

### Summary

The findings are reported of a small survey of the attitudes of mothers using local authority infant and child health and welfare services in three widely contrasted areas of England and Wales. The results are compared and contrasted with those of the National Child Health Survey and the Newcastle-on-Tyne 1,000 Family Study. Special reference is made to the fact that over 60% consultations are made with the health visitor—a circumstance the mothers seem readily to accept; and to the fact that her services are most popular with mothers of all ages who have a young first-born infant.

Some conclusions are drawn on the possible effects these findings may have on the shape of infant and child preventive care that general practitioners are developing within their own practices; in particular it is pointed out that such ventures are unlikely to be successful unless the assistance of a health visitor is obtained.

In addition to the Study Group, whose names are listed above, many people gave invaluable assistance in this survey. Dr. W. H. S. Wallace, London County Council Division 8, Dr. Roy B. Morley-Davies, of Rhondda, Glamorganshire, and Dr. G. W. H. Townsend, of Buckinghamshire, kindly allowed the mothers attending their clinics to be approached and made available unpublished statistics; Miss Newington, Superintendent Health Visitor of Buckinghamshire, was especially helpful in connexion with the work I did in her area. Among the many other colleagues with whom I have discussed this survey I would in particular like to mention Mrs. Margot Jefferys, Dr. Ronald MacKeith, Professor W. S. Walton, and Dr. Michael Warren.

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The general trend for metric measures to be adopted in hospitals led to the publication in 1960 of B.S. 3221, *Medicine Glasses (Metric Units) for Medicine Glasses of 50 ml. Total Graduated Capacity*. The scope of this standard (in future to be known as Part 1) has been extended by issuing Part 2, which deals with glass medicine measures of 30 ml. capacity. The new specification covers materials, design, graduation marking, and tolerances for these measures. Copies of both parts of this standard may be obtained from the B.S.I. Sales Branch, 2 Park Street, London W.1. (Price 3s. each; postage extra to non-subscribers.)

## NEONATAL JAUNDICE IN GLUCOSE-6-PHOSPHATE-DEHYDROGENASE-DEFICIENT INFANTS

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In previous articles (Doxiadis *et al.*, 1960, 1961) we presented evidence that a great proportion of Greek infants who developed severe neonatal jaundice in the absence of incompatibility or immaturity had an inherited deficiency of the red-cell enzyme glucose-6-phosphate dehydrogenase (G.-6-P.D.). Such cases had been described also in other communities (Panizon, 1960; Smith and Vella, 1960; Weatherall, 1960; Gilles and Taylor, 1961; Gaburro *et al.*, 1961).

From neither our own nor any other publications was it possible to assess the incidence of severe neonatal jaundice among the newborn infants with this enzyme defect. Also, no attempt has so far been made to find what other factors, apart from the well-known exogenous precipitating agents such as vitamin-K analogues and naphthalene, may contribute to the development of haemolysis and hyperbilirubinaemia in the G.-6-P.D.-deficient neonates.

The present work was undertaken in order to find out (a) the incidence of the G.-6-P.D. deficiency among the newborns of the Alexandra Maternity Hospital, Athens; (b) the incidence of severe neonatal jaundice among the G.-6-P.D.-deficient newborns; and (c) whether there is any accumulation of cases with severe neonatal jaundice in certain families, suggesting that there are additional factors, genetic or other, contributing to the development of severe jaundice.

### Material and Methods

Two groups of infants were analysed regarding the incidence of neonatal jaundice in relation to red-cell G.-6-P.D. activity. The first group consisted of 786 male infants randomly selected, from whom cord blood samples were collected by the delivery-room personnel at Alexandra Maternity Hospital. A special form was kept for each infant. The mother's place of birth and her previous obstetrical history were recorded. She was also asked whether any of her previous infants had shown neonatal jaundice and whether she or any other member of her family had had an episode of icterus. The infants were seen daily and the presence of jaundice was noted. Blood grouping, direct Coombs test, and estimation of serum bilirubin were performed whenever there was a clinical indication. The doctor responsible for the clinical observation of the infants was unaware of the results of the G.-6-P.D. estimation.

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The second group consisted of 85 infants and their families seen by us in the past three years with severe neonatal jaundice or its sequelae. In these families the only possible cause of the jaundice was the G.-6-P.D. deficiency. Cases with blood-group incompatibility or prematurity and G.-6-P.D. deficiency were excluded from this group. The investigation of these cases included a detailed history, especially concerning possible extrinsic haemolytic agents and the search for neonatal jaundice and other manifestations of G.-6-P.D. deficiency in their relatives. The G.-6-P.D. activity was assessed in as many members of their families as possible.

For the assessment of G.-6-P.D. activity of the red cell the Motulsky and Campbell test as described in our previous paper was used (Doxiadis *et al.*, 1961). The fairly narrow range of the haematocrit values existing normally in cord-blood samples made the use of packed cells unnecessary. Thus 0.02 ml. of whole blood was used instead of 0.01 ml. of packed cells. Samples showing G.-6-P.D. deficiency were retested at least twice. In no case was a false-negative result obtained.

### Results in Randomly Selected Male Newborn Infants

Of the 786 infants, 23 were found to have G.-6-P.D. deficiency, an incidence of 2.92%. In Table I the group is subdivided according to maternal place of birth. As can be seen our material is representative mainly of the

TABLE I.—Regional Distribution of Maternal Place of Birth of Male Infants Tested for G.-6-P.D. Deficiency

Maternal Place of Birth	Total Tested	G.-6-P.D.-Deficient	Incidence of G.-6-P.D. Deficiency
Peloponnese .. .. .	192	7	3.64
Athens .. .. .	146	3	2.05
Sterea Hellas and Euboea .. .. .	192	5	2.60
Aegean Islands and Crete .. .. .	135	5	3.70
All other regions .. .. .	121	3	2.47
Total .. .. .	786	23	2.92

population of southern Greece and the islands. Although the size of the samples is rather small it is unlikely that any striking difference exists in the incidence of G.-6-P.D. deficiency between the regions represented in our material.

Table II shows the incidence of neonatal jaundice among the infants with and without G.-6-P.D. deficiency. The incidence of the different degrees of neonatal jaundice in this group of randomly selected infants was similar to that previously reported (Doxiadis *et al.*, 1961). The group of infants with G.-6-P.D. deficiency showed an excess of moderate and marked jaundice in comparison to the infants with

TABLE II.—Occurrence of Neonatal Jaundice in Randomly Selected Male Infants

	G.-6-P.D. Normal	G.-6-P.D.-deficient
No jaundice .. .. .	260	7
Slight .. .. .	287	7
Moderate .. .. .	38	6
Marked .. .. .	8*	1†
Insufficient information .. .. .	170‡	2‡
Total .. .. .	763	23

\* 1 Rhesus H.D.N. (exchange transfusion); 2 prematures; 3 O-A incompatibility-icterus praecox; 2 no incompatibility.

† Maximum serum bilirubin 20.5 mg./100 ml. on fourth day. No treatment.

‡ 1 Rhesus H.D.N. (early exchange transfusion); 1 stillbirth.

§ It is absolutely certain that no case of marked jaundice is included in this group.

normal G.-6-P.D. activity. Apart from the infants with rhesus haemolytic disease of the newborn (H.D.N.) none of the others required an exchange transfusion.

Of the 763 mothers of infants with normal G.-6-P.D. 357 were primiparae. The other 406 had a total of 624 previous children. Among these previous children there were five infants, belonging to four families, who had had severe neonatal jaundice. One was a case of rhesus H.D.N. which survived after exchange transfusion. In the other four the jaundice was proved either directly or indirectly to be due to G.-6-P.D. deficiency. Of these four infants, three had died with kernicterus (one after exposure to naphthalene inhalation) and the other had survived after exchange transfusion. These four mothers had been advised by us to be delivered in Alexandra Maternity Hospital because of their previous history. Thus although the sampling in this series was completely random, the admissions to Alexandra Maternity Hospital contained a proportion of mothers preselected because of previous infants with severe neonatal jaundice.

Of the 23 mothers of infants with G.-6-P.D. deficiency, 12 were primiparae. The rest had a total of seven male and seven female infants. In one family in which the present infant showed moderate jaundice a previous male infant had died from kernicterus (incompatibility was excluded).

### Results in Families of Infants Presenting Severe Neonatal Jaundice and G.-6-P.D. Deficiency

In the past three years we have examined 85 families in whom there was a combination of G.-6-P.D. deficiency and severe neonatal jaundice, in the absence of blood-group incompatibility or prematurity: 63 of the index cases were male and 22 female (3:1). The number of females may be unduly low because it is quite likely that in some female infants no G.-6-P.D. deficiency was revealed because of the inability of the Motulsky and Campbell test to detect all heterozygous females. Actually only a small proportion of the female infants tested in the neonatal period showed any degree of G.-6-P.D. deficiency by the Motulsky and Campbell test. Their heterozygous state for this abnormal gene was inferred from the finding of G.-6-P.D. deficiency in their fathers.

Of the 85 index cases 45 had kernicterus (31 male, 14 female). These were seen either in the acute stage or with late sequelae, and in a few the infant was already dead when the family asked for our opinion on the advisability of future pregnancies. In these last cases we have attributed the kernicterus to G.-6-P.D. deficiency whenever the genetic evidence showed that this enzyme defect was very likely present in the dead infant and all other causes of severe neonatal jaundice could be excluded.

Thirty-three infants (26 male, 7 female) were treated by us with exchange transfusion and in seven (six male, one female) the serum bilirubin values approached but did not reach our critical level for the performance of exchange transfusion.

In Table III the families were divided according to whether the abnormal gene was passed to the infant through the mother or through the father. In four families with male index cases the father was found to be deficient while the mother gave normal results. In these families either the mother was an undetected

heterozygote or the mode of transmission was not sex-linked as is the rule for G.-6-P.D. deficiency.

The incidence of severe jaundice in the siblings of the index cases is much higher than in the unselected population of G.-6-P.D.-deficient male neonates. Thus in the families with maternal transmission, one-third of the male siblings exhibiting G.-6-P.D. deficiency had severe degrees of neonatal jaundice. This ratio increases to one-half if we also take into consideration the siblings who were not tested; six of these had died of kernic-

TABLE III.—Analysis of 81 Families Selected Through Infants With Severe Neonatal Jaundice Due to G.-6-P.D. Deficiency

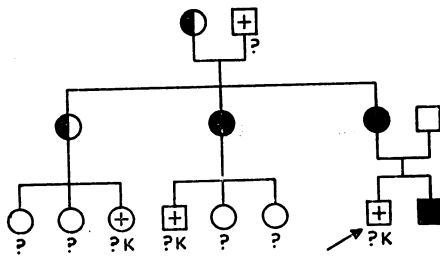
Propositus Families with more than one child .. .. .	Maternal Transmission of G.-6-P.D. Deficiency		Paternal Transmission of G.-6-P.D. Deficiency	
	Male 59 Female 2†		—* Female 20	
	39		15	
	Severe Neonatal Jaundice	No Jaundice	Severe Neonatal Jaundice	No Jaundice
Male siblings:				
Total .. .. .	11 (6)‡	32 (11)	—	7 (3)
G.-6-P.D.-deficient ..	5 (4)	10 (4)	—	—
G.-6-P.D.-normal .. .	—	13 (6)	—	4 (3)
Not tested .. .. .	6 (2)	9 (1)	—	3
Female siblings:				
Total .. .. .	3	16 (5)	2 (1)	13 (6)
G.-6-P.D.-deficient ..	—	1		
G.-6-P.D.-normal .. .	—	4 (3)		
Not tested .. .. .	3	11 (2)	(All considered heterozygous on genetic grounds)	

\* In another four families with male propositus the father was found to have G.-6-P.D. deficiency while the mother gave normal results. In these families either the mother is heterozygous or the mode of transmission is not sex-linked. In these four families there were three male siblings, one of whom died from kernicterus, and three female, two of whom had severe neonatal jaundice.

† Very likely a number of cases remained undetected through the heterozygous infant and mother giving normal results.

‡ Numbers in parentheses represent siblings born after propositus.

terus and it can be safely assumed that they were enzyme-deficient. It is also likely that most of the nine babies not jaundiced and not tested had normal enzyme activity. In contrast only one of the 21 infants of our first group with G.-6-P.D. deficiency and no other cause for neonatal jaundice showed such degrees of hyperbilirubinaemia. It is important to note that the same proportion of G.-6-P.D.-deficient siblings showed severe neonatal jaundice irrespective of whether they were born



Family tree showing cases of severe neonatal jaundice in G.-6-P.D.-deficient family. All mothers group A, D positive. Open square = normal. Closed circles or squares = G.-6-P.D.-deficient. Half-closed circles = intermediate. ? = Not tested. K = Kernicterus. + = Died.

before or after the index case. The female infants of these families were also liable but to a less degree to develop severe neonatal jaundice. In a few instances first cousins of the index cases have also suffered from severe neonatal jaundice (see Family Tree). So far we found no history of severe neonatal jaundice in either the carrier parent or his or her siblings, but on this point we cannot claim our information to be complete.

Discussion

The 3% incidence of G.-6-P.D. deficiency in our material is higher than that reported among 300 Greek male newborn infants originating from various parts of Greece (Zannos-Mariolea and Kattamis, 1961). Other studies confined to the population of certain small localities have shown, in some of them, a much higher incidence of this enzyme defect (Choremis *et al.*, 1962; Stamatoyannopoulos and Fessas, personal communication, 1962; Allison and Blumberg, personal communication, 1962). A higher incidence has also been found in other racial groups (Motulsky and Campbell-Kraut, 1961).

Our previous experience of the incidence of severe unexplained neonatal jaundice among 22,351 full-term newborn infants, together with the frequency of the abnormal gene, suggested that only a small proportion (by calculation around 5%) of the enzyme-deficient male infants develop severe icterus. In fact, only one of the 21 unselected male newborns with G.-6-P.D. deficiency and no other cause of haemolysis showed any marked hyperbilirubinaemia. The size of this group does not allow an accurate assessment of the magnitude of the risk of severe icterus in the G.-6-P.D.-deficient neonates. Nevertheless this risk is unlikely to be much higher than 5% in the absence of any extrinsic precipitating factor.

The fact that few of the G.-6-P.D.-deficient babies develop severe jaundice made us search for other contributing factors. Known extrinsic factors like vitamin-K analogues and naphthalene were absent in over half of our cases of jaundice developing on the basis of G.-6-P.D. deficiency. For these cases two possibilities can be considered. The first was the operation of some extrinsic and so far unsuspected factor. This possibility can be excluded at least for those of our cases born in the Alexandra Maternity Hospital; the same drugs were given to and the same regimen was followed by the mothers of the G.-6-P.D.-deficient babies whether the babies developed severe jaundice or not.

The second possibility would be the existence of an additional endogenous factor. Such endogenous factor could operate through a variety of mechanisms such as hypoglycaemia, anoxia, immaturity of the liver enzyme systems, and others. Assuming that such a factor existed, we tried in the present work to find out whether it was genetically determined or not. Such a possibility was suggested by the observation that in many families with G.-6-P.D. deficiency more than one offspring suffered from severe neonatal jaundice.

The family analysis showed that the siblings of our index cases exhibited a much higher incidence of severe neonatal jaundice than might have been anticipated from the incidence of this type of jaundice in the G.-6-P.D.-deficient babies in general. Thus in the families with maternal transmission of the enzyme defect about half of the male G.-6-P.D.-deficient siblings had severe jaundice. The possibility that a common environmental factor was operating in these families seems unlikely because in the siblings born after the index cases in our hospital under strict observation the proportion of jaundiced babies was the same.

The objection might be raised that our figures are biased because families with two affected children are more likely to be sent to us than families with one

affected child. If this were true we would expect that the incidence of jaundice in babies born after the index cases would not differ from that observed in the G.-6-P.D.-deficient babies in general. As our figures show, the incidence was much higher (four out of eight).

Since a common environmental factor operating in these families or bias in the selection of the material can be excluded, we consider that the high incidence of severe neonatal jaundice in certain families with G.-6-P.D. deficiency must be also genetically determined. In the present material we have not done any quantitative estimation of enzyme activity, and therefore we cannot exclude the possibility that in these families this activity is particularly low. Assuming that the enzyme level is of importance in the development of haemolysis in the neonatal period and that this level is genetically determined, an accumulation of jaundiced babies in certain families can be explained. The fact that some female heterozygotes displaying almost normal enzyme activity develop severe neonatal jaundice seems to be against a close relationship between enzyme level and haemolysis. However, the recent theory that in heterozygous females the red-cell population can be a mosaic for G.-6-P.D. activity invalidates this objection (*Lancet*, 1962).

Another explanation of the accumulation of cases of neonatal jaundice in some families may be the presence of another genetic factor transmitted independently of the G.-6-P.D. deficiency. Since for the development of neonatal hyperbilirubinaemia a multitude of factors may be responsible, this assumed additional genetic factor need not necessarily influence the degree of haemolysis.

An indication for the existence of such an additional genetic factor transmitted independently of the G.-6-P.D. deficiency is our finding that 11 out of 43 male siblings in the families with maternal transmission had severe neonatal jaundice—a ratio of 1 to 4. This is the expected ratio when two independently transmitted factors are needed for the clinical manifestation of a hereditary disorder.

The need of an additional genetic factor for the development of neonatal jaundice may explain the absence of such a clinical manifestation in some racial groups with a high incidence of G.-6-P.D. deficiency.

### Summary

Out of 786 Greek male neonates randomly selected 23 showed G.-6-P.D. deficiency, an incidence of 2.92%.

Only one of the 21 deficient babies who had no other cause for neonatal jaundice developed severe degrees of hyperbilirubinaemia. In contrast, among 43 male siblings of index cases—that is, infants with G.-6-P.D. deficiency and severe neonatal jaundice—there were 11 cases of severe hyperbilirubinaemia.

The accumulation of the cases of neonatal jaundice in certain G.-6-P.D.-deficient families is discussed. The suggestion is made that the additional factors necessary for the development of severe neonatal jaundice in the G.-6-P.D.-deficient babies are genetically determined.

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## DIURETIC ACTION OF TRIAMTERENE IN MAN

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The introduction of a new diuretic (Laragh *et al.*, 1961; Wiebelhaus *et al.*, 1961; Crosley *et al.*, 1962) compound differing from currently available diuretics in its capacity to increase sodium and chloride excretion with little or no increase in potassium output merits further investigation. Furthermore, if it is able alone or in combination with other agents to produce an effective diuresis when other regimes have failed, its place in diuretic therapy demands serious consideration.

The diuretic effect of the administration of triamterene (2,4,7-triamino-6-phenylpteridine; S.K.F. 8542) by mouth to normal individuals and to 10 selected patients with chronic oedema has been studied. In addition, further investigation of the potassium-sparing action of this drug has been made, and its effect on the excretion of uric acid has been studied.

### Methods

The nature of the renal action of triamterene was investigated in four normal subjects maintained on a normal diet with constant fluid, sodium, and potassium intake. The subjects continued moderate activity and no drugs other than those on trial were administered. Urine samples were collected from 8 a.m. to 8 p.m. at two-hourly intervals and a pooled collection was made for the subsequent 12 hours. All the specimens were collected under paraffin and preserved with thymol. After the 24-hour control collection period each individual was given 100 mg. of triamterene by mouth and urine collections were obtained at similar intervals over a further 24 hours.

Clinical trials of triamterene were conducted on 10 selected patients with chronic oedema of varied aetiology. The clinical details are summarized in Table I. Fluid consumption was maintained at 1.5 litres daily and sodium intake was restricted to 25 mEq a day (1.5-g. NaCl diet). All patients were weighed daily, and 24-hour collections of urine were made throughout the period of study. If treatment other than diuretics was