from the depletion of intracellular phosphate after its immobilization as fructose-1-phosphate, though this is still uncertain (Desbuquois, 1965). The severe hypoglycaemia resulting from a dose of fructose appears to be the resultant of a failure of glycogenolysis in the liver, with continued peripheral utilization of glucose by the tissues. The cause of the liver damage itself remains unexplained ; it is possible that the intrinsic metabolism of the liver cell is damaged, owing to depletion of cellular adenosine triphosphate (Levin *et al.*, 1963).

Treatment and Prognosis

Treatment consists in the exclusion of sucrose and fructose from the diet, with the addition of ascorbic acid, as the daily intake is otherwise likely to be low. Difficulties often arise in the prescription of medicines or antibiotic syrups, and the patients and their doctors need to be warned specifically about this point.

Severe or fatal liver damage is likely to occur in infancy if the diagnosis is not suspected. As the case histories show, the diagnosis is commonly made by an observant mother if she has already had a similarly affected infant, but the exclusion of fructose-containing substances from the diet by the mother, or later by a self-selected diet, is not usually strict enough to prevent the development of hepatomegaly. It is probable, therefore, though there is as yet no certain evidence of this, that the fatty infiltration of the liver will in due course be followed by cirrhosis. Our own observations suggest that a strict fructose-free diet in children will cause a complete return to normality, though a long follow-up has not yet been possible.

Summary

Fructose intolerance is a genetically determined metabolic disorder inherited as an autosomal recessive. It is probably as common as the more widely recognized galactose intolerance.

In affected individuals fructose given orally or intravenously causes profound hypoglycaemia, with a rise of the level of fructose in the blood to 20 mg./100 ml. or more. The essential abnormality is an absence of the liver enzyme fructose-1-P. aldolase. The condition may present in infancy as neonatal jaundice with hepatomegaly, or with vomiting and failure to thrive: in older children hypoglycaemic fits may occur or glycogen storage disease may be suspected on account of the enlarged liver. In adults the symptoms are less obvious, and may be dismissed as "neurotic ill-health."

The diagnosis is made by an oral or I.V. fructose tolerance test or by estimation of the activity of the specific aldolase in a fresh or frozen liver biopsy.

Treatment is by the exclusion of fructose and sucrose from the diet.

Five children with this condition are described.

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Abnormal Splitting of the Second Heart Sound in Renal Failure

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Abnormally wide splitting of the second heart sound due to delay in the pulmonary component is a significant physical sign (Leatham, 1958). Though it is most frequently due to right bundle-branch block or an atrial septal defect, it may also result from any condition causing mechanical prolongation of right ventricular systole, such as pulmonary valve stenosis, or from right ventricular failure due to severe pulmonary hypertension (Shapiro *et al.*, 1965). However, delay in pulmonary valve closure by more than 0.03 second, the value usually taken as the upper limit of normal (McKusick, 1958), has been observed in a number of patients with advanced renal failure in whom none of these conditions was present. Since its recognition has proved to be of value in the management of such patients, it is documented here, and its clinical associations are defined more precisely.

Material and Methods

Observations were made during the routine management of eight patients with advanced renal failure. All had radiological evidence of perihilar or interstitial pulmonary oedema, and all but one had dyspnoea, orthopnoea, and crepitations over the lungs. Further clinical, biochemical, and haemodynamic data are summarized in Table I. The haemodynamic data form part of those presented in a previous communication (Gibson, 1966). Biochemical estimations were performed by autoanalyser techniques. The total fluid loss during peritoneal dialysis was calculated from the cumulative balance of each exchange, and during haemodialysis from the weight loss of the patient. Drug therapy was not altered during the procedure, except in Case 8, where ethanol inhalations, morphine, aminophylline, and pentolinium were given without effect on the pulmonary oedema.

Phonocardiograms were recorded from the position along the left sternal edge where the splitting of the second sound was most obvious clinically. A Mingograf direct writing recorder was used, running at a paper speed of 100 mm. per second. On account of the patients' dyspnoea, it was not always pos-

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TABLE I.—*Clinical Data*

Case No.	Age	Sex	Diagnosis	Blood Pressure (mm. Hg)		Haemoglobin (g./100 ml.)		Blood Urea (mg./100 ml.)		Plasma Bicarb. (mEq/l.)		Mean Right Atrial Pressure (mm. Hg)		Mean Pulmonary Arterial Pressure (mm. Hg)		Fluid Volume Removed (−) or Administered (+) (litres)	Anti-hypertensive Agents
				A	B	A	B	A	B	A	B	A	B	A	B		
1	25	M	Chronic glomerulonephritis	130/80	160/110	6·1	12	431	215	15	235	—	—	—	—	−10·3	Methyldopa
2	60	M	Malignant hypertension	180/130	120/80	9·2	9·0	550	370	14	17	1	—	32†	—	−5·6	Nil
3	26	M	Chronic glomerulonephritis	140/90	110/70	6·1	5·4	396	258	13	21	1	1	16	17	−7·5	,,
4	24	M	Chronic glomerulonephritis	240/120	220/140	6·7	5·6	560	247	11	25	4	3	30	19	−6·9	,,
5	50	M	Chronic pyelonephritis	150/90	160/90	9·2	11·1	233	143	17	27	—	—	—	—	−10·0	Methyldopa
6	59	M	Streptococcal septicaemia	130/60	180/110	13	11·5	290	181	23	17	1	3	21	27	−2·6	Nil
7	26	M	Chronic pyelonephritis	150/90	150/100	5·7	8·3	238	235	25	27	—	—	—	—	+1·2	Methyldopa
8	27	M	Chronic pyelonephritis	140/80	*	6·8	7·9	200	112	22·5	21	—	—	—	—	*	Guanethidine. Pentolinium

A = Before dialysis (Cases 1–6 and 8) or transfusion (Case 7). B = After dialysis (Cases 1–6 and 8) or transfusion (Case 7).
* Please see Table III. † Peak R.V. pressure—the pulmonary artery was not entered. Pressures are expressed in mm. Hg above a point 5 cm. below the sternal angle.

sible to use an indirect carotid pulse transducer, and in these patients the aortic component of the second sound was identified from an apical phonocardiogram. For the same reason, recordings were made during spontaneous respiration rather than held expiration. The heart sounds were timed from their initial deflections. Specimen phonocardiograms are reproduced in Figs. 1–6.

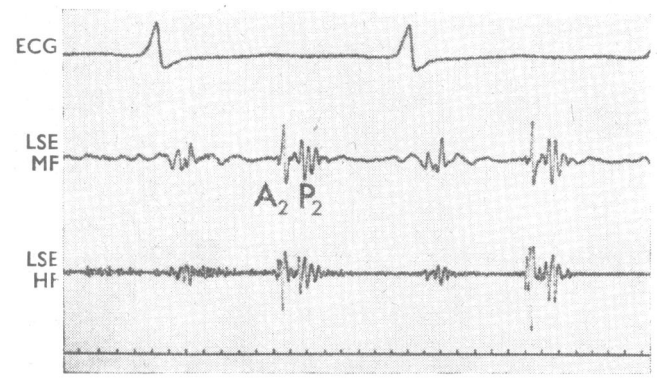

FIG. 1.—Case 2. Phonocardiogram before treatment, recorded from the left sternal edge (LSE) at high (HF) and medium (MF) frequencies. The pulmonary component of the second sound (P_2) occurs 0.055 second after the aortic (A_2), during spontaneous expiration. In this and the other phonocardiograms, the marker represents time intervals of 0.04 second.

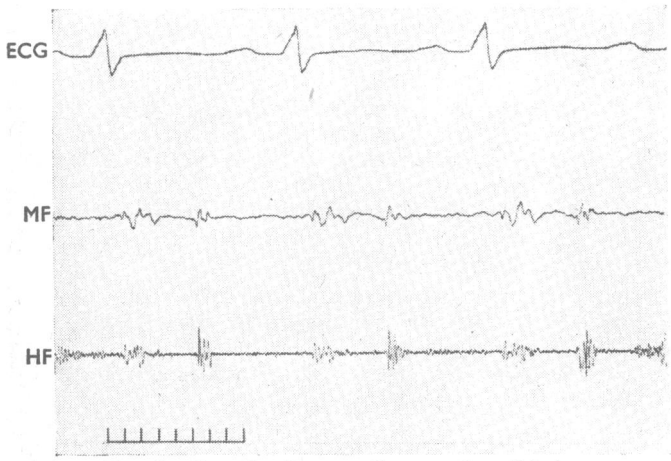

FIG. 2.—Case 2. Phonocardiogram after dialysis.

Cases 1–6 were admitted in pulmonary oedema and were treated with hypertonic peritoneal dialysis. Phonocardiograms were recorded before and after the procedure.

Case 7.—This patient had radiographic evidence of pulmonary oedema though it was not causing symptoms. His anaemia was therefore treated with slow infusion of 1.2 litres of packed cells. This caused the appearance of abnormal splitting of the second heart sound and transient dyspnoea, but there were no other untoward effects. Phonocardiograms were recorded before and after the transfusion.

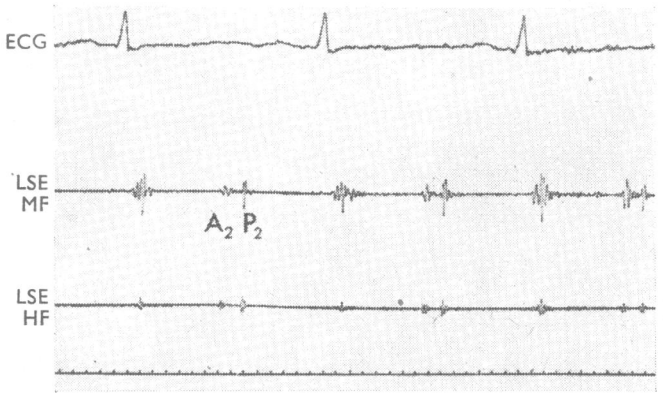

FIG. 3.—Case 3. Phonocardiogram before treatment, showing separation of the two components of the second sound by 0.06 second in expiration.

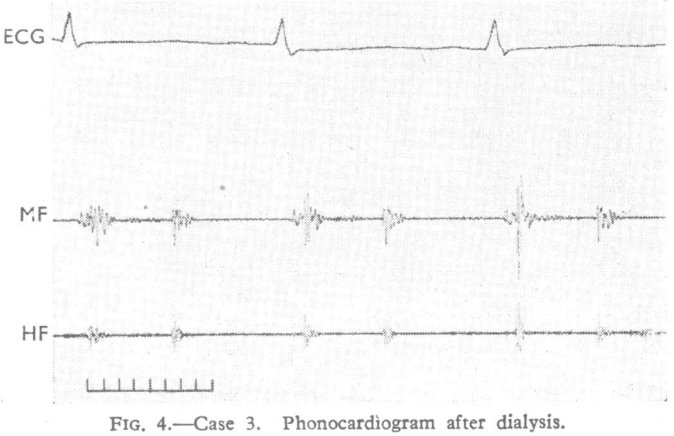

FIG. 4.—Case 3. Phonocardiogram after dialysis.

Case 8.—This patient had radiographic evidence of pulmonary oedema, but no undue dyspnoea or orthopnoea. However, wide splitting of the second heart sound was noted clinically and recorded phonocardiographically (P.C.G. 1 in Table III and Fig. 5). To treat his anaemia a slow transfusion of packed cells was started, but after only 100 ml. had been given he developed a severe attack of acute pulmonary oedema which proved resistant to the usual methods of treatment. Haemodialysis by means of a hypertonic bath was therefore started, and within 45 minutes his symptoms had subsided,

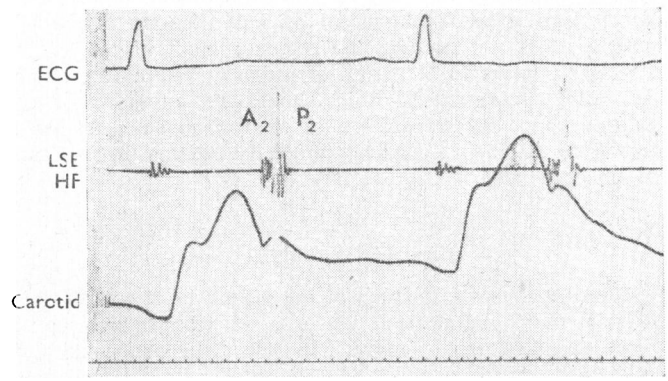

FIG. 5.—Case 8. Phonocardiogram before the initial blood transfusion, taken during spontaneous expiration. The aortic component of the second sound, occurring with the incisura on the carotid pulse recording, precedes the pulmonary component by 0.055 second.

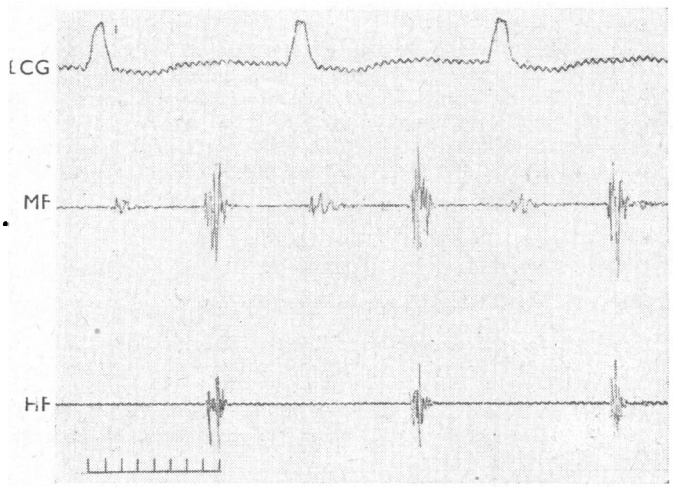

FIG. 6.—Case 8. Phonocardiogram after dialysis.

after the net removal of 500 ml. of fluid. P.C.G. 2 was recorded at this time. When the rate of infusion of the blood was increased so that the net fluid loss dropped to 200 ml. mild symptoms recurred and abnormal splitting of the second sound was again evident (P.C.G. 3), but both resolved on further dehydration. P.C.G. 4 was recorded towards the end of the dialysis.

Results

The phonocardiographic observations are summarized in Table II. Wide splitting of the second heart sound in expiration was recorded at some stage in all the patients. This was due to delay in closure of the pulmonary valve relative to that of the aortic by 0.04 to 0.06 second. There was normal inspiratory augmentation of the A_2-P_2 interval. In Case 7 abnormal splitting appeared after blood transfusion. The relation between changes in blood volume and abnormal splitting was investigated in more detail in Case 8. In this patient the abnormality was relieved after the removal of plasma ultrafiltrate and recurred after blood transfusion. Details of the total volume of blood administered, the net fluid balance of the patient, and the phonocardiographic data are given in Table III.

Other Factors.—There was no consistent reaction between changes in the blood urea level and the development of abnormal splitting. In Cases 1–6 the blood urea was reduced during peritoneal dialysis, as the abnormality was corrected, while in Case 7 it remained unchanged as delay in pulmonary valve closure was provoked by blood transfusion. In Case 8 it fell throughout the haemodialysis as abnormal splitting was precipitated by blood transfusion and relieved by dehydration. Similarly, the return of the heart sounds to normal could be dissociated from changes in the systemic arterial pressure, or from correction of the anaemia, hyperkalaemia, or metabolic acidosis present initially in some of the patients.

TABLE II.—*Phonocardiographic Data in Cases 1–7*

Case No.	Before Dialysis: Pulse Rate (Beats/min.)	Before Dialysis: Q-A2 Interval (sec.)	Before Dialysis: A_2-P_2 Interval (sec.)	Before Dialysis: Inspiratory Augmentation of A_2-P_2 Interval (sec.)	After Dialysis: Pulse Rate (Beats/min.)	After Dialysis: Q-A2 Interval (sec.)	After Dialysis: A_2-P_2 (sec.)	After Dialysis: Inspiratory Augmentation (sec.)
1	74	0·36	0·06	0	90	0·34	0·02	0·01
2	105	0·30	0·055	0·01	125	0·26	0·01	0·02
3	105	0·305	0·056	0·015	105	0·29	0·01	0·02
4	90	0·31	0·05	0·01	86	0·32	0·02	0·02
5	83	0·36	0·05	0·02	72	0·38	0·02	0·03
6	81	0·31	0·04	0·02	80	0·32	0·02	0·02
	Before Transfusion				After Transfusion			
7	88	0·40	0·02	0·02	82	0·41	0·045	0·01

The Q-A2 interval is the time interval between the initial deflection of the E.C.G. and the onset of aortic valve closure. The Q-P2 interval is the time interval between the initial deflection of the E.C.G. and the onset of pulmonary valve closure.

TABLE III.—*Phonocardiographic Data in Case 8*

P.C.G. No.	Time After Start of Haemodialysis (min.)	Blood Pressure (mm. Hg)	Volume of Blood Given (ml.)	Net Fluid Balance* (ml.)	Phonocardiogram: Pulse Rate (Beats/min.)	Phonocardiogram: Q-A2 (sec.)	Phonocardiogram: A_2-P_2 (sec.)	Phonocardiogram: Inspiratory Augmentation of A_2-P_2 (sec.)
1	—	140/80	0	0	70	0·39	0·055	0·015
2	50	180/100	200	−500	100	0·26	0·02	0·02
3	105	200/130	800	−200	102	0·26	0·04	0·01
4	255	210/130	1,600	−900	103	0·26	0·02	0·03

* Net loss of fluid from the patient is expressed as a negative balance.

Discussion

In the present series of patients, right bundle-branch block as a cause of the abnormal splitting of the second heart sound could be excluded by the absence of the characteristic E.C.G. pattern. There was no supportive evidence of an atrial septal defect, or other congenital heart disease, and, in any case, normal splitting was observed at some stage in all the patients. In no case was there any clinical evidence of severe pulmonary hypertension causing right ventricular failure, and in four patients it was excluded by direct measurement of the right atrial and pulmonary arterial pressures. There was, however, strong correlation with the degree of hydration of the patients. Abnormal splitting was relieved in all patients in whom it was initially present by dehydration, while in two patients the abnormality developed after the administration of blood. Alwall *et al.* (1953) have stressed that pulmonary oedema in renal failure is also a manifestation of fluid overload, and have demonstrated resolution of the radiographic appearances with dehydra-

tion, even in the presence of a rising blood urea. It was therefore of interest that though abnormal splitting was sought in a large number of patients with renal failure it was found only in the presence of pulmonary oedema: in particular, it was not found in patients with gross peripheral oedema due to the nephrotic syndrome, in the absence of pulmonary oedema.

The mechanism by which fluid overload causes delay in pulmonary valve closure is not clear. Theoretically, it might be due to prolongation of right ventricular activation, isovolumic contraction, or ejection. With a normal E.C.G. it is unlikely that selective prolongation of right ventricular activation occurred. In the absence of mechanical obstruction to right ventricular ejection, pulmonary hypertension, or a left-to-right shunt, prolongation of either right ventricular isovolumic contraction or right ventricular ejection implies impairment of the function of the right ventricle relative to that of the left. This might be due to the effect of some toxic metabolite retained as a result of the renal failure. Though the results in Case 8 suggest that external fluid balance is important, such prolongation of right ventricular systole does not occur in normal subjects after the administration of relatively small volumes of fluid. Alternatively, impairment of right ventricular function may be caused by reflex activity. It has been demonstrated that stimulation of the carotid sinus baroreceptors (Daly and Luck, 1958) and also of efferent fibres in the vagus (Daggett *et al.*, 1966) may lead to a reduction in ventricular contractility. In the abnormal circulatory state present in these patients, such reflex activity might have been present.

Delay in the pulmonary component of the second sound has been recorded in a number of similar clinical situations. Though abnormal splitting appears to be unusual in the presence of pulmonary oedema due to left ventricular failure or mitral stenosis, it has been recorded inconstantly in association with the pulmonary oedema of high altitude (Fred *et al.*, 1962), and also under certain circumstances in cholera (Greenough, 1966). In the former condition, cardiac catheterization has revealed high pulmonary arterial pressures, which would provide a satisfactory explanation of a prolonged right ventricular ejection time. In cholera, acute pulmonary oedema, gallop rhythm, and wide splitting of the second heart sound may be provoked by the administration of excess saline in the presence of an uncorrected metabolic acidosis. Though haemodynamic and phonocardiographic data are not yet available, the clinical picture has features in common with that occurring in renal failure. In severe systemic hypertension the interval between the Q wave on the E.C.G. and aortic valve closure is often longer than that predicted from the pulse rate; yet splitting of the second heart sound is usually normal. It has been pointed out that the concomitant delay in pulmonary valve closure has not been adequately explained (Shah and Slodki, 1964). Since seven out of the eight cases described in the present series were hypertensive, it is possible that a similar mechanism was involved.

In a study of the second heart sound in 118 cases of ostium secundum atrial septal defect, Aygen and Braunwald (1962) found that the mean A_2-P_2 interval was 0.05 second and that if the inspiratory augmentation of the A_2-P_2 interval was less than 0.01 second then the split might be regarded as "fixed." Thus the abnormality described in the present series of patients is comparable to that seen in the average case of atrial septal defect, and is readily apparent on auscultation. Though its absence does not exclude the presence of fluid overload, its presence appears to be a sign of incipient pulmonary oedema. In such circumstances fluid should be administered with caution, since the transfusion of even small amounts has led to the development of acute pulmonary oedema (as in Case 8) or epileptic fits.

Summary

Abnormally wide splitting of the second heart sound, due to delay in the pulmonary component, is described in eight patients with advanced renal failure. In seven the abnormality was relieved after the removal of extracellular fluid by peritoneal dialysis or haemodialysis, and in two it was provoked by blood transfusion. Though the mechanism of its production is not clear, it appears to be a useful sign of fluid overload in the uraemic patient.

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