rings. Tricuspid regurgitation adds to the burden of congestion behind the already failing right heart. Thus passive congestion of the liver progresses from a stage of centrilobular necrosis to cardiac cirrhosis, leading to clinically apparent jaundice. This experience is reminiscent of Sherlock's dictum that "Most patients with heart failure and deep jaundice also have a cardiac cirrhosis."

There is a striking similarity of the histories, clinical findings and the pathological changes in all three cases. Each had a history of chronic alcohol addiction over many years. A clinical diagnosis of alcoholic myocardiopathy was arrived at in all three cases by noting the patients' alcohol consumption and by excluding other common causes of heart disease. Congestive failure, with prominent peripheral edema, auricular arrhythmias and jaundice, was common to these cases.

At autopsy global enlargement of the heart due to hypertrophy and dilatation of all chambers and mural auricular thrombi[23] were the only significant gross abnormalities. The histological changes, ranging from hydropic degeneration to focal myocardial necrosis and fibrosis, have been previously described under various headings including idiopathic myocardiopathy[2, 12, 20] and beri-beri heart disease.[1]

The degenerative changes in the small branches of coronary arteries, to our knowledge, have not previously been described in cases of alcoholic cardiomyopathy.

In 1963, in a study of chronic alcoholics, Benchimol and Schlesinger[1] described edema of coronary vessels in an early stage of the disease. Shiian[21] found a marked increase in vascular permeability together with changes in vascular tone in chronic alcoholics. The increased vascular permeability is responsible for the interstitial edema in the myocardium and in the vessel walls. The protein-rich plasma accumulates between the layers of the arteriolar wall, producing gradual narrowing and distortion of the vessel lumen. This can progress to complete occlusion with subsequent focal myocardial necrosis; the latter heals leaving a small scar, so commonly observed in cases of alcoholic cardiomyopathy. If a sufficient number of sections are examined, one or more microscopic foci of fresh myocardial necrosis may be seen; these are sometimes followed by dystrophic calcification.

It is of interest that somewhat similar changes have been produced experimentally in dogs rendered hypomagnesemic over a long period of time,[28] and that hypomagnesemia has been reported in chronic alcoholics.[6]

Mural thrombi and endocardial fibrosis may be due to foci of myocardial necrosis in the subendocardial heart muscle. Alternatively, if the endocardium is looked upon as modified intima, a focal hyperpermeability may lead to subendocardial plasma deposits with subsequent transformation into collagen fibres. This results in thickened endocardial patches, and mural thrombi may form subsequently in such altered areas.

Frederiksen and Hed,[10] in their clinical study of chronic alcoholism, stated that it could not be determined from their investigation which mechanism (vitamin B deficiency, protein deficiency or the toxic effect of alcohol) was of the greatest importance in the pathogenesis of the cardiac lesions. Weiss and Wilkins,[26] in discussing the clinical aspects of occidental and oriental beri-beri, stated that a great majority of such cases were due to chronic alcoholism.

Langeron[16] distinguished two phases in the development of the alcoholic heart disease. The first, beri-beri, is reversible and responds to vitamin B therapy;[3] the second is irreversible and does not respond to vitamin B supplements.

Considering the increased vascular permeability due to alcoholic intoxication reported by Shiian,[21] one can readily visualize interstitial edema, as well as vessel wall edema in the early phase of alcoholism, as being due either to the direct effect of alcohol on the small coronary vessels or to an indirect metabolic effect, e.g. hypomagnesemia. This edema is reversible. With time and repeated injury, the vascular change will progress to degeneration of the wall and finally to occlusion of the lumen, resulting in small foci of myocardial necrosis followed by scarring. At this stage the changes become irreversible.

It is conceivable that a similar process takes place in the course of the development of the pathologic changes in other organs of alcoholics.[13-15] A hint that this may indeed occur was provided by Shorter and Baggenstoss[22] in their papers on the histogenesis of liver cirrhosis in chronic alcoholism, in which they remarked that increased protein exudation may be considered responsible for the increased amount of collagen in the liver in such patients.

SUMMARY

Three patients who died following chronic alcoholic cardiomyopathy are described and the pertinent clinical and pathological findings are presented. The generalized cardiac enlargement and progressive heart failure was due to microscopical scarring of the myocardium. This scarring was associated with edema, degeneration and finally occlusion of small branches of coronary arteries, a chain of events suggesting increased vascular permeability. The vascular changes are thought to be the result of damage produced either directly by alcohol or through an indirect metabolic effect.

We would like to express our thanks to Dr. H. Shister for providing one of these cases.

REFERENCES

1. BENCHIMOL, A. B. AND SCHLESINGER, P.: *Amer. Heart J.*, 46: 245, 1953.
2. BRIGDEN, W.: *Lancet*, 2: 1179, 1957.
3. BURCH, G. E. AND WALSH, J. J.: *Amer. J. Cardiol.*, 6: 864, 1960.
4. CORTIS, B., GRANDE, A. AND TARQUINI, A.: *Atti. Soc. Ital. Cardiol*, 2: 208, 1962.
5. COUTU, L. L.: *Un. Méd. Canada*, 90: 257, 1961.
6. MARTIN, H. E. AND BAUER, F. K.: *Proc. Roy. Soc. Med.*, 55: 912, 1962.
7. ELIASER, M., Jr. AND GIANSIRACUSA, F. J.: *Calif. Med.*, 84: 234, 1956.
8. EVANS, W.: *Brit. Heart J.*, 21: 445, 1959.
9. *Idem*: *Amer. Heart J.*, 61: 556, 1961.
10. FREDERIKSEN, P. AND HED, R.: *Acta Med. Scand.*, 162: 203, 1958.
11. GOLDBERG, M.: *Amer. J. Psychiat.*, 119: 255, 1962.
12. HIGGINSON, J., ISAACSON, C. AND SIMSON, I.: *A.M.A. Arch. Path.*, 70: 497, 1960.
13. HOWARD, J. M. AND EHRLICH, E. W.: *Surg. Gynec. Obstet.*, 113: 167, 1961.
14. KESSEL, L.: *Amer. J. Med.*, 32: 747, 1962.
15. KLATSKIN, G.: *A.M.A. Arch. Intern. Med.*, 104: 899, 1959.
16. LANGERON, L.: *J. Sci. Méd. Lille.*, 81: 3, 1963.
17. NIEHAUS, F. W.: *J. Mich. Med. Soc.*, 54: 54, 1955.
18. SATALINE, L. R. AND MATRE, W. J.: *Amer. J. Med.*, 35: 323, 1963.
19. SCHLESINGER, P. AND BENCHIMOL, A. B.: *Amer. Heart J.*, 42: 801, 1951.
20. SERBIN, R. A. AND CHOJNACKI, B.: *New Eng. J. Med.*, 252: 10, 1955.
21. SHIIAN, I. V.: *Ter. Arkh.*, 33: 32, May, 1961.
22. SHORTER, R. G. AND BAGGENSTOSS, A. H.: *Amer. J. Clin. Path.*, 32: 422, 1959.
23. SMITH, J. J. AND FURTH, J.: *Arch. Intern. Med. (Chicago)*, 71: 602, 1943.
24. SUTTON, G. C.: *Illinois Med. J.*, 124: 50, 1963.
25. WALSHE, W. H.: A practical treatise on diseases of the heart and great vessels, 4th ed., London, 1873.
26. WEISS, S. AND WILKINS, R. W.: *Ann. Intern. Med.*, 11: 104, 1937.
27. ZEIFER, H. D.: *Ann. Surg.*, 154: 956, 1961.
28. WENER, J. *et al.*: *Amer. Heart J.*, 67: 221, 1964.
29. JAMES, T. N.: *Prog. Cardiov. Dis.*, 7: 43, 1964.
30. KLAVINS, J. V., KINNEY, T. D. AND KAUFMAN, N.: *Arch. Path. (Chicago)*, 78: 200, 1964.

Deformity of Ears and Kidneys

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ABSTRACT

Ten children with gross deformity of the external ear were observed. In six the facial bones were underdeveloped on the same side as the deformed ear. In all six there was a congenital abnormality of the kidney or upper urinary tract, usually on the same side as the deformed ear. In addition there were usually other associated congenital defects in each case.

In the remaining four children the facial bones appeared normal, and pyelography showed no abnormality of the urinary tract. In these four children there were no other associated defects.

These observations emphasize the importance of investigating the urinary tract in children with gross deformity of the external ear, especially where there is an associated underdevelopment of the facial bones.

SOMMAIRE

On a observé dix enfants porteurs d'une forte difformité de l'oreille externe. Chez six d'entre eux, les maxillaires étaient sous-développés du côté de l'oreille difformée. Chez ces six enfants, on constatait une anomalie congénitale du rein ou des voies urinaires supérieures d'ordinaire du même côté que l'oreille difformée. En outre, dans chaque cas, on notait habituellement d'autres défauts congénitaux concomitants.

Chez les quatre autres enfants, les os de la face étaient normaux et la pyélographie ne révélait aucun trouble des voies urinaires. Chez ces quatre enfants, on ne constatait non plus aucune autre anomalie.

Ces observations mettent en lumière l'importance qu'il y a à étudier les voies urinaires chez les enfants qui présentent de fortes difformités de l'oreille externe, surtout dans les cas où coexiste un manque de développement des os de la face.

IN 1946 Potter first drew attention to the association of certain facial abnormalities with renal agenesis.[1] The facial abnormalities included prominent epicanthic folds, flattened nose, prominent depression below the lower lips, and flattened low-set ears deficient in cartilage.[2] These appearances have been accepted as sufficiently reliable to alert the clinician or the pathologist to the possibility of renal agenesis.

Hilson[3] described 23 patients and 18 of their relatives with deformities of the external ear associated with congenital abnormalities of the genitourinary tract. The deformed ears were described as large and flabby, folded over with the helix squared, folded forward to mimic a cockle shell or, in some cases, shaped like elfin ears. A unilateral deformity of the ear was frequently associated with a deformity of the renal tract on the same side. There was a definite familial incidence in patients

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