was by caesarean section in 50.4% of cases. The gross foetal loss was 43% and the maternal mortality 2.1%. The six cases of maternal death are summarized.

The dangers of subjecting a patient who has had an antepartum haemorrhage to vaginal examination are emphasized. The attendant who first sees the patient has a great responsibility. A high incidence of prematurity is unavoidable in cases of placenta praevia; therefore to obtain good results an efficient paediatric service is essential.

The social problem of poverty and ignorance in Singapore is underlined, and a plea made for educating the public to a better understanding of the aims of obstetrics.

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GLYCOGEN-STORAGE DISEASE OF LIVER

BY

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Von Gierke (1929) first described a peculiar glycogen-storage disease under the title of "Hepatonephromegalia-glycogenica." It is a rare congenital disorder of carbohydrate metabolism occurring in infants and young children and is characterized by the storage of abnormally large amounts of glycogen not only in the liver but also in the kidneys, heart, skeletal muscles, and other organs (Humphreys and Kato, 1934).

The number of cases published is limited. Crawford (1946) could find under 50 cases described in the literature. Since then, however, further cases have been described by Van Creveld (1952) and Cori (1952).

No case of this disease had been reported from the Orient up to 1946 (Crawford, 1946), and so far as we know none has been reported since. The following cases are therefore of interest, and show that the disease exists in India.

Glycogen-storage disease includes five more or less distinct entities which may exist separately. Often, however, two or more are present at the same time. Occasionally a patient may initially show one of the manifestations and later have one or more of the remaining features superadded. Of the following groups Mason and Andersen (1941) consider as genuine Von Gierke's type only those with enlarged liver accompanied by impaired glycogen mobilization: (1) glycogen-storage disease of the liver, regarded by some as true Von Gierke's disease; (2) glycogen-storage disease of the heart and muscles; (3) patients showing enlarged liver with galactosuria; (4) cases associated with hyperinsulinism, the enzyme system being otherwise normal; and (5) an assorted group of cases, many of which show cirrhosis of liver.

An Indian family of seven children with two proved cases of disease came under our observation and are reported below. Besides these, three other siblings showed presumptive evidence of the disease, two others showed congenital malformation, and the parents showed some anomalies of carbohydrate metabolism (see family tree). All these are described later.

Case Reports

A soldier of the Indian Army reported to the out-patient department of the Military Hospital, Poona, in the beginning of 1952 for the treatment of two of his children.

The father, aged 39, and the mother, aged 32, were both healthy and were not blood relations. Both were Hindus and of Indian parentage. The family consisted of seven children, all sons aged from 1 to 14 years.

Case 1

The first son, aged 14, was born at full term after a normal pregnancy and confinement, and appeared healthy at birth. There was no history of birth injury or of neonatal ailments. He was breast-fed for about one and a half years, and was then put on the normal Indian diet, which is of a high carbohydrate and low protein content. He raised his head by the fourth month, cut his first tooth between the sixth and eighth months, sat up by the sixth or seventh month, and walked by about the first year. He talked a few words when 18 months old. Up to about the third year he was apparently normal and like other children. He then had an attack of pneumonia, and thereafter growth seemed to be retarded and the abdomen looked full.

His complaints on admission were a vague pain in his right hypochondrium, particularly when up and about; voracious appetite and marked flatulence; slight giddiness and

headache after comparatively slight physical exertion; and easy fatigability. These complaints dated from the time he was old enough to express himself.

Physical examination showed an underdeveloped boy with a normal mental make-up for his age. The facial expression was that of an elderly man. The genitalia were well developed, but there was no growth of hair on the lips, pubis, or axillae (Fig. 1). His height and weight were below normal (Table I).

The abdomen was protuberant and the liver was enlarged three fingerbreadths below the costal margin at the level of the right ninth costal cartilage. The enlargement was diffuse, the surface smooth, and the edge firm. Liver dullness extended to the fifth rib in the mid-axillary line and the seventh space in the scapular line on the right side. There was no ascites, oedema of the feet, or jaundice. The spleen was not enlarged and the veins over the abdomen were not prominent. The heart and lungs showed no abnormality, clinically or radiologically. There were no abnormal neurological features. On admission routine laboratory investigations showed a ketonuria but no other abnormality. The results are recorded in Table II. Special tests carried out are described later.

Case 2

The second son, aged 12, was born at full term after a normal pregnancy and confinement. There was no history of birth injuries or other neonatal ailments. His development and various milestones were normal until he was 2 years old, when he had an attack of dysentery lasting seven days. After that it was noticed that he did not grow normally and that he used to sleep a good deal. He would lie in his bed for hours in the morning and when he did get up he was sick. He developed sluggish habits and would prefer to lie down in bed rather than be up and about. Appetite was voracious. He was easily fatigued by physical exertion and could not compete with other boys of his age.

On admission he complained of headache and giddiness on exertion, flatulence, vague pain in the right hypochondrium,

TABLE II

	Case 1	Case 2
1. Urine	Ketone bodies Rothera's tests ++	Ketone bodies Rothera's test +++
2. Blood examination:		
Hb.	14 g./100 ml.	13 g./100 ml.
R.B.C.	4,600,000/c.mm.	4,600,000/c.mm.
W.B.C.	7,800/c.mm.	8,400/c.mm.
Polymorphs ..	49%	70%
Lymphocytes ..	43%	20%
Eosinophils ..	6%	5%
Monocytes ..	2%	5%
3. Liver-function test:		
van den Bergh ..	Negative direct	Negative direct
Serum bilirubin ..	0.2 mg./100 ml.	0.2 mg./100 ml.
Icteric index ..	3	3
Proteins	7.5 g./100 ml.	7.0 g./100 ml.
Albumin	5 g./100 ml.	5.5 g./100 ml.
Globulin	2.5 g./100 ml.	1.5 g./100 ml.
Cephalin-flocculation test ..	Negative	Negative
Lugol's iodine test ..	"	"
4. Blood cholesterol ..	225 mg./100 ml.	240 mg./100 ml.
	221 "	
5. Fasting blood sugar ..	58.8 mg./100 ml. (first) 71.0 " (repeat)	45 mg./100 ml. —
6. Blood calcium ..	7.2 mg./100 ml.	7.6 mg./100 ml.
7. Serum chloride ..	560 mg./100 ml. as NaCl	590 mg./100 ml. as NaCl
8. W.R. and Kahn ..	Negative	Negative
9. Aldehyde and Chopra test	"	"
10. Blood diastase (normal 33 to 200 El.u./ml.)	140 mg. concentration	137 mg. concentration
11. Urinary diastase (normal 6-33 W.u./100 ml.)	20 units/ml.	3.3 units/ml.
12. Urinary chloride ..	10 g./litre	15 g./litre
13. Stool	Ova of <i>Giardia lamblia</i>	N.A.D.
14. X-ray of sella turcica	N.A.D.	N.A.D.
15. Fundus examinations	N.A.D.	N.A.D.

TABLE I

Case	Age in Years				Height	Normal Height	Weight	Normal Weight	Genitalia
	Actual	Apparent	Bony Age as Judged from Ossification Centres	Dental					
					in. cm.	in. cm.	lb. kg.	lb. kg.	
1	14	10	13	14	54 137	60 152	64 29	94 42.6	Normal Rudimentary testes
2	12	8	10	10	47 119	56 142	42 19	78 35.4

FIG. 1.—Appearance of three eldest sons of the family. Case 2 on left, Case 1 in centre, and the third son on right.

FIG. 2.—Case 2. Showing enlargement of liver and prominent abdominal veins.

and easy fatigability. These complaints dated from the time he was old enough to express himself.

Physical examination showed the growth to be stunted, but the boy looked otherwise well covered; in fact, the face was somewhat full and chubby. Mental development was normal for his age. The testes were rudimentary. The penis was on the small side and he had no signs of any hair in the axillae or over the pubis (Figs. 1 and 2).

His height and weight were substandard (Table I) for his age. The abdomen was protuberant and there were prominent veins over the front and sides of the chest and abdomen (Fig. 2). The liver was enlarged four finger-breadths below the costal margin at the level of the right ninth costal cartilage. The enlargement was diffuse, the surface smooth, and the edge firm. The liver dullness extended upwards to the fifth intercostal space in the mid-clavicular line, the sixth in the mid-axillary line, and the seventh in the scapular line on the right side. There was a slight amount of fluid in the abdomen but no oedema of the feet. Jaundice was absent. The spleen was not enlarged. The heart and lungs showed no abnormality on clinical and radiological examination. No neurological abnormality was present.

Apart from ketonuria, no other abnormality was found on routine laboratory investigation (Table II). Special tests carried out are described below.

The chief clinical features of the two cases are summarized in Table III and the results of other investigations in Table II.

TABLE III.—Summary of Clinical Features of Cases 1 and 2

	Case 1	Case 2
Age symptoms first noticed	2 years	2 years
Main complaint	Abdominal distension	Stunted growth and abdominal distension
Hypoglycaemic symptoms	Nil	Nil
Hepatic enlargement	+++	+++
Renal enlargement	Nil	Nil
Cardiac enlargement	Nil	Nil
Portal hypertension	Nil	Slight ascites
Mental development	Normal	Normal
Physical development	Slightly impaired	Impaired
Endocrine features	Progeria type	Brissaud type

Remainder of Family

Physical examination of the rest of the family showed that the sixth son, aged 2½ years, had a ventricular septal defect. The seventh son, aged 1 year, had a large capillary naevus on the right side of the face. The others had no complaints and showed no physical abnormality.

The family was subjected to the following tests: (a) urine examination for ketone bodies; (b) adrenaline-sensitivity test (Cantarow and Trumper, 1949); (c) combined glucose-tolerance test (oral) and adrenaline-sensitivity test (original technique of Dr. Sehra); and (d) intravenous glucose-tolerance test (Crawford, 1938).

Ketonuria.—Specimens of urine of the whole family were tested for ketone bodies by both the Rothera nitroprusside and the Gerhard ferric chloride test. The ferric chloride test was never positive in any of the specimens. The Rothera test was positive in four members of the family—namely, Case 1, Case 2, and the fourth and sixth sons. The intensity of the colour and the rapidity with which it appeared varied. Depending on these, the results were classified as trace to three plus. While the fourth and sixth sons showed only occasional traces of ketones in urine at intervals, in Cases 1 and 2 the reaction varied from ++ to +++.

In Case 2 the urine was more often positive to Rothera's test than in Case 1, and it also showed a stronger reaction. In these two boys the Rothera test was persistently positive after the administration of 50 g. of glucose for the glucose-tolerance test. Sometimes a negative Rothera test coincided with a postprandial phase of a mixed carbohydrate diet.

Adrenaline-sensitivity Test.—Four members of the family were subjected to this test—namely, Case 1, Case 2, and the third and fourth sons. Intramuscular injection of 0.25 ml. of a 1 in 1,000 solution of adrenaline hydrochloride was given. The capillary blood sugar was determined immediately before the injection and at 15-minute intervals for the next hour. The blood-sugar response is shown in Table IV. The maximum rise of blood sugar in Cases 1 and 2

TABLE IV.—Adrenaline-sensitivity Test

	Tests	Fasting	½ Hour	½ Hour	1 Hour	Maximum Rise of Blood Sugar
			Inject 0.25 ml. Adrenaline I.M.			
Case 1	Blood sugar	66 mg.	100 mg.	67 mg.	63 mg.	34 mg.
	Urine sugar	—	—	—	—	—
	Ketone bodies	+++	+++	+++	+++	—
Case 2	Blood sugar	44 mg.	71 mg.	59 mg.	63 mg.	27 mg.
	Urine sugar	—	—	—	—	—
	Ketone bodies	+++	+++	+++	+++	—
3rd Son Age 8½	Blood sugar	67 mg.	105 mg.	95 mg.	69 mg.	38 mg.
	Urine sugar	—	—	—	—	—
	Ketone bodies	—	—	—	—	—
4th Son Age 6	Blood sugar	77 mg.	119 mg.	77 mg.	69 mg.	42 mg.
	Urine sugar	—	—	—	—	—
	Ketone bodies	—	—	—	—	—

was 34 and 27 mg. per 100 ml. respectively, and in the third and fourth sons it was 38 and 42 mg. per 100 ml. respectively. Cases 1 and 2 showed ketone bodies in all the urine specimens. Identical tests performed on normal subjects showed a minimum rise of at least 50 mg. per 100 ml. after such an injection.

Combined Glucose-tolerance Test (Oral) and Adrenaline-sensitivity Test.—These were done in four members of the family (Table V). Only a glucose-tolerance test could be

TABLE V.—Combined Glucose-tolerance Test and Adrenaline-sensitivity Test

	Test	Fasting		½ Hr.	1 Hr.	1½ Hr.	2 Hr.		2½ Hr.	3 Hr.	3½ Hr.	Comments on	
												G.T.T.	Adrenaline Response
Father	Blood sugar	79 mg.	Glucose 50 g. oral	138 mg.	153 mg.	111 mg.	74 mg.	Inject 0.25 ml. Adrenaline intramuscular	105 mg.	110 mg.	79 mg.	Normal	Rise of 36 mg. sub-normal
	Urine sugar	—		—	—	—	—		—	—	—		
	Ketone bodies	—		—	—	—	—		—	—	—		
Mother	Blood sugar	82 mg.		108 mg.	151 mg.	122 mg.	94 mg.		83 mg.	82 mg.	61 mg.	"	Fall of 11 mg. abnormal
	Urine sugar	—		—	—	—	—		—	—	—		
	Ketone bodies	—		—	—	—	—		—	—	—		
Case 1	Blood sugar	71 mg.		108 mg.	115 mg.	120 mg.	125 mg.		137 mg.	115 mg.	—	Broad base	Rise of 12 mg. sub-normal
	Urine sugar	—		—	—	—	—		—	—	—		
	Ketone bodies	++		++	++	++	++		++	++	—		
Case 2	Blood sugar	45 mg.		72 mg.	77 mg.	84 mg.	105 mg.		130 mg.	133 mg.	—	"	Rise of 28 mg. sub-normal
	Urine sugar	—		—	—	—	—		—	—	—		
	Ketone bodies	++		++	++	++	++		++	++	—		
3rd Son	Blood sugar	68 mg.		101 mg.	103 mg.	68 mg.	61 mg.		—	—	—	Flat type	Not done
	Urine sugar	—		—	—	—	—		—	—	—		
	Ketone bodies	—		—	—	—	—		—	—	—		

[illegible]

has been questioned by Von Gierke (Miller *et al.*, 1947) whether there is any pituitary abnormality at all. But our two cases showed clinical abnormality suggesting pituitary dysfunction—namely, the progeria-like features in Case 1 and a Brissaud type of picture in Case 2 (see Fig. 1). Case 2 showed signs of cirrhosis of the liver manifested by engorged abdominal veins and slight ascites, but no evidence of defective liver function was detected biochemically.

That the disease is a congenital disturbance occurring in the same family has been noted by Ellis and Payne (1940) and by Sarmiento and Gortes Mendoza (1947). When the disease occurs in one member of the family there is a possibility that other members of the same family may have the disorder in a mild form. The cases described by us are brothers, and six members of the family, including the father and mother, showed an abnormal adrenaline response. Other abnormalities, such as transient ketonuria, septal defect in the heart, a flat glucose-tolerance curve, and naevus, were also noted in other members of the family (Table VI). The father and mother were, however, not consanguineous.

It is tempting to postulate that the factors contributing to an abnormal adrenaline response may be regarded as recessive characters, the presence of which in the parents has produced full-fledged cases of glycogen disease in two sons and minor disabilities manifested by an abnormal adrenaline response and transient ketonuria in two other siblings. The presence of such congenital abnormalities as a ventricular septal defect in one son and a capillary naevus in another is of interest.

Summary

Von Gierke in 1929 gave a clear account of the disease, now named after him, under the heading of "hepatonephromegalia-glycogenica." Fewer than 50 cases had been described in the literature up to 1946. A few more have since been reported. No case, to our knowledge, has been reported from the Orient.

Two brothers suffering from the disease came under our observation. The clinical features and results of investigation are described.

The other members of the family—five siblings (all boys), the father, and the mother—were also investigated. Three of these other brothers showed presumptive evidence of the disease and the parents showed some anomalies of carbohydrate metabolism. Two other brothers showed some congenital defects.

The significance of various tests and some theories of causation are discussed.

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PINK DISEASE AND MERCURY IN SHEFFIELD, 1947-55

BY

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The early reports on mercury as a possible factor in the aetiology of pink disease appeared some years ago (Fanconi *et al.*, 1947; Warkany and Hubbard, 1948). There is still some disagreement on the subject (Naish, 1955), but repeated warnings that mercury may be dangerous to infants (Gaisford, 1949; James, 1951; Holzel and James, 1952; Farquhar, 1953; Dathan, 1954) have deterred doctors from prescribing the metal and caused manufacturers of teething powders to remove it from their products. The consequent reduction in the number of infants receiving mercury must be considerable, and it becomes important in any appraisal of the hypothesis to know if there has been a corresponding fall in frequency of the disease. Since the incidence of pink disease (Logan, 1949) and the extent of the teething-powder habit (Holzel and James, 1952) vary in different parts of the country, the requisite inquiries can with advantage be made on a local scale, and it is the object of this report to give the findings in Sheffield.

Sheffield has been a suitable centre for such an inquiry, for the disease is relatively common in the area and its study has been encouraged by the establishment of a special clinic for pink disease at the Children's Hospital (Colver, 1955).

Mercury Ingestion Among Infants in Sheffield, 1946-8 and 1953-5

Warkany and Hubbard's (1948) report led clinicians to inquire into teething-powder customs in this country (Leys, 1949; Holzel and James, 1952), and one such inquiry was made retrospectively in 1948 among the parents of patients undergoing treatment at the Children's Hospital. Two hundred mothers were selected who had other children, aged 12 months to 2 years, not attending the hospital. They were asked if they had given these latter infants teething powders between the ages of 4 and 12 months: 64 recalled that they had, and 60 were able to name the brands used. It emerged that 52 had administered brands known to contain mercury. Six mercury-containing brands, which may be termed A, B, C, D, E, and F, were involved, and they had been used as follows: 19 mothers used brand A, 17 B, 7 both A and B, 5 C, 1 both B and C, 1 D, 1 E, and 1 F. These powders had been purchased without prescription from chemist or general dealer almost equally. It was estimated from the foregoing figures that roughly a quarter of Sheffield infants were receiving mercury in the form of teething powders at the age when pink disease usually occurs.

A similar retrospective inquiry, differing in that 45 of the mothers questioned attended the Jessop Hospital for Women, was conducted in 1955. Of the 200 mothers, 39 had this time administered one or more of the brands A, B, C, and F, but not brands D and E. They had been used as follows: 22 mothers A, 8 B, 4 both A and B, 4 C, and 1 F. There had been no marked reduction, therefore, in frequency of purchase since 1946-8. There is to-day, however, the important difference that mercury is no longer present in a large proportion of the powders which formerly contained the metal. For instance, among 183 of the aforementioned powders recently bought by myself from 80 chemists and 80 general dealers mercury was not present in 131 (47 of