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Red Cell Glucose-6-Phosphate Dehydrogenase Deficiency—A Newly Recognized Cause of Neonatal Jaundice and Kernicterus in Canada

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ABSTRACT

Seven male newborns of Chinese, Greek and Italian origin presented with severe hemolytic jaundice due to red cell glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. In five, the hemolysis was precipitated by inhalation of mothball vapours in the home. Kernicterus was evident upon admission in six infants and was fatal in four of these.

G-6-PD deficiency should be suspected as a cause of jaundice in all full-term male infants of these ethnic groups. The diagnosis can be confirmed in any hospital by the methemoglobin reduction test. In areas similar to Toronto, Canada, where these high-risk ethnic groups prevail, the following measures are recommended: (1) detection of G-6-PD deficient newborns by screening cord bloods of all infants of these ethnic groups; (2) protection of affected infants from potentially hemolytic agents such as naphthalene, certain vitamin K preparations, and sulfonamides; and (3) observation of serum bilirubin levels to assess the need for exchange transfusion for hyperbilirubinemia.

SOMMAIRE

Sept nouveau-nés de sexe masculin et d'origine chinoise, grecque et italienne présentaient un ictère hémolytique grave attribuable à une insuffisance du glucose-6-phosphate de déhydrogénase (G-6-PD) dans les globules rouges. Chez cinq d'entre eux, l'hémolyse a été déclenchée par inhalation des vapeurs de naphtaline (boules à mites) présentes dans la maison. Un kernictère était manifeste dès l'admission de 6 nourrissons et eut une issue fatale chez quatre d'entre eux.

Il faut soupçonner l'insuffisance en G-6-PD, comme cause possible d'ictère chez tous les nourrissons mâles nés à terme et appartenant à ces groupes ethniques. Le diagnostic peut être facilement confirmé dans n'importe quel hôpital par l'épreuve de la réduction de la méthémoglobine. Dans des régions comme celle de Toronto, où ces groupes ethniques fortement prédisposés prédominent, on conseille de prendre les mesures suivantes: (1) découvrir les cas d'insuffisance en G-6-PD chez les nouveaunés de ces ethnies, par examen du sang du cordon ombilical, (2) protéger les enfants atteints du danger que représentent certains agents hémolytiques comme la naphtaline, certains produits à base de vitamine K et les sulfamides et (3) étudier la bilirubinémie de façon à évaluer le besoin d'une exsanguinotransfusion en cas d'hyperbilirubinémie.

AN inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) was first discovered in 1956,[1] and was found to be the basic defect in cases of hemolytic anemia following exposure to certain drugs (e.g. primaquine and sulfonamides), mothballs and fava beans. Since 1960, G-6-PD deficiency has been implicated as a cause of severe neonatal jaundice and kernicterus in countries such as Sardinia,[2] Greece[3] and Malaya,[4, 5] where the abnormal gene is particularly prevalent. A recent influx of immigrants from these countries has led to the discovery in Toronto of seven newborn infants with this condition. In view of the rising incidence and the serious conse-

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quences of this disease, it is important that physicians be aware of this problem as it relates to the differential diagnosis of neonatal jaundice.

CASE REPORTS (Table I)

The seven infants described in this report were born at full term and had no evidence of blood group incompatibility.

TABLE I.—PERTINENT CLINICAL AND LABORATORY FINDINGS IN SEVEN INFANTS WITH G-6-PD DEFICIENCY

Case No.	Patient	Sex	Onset (age in days)	Age (days) on admission	Death (age in days)	Nationality	Possible offending agents	Cerebral signs	Blood counts Hb. (g.%)	Blood counts Retic. (%)	Serum bilirubin (mg.%) Direct	Serum bilirubin (mg.%) Total	Erythrocyte G-6-PD level* (units/100 ml. RBC)	Treatment	Outcome	Postmortem findings
1	J.G.	M	6	7	—	Chinese	? Spray deodorant	+	6.8	—	—	36.0	11	Nil	Alive with cerebral palsy (kern-icterus)	—
2	P.W.	M	5	7	8	Chinese	Mothballs	+	7.5	—	15.1	32.6	—	Antibiotics, blood transfusion	Died	Kern-icterus
3	Boy W.	M	5	5	6	Chinese	Mothballs	+	9.8	—	—	42.2	0	Exchange transfusion	Died	Kern-icterus
4	P.V.	M	11	11	—	Greek	Mothballs, urinary tract infection	—	11.4	5.4	1.1	31.1	14	Chloram-phenicol, sulfisoxazole, blood transfusion	Alive and well	—
5	B.C.	M	7	15	16	Italian	Mothballs	+	8.4	0.8	—	52.5	0	Blood transfusion	Died	Not done
6	J.Ch.	M	6	6	7	Chinese	Mothballs	+	—	—	—	—	—	Antibiotics	Died	Kern-icterus
7	I.D.	M	2	4	—	Italian	?	+	18.3	—	4.6	33.3	22	Exchange transfusion	Alive with cerebral palsy (kern-icterus)	—

*Normal values in newborn infants: 220-406 units/100 ml. RBC.

CASE 1.—J.G., a Chinese male infant, was first seen at one week of age because of jaundice of 36 hours' duration. His hemoglobin was 6.8 g. % and serum bilirubin 36 mg. % (almost all indirect). The jaundice subsided without treatment but recurred at 6 months of age. When admitted to The Hospital for Sick Children, Toronto, at that time, the infant was irritable, spastic, and severely retarded. Moderate jaundice was evident. The liver edge was felt 4 cm. below the right costal margin, and the tip of the spleen was palpable. Abnormal liver function tests suggested active hepatocellular disease. This was confirmed by liver biopsy, which showed changes of giant-cell hepatitis and early cirrhosis. Red cell G-6-PD activity was only 11 units/100 ml. of red blood cells (RBC).

This child probably developed kernicterus during the period of neonatal hyperbilirubinemia. Although it is not certain what bearing the hemolytic anemia had on the subsequent development of giant-cell hepatitis, it is tempting to associate the two conditions etiologically. This interpretation derives support from reports in the literature of giant-cell hepatitis following neonatal hemolytic jaundice due to other causes (erythroblastosis fetalis[6] and hereditary spherocytosis[7]).

CASE 2.—P.W., a Chinese male infant, was admitted to hospital in 1960 at 7 days of age with anemia, jaundice and dehydration. He had been feeding poorly for two days. A feeble cry, neck stiffness, poor Moro reflex, and umbilical infection were noted on examination. His hemoglobin was 7.5 g. % and serum bilirubin was 32.6 mg. %, of which 15.1 mg. % was direct-reacting. He developed apneic spells and in spite of supportive therapy died 19 hours after admission. Postmortem examination revealed kernicterus.

CASE 3.—Boy W., the brother of P.W. (Case 2), was admitted to hospital in 1963 at 5 days of age with vomiting, diarrhea and jaundice. He was limp, lethargic, and developed periodic tonic-clonic convulsions. His hemoglobin was 9.8 g. % and serum bilirubin 42.2 mg. %. His blood smear showed anisocytosis, poikilocytosis and many spherocytes and crenated cells. Red-cell G-6-PD activity could not be detected. Despite exchange transfusion while on a Bird respirator, he died nine hours after admission. Postmortem examination revealed kernicterus. On retrospective questioning it was found that the bedclothes of this infant and his brother had been stored in mothballs in the home.

The first sibling (P.W.) was not examined for G-6-PD deficiency but the existence of this deficiency in Boy W. and in the mother is presumptive evidence that he was similarly affected.

CASE 4.—P.V., a Greek male infant, was well until 11 days of age when he developed listlessness, poor feeding and jaundice. Physical examination revealed an alert, markedly jaundiced infant, with physiologic reflexes. His hemoglobin was 11.4 g. % and reticulocyte count 5.4%. The serum bilirubin was 31.1 mg. %, of which 1.1 mg. % was direct-reacting. Anisocytosis and spherocytosis were noted in the blood film, and a Heinz-body preparation was negative. Urinalysis and culture led to the diagnosis of *E. coli* pyelonephritis, for which he was treated with chloramphenicol. After

two blood transfusions the infant improved and was discharged on a three-month course of sulfisoxazole (Gantrisin). A history of mothball exposure at the time of the initial hemolytic episode suggested the possibility of G-6-PD deficiency. This was confirmed by enzyme assay at five months of age, at which time the infant was well and appeared to be developing normally.

Either the mothball exposure or the urinary tract infection may have precipitated the episode of acute hemolytic jaundice in this infant. It is interesting that no further hemolysis resulted during the administration of chloramphenicol and sulfisoxazole, drugs which have been reported to cause hemolysis in G-6-PD-deficient persons.

CASE 5.—B.C., an Italian male infant, required resuscitation at birth because the umbilical cord had encircled his neck. He improved and remained well until 7 days of age, when jaundice was first noted. His serum bilirubin at that time was 21 mg. %. This fell to 18 mg. % on the following day and he was discharged from the nursery. Jaundice was observed again at 14 days of age and he was admitted to hospital the following day. Physical examination revealed deep jaundice, lethargy, increased muscle tone, and a weak, high-pitched cry. His hemoglobin was 8.4 g. %, and reticulocyte count 0.8%. A blood smear showed spherocytes and crenated and fragmented red cells (Fig. 1). His serum bilirubin was 52.5 mg. %. Red-cell G-6-PD activity was not detectable. The infant developed apneic spells and died 20 hours after admission despite artificial ventilation. Further inquiry revealed that the infant's bedclothes had been stored in mothballs at home.

The development of clinical kernicterus in this infant at 2 weeks of age is a reminder that there is no "safe" time in the neonatal period beyond which hyperbilirubinemia will not cause brain damage.

CASE 6.—J.C., a Chinese male infant, was seen at 6 days of age when he was first noticed to be jaundiced, lethargic, and anorexic. On examination he was severely jaundiced and listless, and reacted poorly to stimulation. He developed irregular respirations with apneic spells and died eight hours after admission, before laboratory examinations could be carried out. Postmortem examination revealed kernicterus.

The diagnosis of G-6-PD deficiency was made four years later by family studies which revealed low enzyme values in the mother and a healthy brother (born in 1961, but not jaundiced). Inquiry revealed that the deceased infant was exposed to mothballs in the home after discharge from the nursery.

In this case, as in Case 2, the diagnosis was not confirmed until family studies were carried out. These studies are especially important with respect to the management of the mother's future pregnancies.

CASE 7.—I.D., an Italian male infant, was transferred to The Hospital for Sick Children at 4 days of age because of increasing jaundice since the age of 2 days. Physical examination revealed an infant with marked jaundice, opisthotonos and a high-pitched cry. His hemoglobin was 18.3 g. % and the blood smear showed a few fragmented and crenated red blood cells. The serum bilirubin was 33.3 mg. %, of which 4.6 mg. % was direct-reacting. Red-cell G-6-PD activity was markedly decreased. After exchange transfusion the jaundice gradually cleared. Athetoid movements persisted however, and were associated with electroencephalographic evidence of diffuse seizure activity. When seen at 2 months of age, the infant's condition had not changed.

The rapid development of hyperbilirubinemia and kernicterus in this infant emphasizes the need for early diagnosis and treatment by exchange transfusion.

FAMILY STUDIES

G-6-PD determinations were carried out by the spectrophotometric method of Zinkham;[8] normal values for this enzyme are 220-406 units/100 ml. RBC in newborn infants, and 150-216 units/100 ml. RBC in adults. In most cases preliminary screening with the methemoglobin reduction test of Brewer, Tarlov and Alving[9] was carried out. This test depends on the inability of G-6-PD-deficient erythrocytes to generate reduced nicotinamide adenine dinucleotide phosphate (NADPH)* for the reduction of methemoglobin in the presence of glucose and methylene blue; in its simplest form it will detect all affected males and about 50% of heterozygous females.

From Table II it is apparent that all mothers of the affected infants had moderately decreased

TABLE II.—FAMILY STUDIES

Case No.	Family	Relation	Age (yr.)	G-6-PD activity: Methemoglobin reduction test*	G-6-PD activity: Enzyme assay** (units/100 ml. RBC)
1	G.	Mother	32	Intermediate	84
		Father	33	Negative	153
2, 3	W.	Mother	32	——	96
		Father	36	——	170
		Sister	2	——	150
		Brother	5	——	0
4	V.	Mother	35	Negative	108
		Father	42	Negative	170
		Mat. Grandmother	58	Negative	280
		Mat. Grandfather	64	Positive	0
5	C.	Mother	38	Intermediate	101
		Father	39	Negative	191
		Brother	5	Positive	0
		Brother	16	Negative	163
6	Ch.	Mother	30	Negative	136
		Father	30	Negative	164
		Brother	3	Positive	0
		Sister	7	Negative	164
7	D.	Mother	30	Intermediate	109
		Father	28	——	——
		Sister	2	Negative	164
		Brother	4	Negative	174

Interpretation of results:
Positive—G-6-PD deficiency (male hemizygote).
Negative—normal.
Intermediate—heterozygous for G-6-PD deficiency (approximately 50% of female heterozygotes will yield a negative result by this test).

**Normal values:*
Adults —150-216 units/100 ml. RBC.
Newborns—220-406 units/100 ml. RBC.

*Also known as reduced triphosphopyridine nucleotide phosphate (TPNH).

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enzyme activity. All fathers were normal. Three of five male siblings had practically no enzyme activity and the remaining two were normal. In none of these G-6-PD-deficient male children was there a history of neonatal jaundice. All three female siblings had levels within the normal range. One maternal grandfather had no measurable activity of this enzyme.

These results confirm the sex-linked partially dominant mode of transmission that has been previously shown. The fact that the present families were selected on the basis of severe jaundice, which is more likely to occur in affected males (on the basis of their lower enzyme levels), explains the preponderance of maternally transmitted pedigrees in this study and in similar reports in the literature.

DISCUSSION

The biochemical effect of G-6-PD deficiency can best be appreciated by first considering the role of this enzyme within the framework of glucose metabolism in the normal erythrocyte. The major portion of glucose that enters the red cell is metabolized by way of the glycolytic (Emden-Meyerhof) cycle to lactate, with the production of energy in the form of adenosine triphosphate (ATP). Energy derived from hydrolysis of ATP is used to regulate active cation transport across the red cell membrane, thus maintaining osmotic integrity. The remainder of glucose utilization (approximately 10%) is "shunted" through the pentose-phosphate pathway (Fig. 2). The enzyme G-6-PD acts in the first step of this shunt, catalyzing the oxidation of glucose-6-phosphate to 6-phosphogluconic acid, with concomitant generation of NADPH (TPNH). The latter is an essential cofactor in two important enzymatic processes within the red cell—maintenance of glutathione in the reduced state (GSH), and conversion of methemoglobin to oxyhemoglobin.

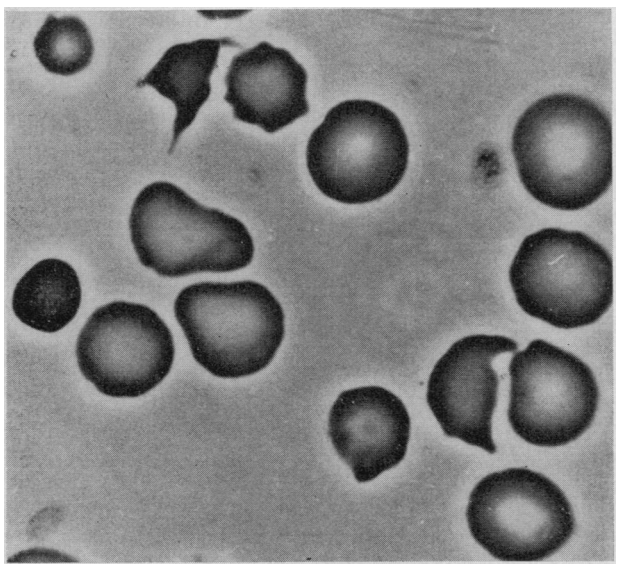

Fig. 1.—Peripheral blood smear from Case 5. Note fragmented and distorted erythrocytes, with spherocyte on left. (3500 ×.)

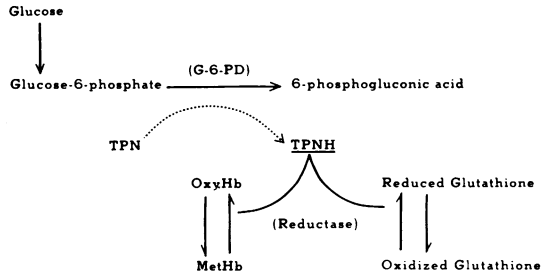

Fig. 2.—Pentose phosphate pathway. (TPN and TPNH are synonymous with NADP and NADPH, respectively—see text.)

Although the precise mechanism by which a deficiency of G-6-PD leads to hemolysis is not clear, a variety of metabolic abnormalities have been observed in such erythrocytes.[10] Two of these, the low content of GSH and the low content of ATP (both accentuated by exposure to certain drugs), have received the greatest attention with regard to their role in predisposing the erythrocyte to premature death. GSH, by serving as substrate for the enzyme glutathione peroxidase, protects the cell from the toxic effects of hydrogen peroxide generated by oxidant drugs;[11] a deficiency of GSH will therefore render the G-6-PD-deficient erythrocyte susceptible to hemolysis by such drugs (see list of agents in Table III[12]). The low level of ATP has been interpreted as a secondary phenome-

TABLE III.—AGENTS REPORTED TO INDUCE HEMOLYTIC ANEMIA IN SUBJECTS WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY*

Antimalarials	*Antipyretics and analgesics*
*Primaquine	Acetylsalicylic acid
*Pamaquine	*Acetanilide
*Pentaquine	Acetophenetidin (Phenacetin)
*Plasmoquine	Antipyrine
	Aminopyrine (Pyramidon)
	P-aminosalicylic acid
Sulfonamides	*Others*
*Sulfanilamide	Sulfoxone
*Sulfapyridine	*Naphthalene
Sulfisoxasole (Gantrisin)	Methylene blue
*Salicylazosulfapyridine (Azulfidine)	?Vitamin K
	*Phenylhydrazine
*Sulfamethoxypyridazine (Kynex, Midicel)	*Acetylphenylhydrazine
	Probenecid
Sulfacetamide (Sulamyd)	*Fava bean
	Benadryl
	Pyribenzamine
Nitrofurans	*Infections*
*Nitrofurantoin (Furadantin)	Viral respiratory infections
Furazolidone (Furoxone)	Infectious hepatitis
Furaltadone (Altafur)	Infectious mononucleosis
	Bacterial pneumonias and septicemias

The relative hemolytic potential of these drugs varies. Those marked with an asterisk are most likely to induce hemolysis. For the others, a relatively high dose may be required; in addition, other factors such as infection, enzyme level of the patient, etc., are of importance. It is wise to avoid use of such drugs where possible, but in a situation where no other drug will suffice, their administration should be undertaken with caution and stopped at the earliest sign of hemolysis.

This list is not necessarily complete.

*Reproduced with permission, from Gross, R. T., *Bull. N.Y. Acad. Med.*, 39: 92, 1963.

mon, resulting from drug-induced damage of the red cell membrane.[13] Increased permeability to cations (Na^+ and K^+) leads to a compensatory increase in activity of the ATP-dependent active cation transport mechanism and eventually depletion of ATP, with failure of compensation, loss of osmotic equilibrium and hemolysis. The relative importance of these two postulated mechanisms and the pathogenesis of hemolysis occurring in the absence of drug exposure (as in the newborn infant) are matters that remain to be elucidated.

G-6-PD deficiency is transmitted by a sex-linked gene of intermediate dominance. Enzyme levels are lowest (often undectectable) in male hemizygotes and in the rare female homozygotes, and are intermediate in female heterozygotes. Although persons with the lowest enzyme levels are most susceptible to hemolysis, thereby accounting for the preponderance of males among clinical reports, other factors are of importance. These include the nature and dosage of the drug, the presence of infection, and physico-chemical variations in the mutant enzyme.

TABLE IV.—APPROXIMATE INCIDENCE OF G-6-PD DEFICIENCY IN METROPOLITAN TORONTO
(Based on gene frequency estimate of 0.05)

Group	Census (1960)	G-6-PD deficiency		
		Males (hemizygotes)	Females (heterozygotes)	Females (homozygotes)
Italian	130,000	6500	12,500	325
Greek	23,000	1150	2200	60
Negro	8000	400	760	20
Chinese	6000	300	570	15
Others	34,000	1400	2650	70
Totals	201,000	9750	18,680	490
Total				28,920

The gene for G-6-PD deficiency occurs mainly in persons of certain racial and ethnic backgrounds, Negroes, Orientals, Caucasians originating in the Mediterranean area (Greeks, Italians and Sephardic Jews in particular) and Asiatic Indians. The incidence in these groups varies from approximately 2 to 15%, but figures as high as 58% have been found in certain areas (Kurdistan Jews in Israel[14]). It has been estimated that G-6-PD deficiency is probably present in more than 100,000,000 people in the world.[15] From recent census figures of the above-mentioned population groups[16] and an overall gene frequency estimate of 0.05 (based on an average obtained from various population surveys), the approximate incidence of G-6-PD deficiency in Metropolitan Toronto can be calculated (Table IV). It is evident that in this city of about 1,600,000 persons, approximately 30,000 persons (1.9%) may carry the gene. Of these, however, only a small proportion would be expected to manifest clinical evidence of the gene, a fact which is borne out by reports of others and the family studies in the present cases.

Observations in Greece[3] and Thailand[17] have shown that among Caucasian newborns with G-6-PD deficiency, only about 5% develop serious jaundice. In most of these cases no precipitating agents could be incriminated. Negroes with this deficiency do not appear to show an increased tendency to develop neonatal jaundice. Although the reasons for this discrepancy are not known, recent biochemical studies of the purified enzyme from affected persons of various racial groups have shown differences which have resulted in the characterization of several functionally distinct variants of G-6-PD.[18] However, the reason why spontaneous hemolysis develops in newborn infants with certain of these variants, but not with others, is not yet known. It is apparent, both from the seven cases reported here and from other reports in the literature, that severe neonatal jaundice is a crippling and often fatal complication of G-6-PD deficiency. Panizon[2] in 1960 described 11 such cases seen in Sardinia; two of these died and another five survived but were left with severe brain damage due to hyperbilirubinemia. In the same year, from Singapore, Smith and Vella[4] reported 13 Chinese newborn infants with kernicterus associated with G-6-PD deficiency. Although they observed that jaundice seemed to result from sudden hemolysis, they were unable to determine the precipitating factors, even though it was known that in older persons hemolysis can usually be attributed to some offending agent. Weatherall,[5] in reporting four similar patients in Singapore, was likewise unable to detect any precipitating agent. Doxiadis, Fessas and Valaes[3] in Greece reported that one-third of the cases of neonatal jaundice requiring exchange transfusion at their hospital were not associated with blood group incompatibility; nearly all of these infants were found to have G-6-PD deficiency. Although males predominated in that series, a number of heterozygous females were also seen, a finding which is in keeping with the partial dominance of this sex-linked gene. In only a few cases could such agents as naphthalene and vitamin K be incriminated as etiologic factors. Neonatal jaundice due to G-6-PD deficiency has since been reported from Italy,[19] Switzerland,[20] Thailand,[17] Israel,[14] Nigeria,[21] China[22] and Hawaii.[23] Immigration from these high-incidence areas has accounted for spread of this problem to other countries such as Australia, where several cases of neonatal jaundice with G-6-PD deficiency have recently been discovered.[24] The present report is evidence of a similar situation arising in Canada. Undoubtedly many more cases will be found now that we are aware of the problem and are able to diagnose it with relative ease by the methemoglobin reduction test.

From our experience with the seven infants reported here and from a review of the literature, the problem of neonatal jaundice due to G-6-PD deficiency may be summarized as follows.

Onset and course.—In contrast to the jaundice due to blood-group incompatibility, jaundice in infants with G-6-PD deficiency does not usually

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appear until after the first 24 to 48 hours of life, and in some cases not until the third or fourth week. Harley described five cases occurring between the ages of 10 and 23 days, and stressed the hazard of hemolytic drugs transmitted from the mother via breast milk. Mothball exposure from stored blankets and bedclothes in the home is another important factor causing this "late" neonatal jaundice. A history of such an exposure was discovered in five of the seven infants described in the present report. Valaes, Doxiadis and Fessas[25] reported 12 such infants from Greece, of whom six developed kernicterus. The danger of kernicterus from rapidly progressive jaundice in these infants is especially great, since in many cases the infant is not brought to the physician until symptoms of brain damage have already appeared.

Physical findings.—Jaundice, pallor and signs of bilirubin encephalopathy (when present) are the chief findings of significance. Enlargement of the liver or spleen is not common, in contrast to erythroblastosis fetalis in which these organs are usually enlarged.

Laboratory findings.—Anemia of varying degree is usually present and is associated with elevated reticulocyte counts. In some cases, however, both hemoglobin and reticulocyte counts are normal, suggesting that the hemolysis affects only a small proportion of the red-cell population but is sufficient to produce hyperbilirubinemia in the presence of physiologic immaturity of the bilirubin excretion mechanism at this age. Morphologic abnormalities on blood smear consist of varying numbers of nucleated red cells, spherocytes, poikilocytes, and crenated and fragmented cells, features consistent with metabolic damage of red cells. All of these abnormalities disappeared in the few patients who survived the episode of neonatal hemolysis.

Serum bilirubin is uniformly elevated. In the present group of seven cases the peak total bilirubin ranged from 31 to 52 mg. %. However, not all reported cases show this degree of hyperbilirubinemia. It is quite likely that many affected infants develop only mild jaundice which is not recognized. Although most of the bilirubin is indirect-reacting, in some cases, particularly later in the newborn period, moderate elevations of the direct-reacting fraction may occur.

Red cell G-6-PD activity in affected newborns was usually undetectable or at most 10% of normal activity. This was reflected in the methemoglobin reduction test which gave unequivocally positive results. In all cases it was possible to establish the diagnosis further by demonstrating the enzyme deficiency in one of the parents (the mother, in the case of affected males).

Management of the newborn infant with G-6-PD deficiency.—Results of treatment of neonatal jaundice due to G-6-PD deficiency have been poor. The main reasons for this are: (1) failure to recognize the condition before brain damage has occurred, and (2) the relatively late onset and rapid progression of jaundice, often at a time when the infant is beyond close medical surveillance. Since six of the seven infants reported here had evidence of brain damage by the time they were admitted to hospital, it is clear that early diagnosis is essential. This is true even though only 5% of G-6-PD-deficient infants will develop severe hyperbilirubinemia. The methemoglobin reduction test, which is simple and inexpensive, could be readily applied to all newborn infants of high-risk ethnic groups. In infants found to be G-6-PD deficient the following measures are recommended:

(i) Feeding.—Agents that are potentially hemolytic to G-6-PD-deficient infants may be transmitted in breast milk and should therefore not be given to nursing mothers. Furthermore, in view of the recent reports of indirect hyperbilirubinemia in a small percentage of breast-fed infants[26] (due to a factor in breast-milk which inhibits bilirubin glucuronide conjugation), it might be wise to discourage breast-feeding in G-6-PD-deficient newborns, in whom an increased bilirubin "load" (from hemolysis) may aggravate such a handicap in excretion.

(ii) Vitamin K.—*In vitro* studies have shown that menadione (vitamin K_3) and its synthetic water-soluble analogues (e.g. Synkavite, Hykinone) can induce methemoglobin formation, loss of reduced glutathione, and hemolysis.[27] This does not occur with natural vitamin K_1.[28] Since reversal of these effects requires the generation of NADPH from an intact pentose phosphate pathway, it would be expected that persons with G-6-PD deficiency would be prone to hemolysis upon receiving such drugs. Studies of Negro newborns with G-6-PD deficiency have not shown this to be the case.[29, 30] However, similar studies in Caucasian newborns have not yet been reported. Since neonatal jaundice in G-6-PD deficiency is a problem occurring mainly in the Caucasian newborn, it would appear wise to use greater than usual caution in the administration of vitamin K to such infants. Therefore, recent recommendations for giving the minimum dose (1 mg. intramuscularly to the infant—full-term or premature) of the least toxic preparation, natural vitamin K_1,* would seem especially applicable.[31]

(iii) Where possible, the use of all drugs such as sulfonamides and chloramphenicol, which may cause hyperbilirubinemia not only by hemolysis but also by competition with bilirubin for the glucuronide-conjugating mechanism, should be avoided.

(iv) Exposure to naphthalene (mothballs or mothflakes), in which blankets, diapers and bedclothes used by a previous infant may have been stored, should likewise be avoided.

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*Examples of this latter preparation are Konakion and Aquamephyton; both are supplied in convenient 0.5-c.c. ampoules containing 1 mg.

(v) As soon as jaundice develops in an affected infant, blood counts and serum bilirubin levels should be followed closely, until the end of the second week of life, if indicated. Upon discharge from the nursery the parents should be cautioned to watch for subsequent jaundice and report this immediately.

(vi) Exchange transfusion.—In the presence of high or rapidly rising serum bilirubin levels *at any age*, exchange transfusion should be carried out. As in the case of erythroblastosis fetalis, the serum indirect bilirubin level should not be allowed to exceed 20 to 25 mg. %. After the first week of life, exchange transfusion may necessitate femoral or saphenous vein cut-down. If performed before the serum bilirubin is very high, one exchange transfusion should suffice.

Finally, what advice should be given to the family of an affected child who has survived a bout of neonatal jaundice? The main points to be communicated to the parents, and this will often require the assistance of an appropriate interpreter, are:

(i) The importance of avoiding exposure to the known offending agents, and in particular to such commonly used substances as mothballs, fava beans and sulfonamides.

(ii) The need to learn to recognize and report early signs of hemolysis such as pallor, dark urine, and so on.

(iii) In the light of our present genetic knowledge, the parents should be advised about the chances of a future child being affected. Although this condition should not be a deterrent to future pregnancies, it is important to anticipate the possibility that a subsequent newborn child might be affected and require special medical attention (as outlined above).

(iv) The parents should be reassured that, after the neonatal period and with the avoidance of offending agents, this is a benign condition compatible with normal life expectancy. Periodic follow-up visits could help to ensure this.

SUMMARY

Clinical, biochemical and genetic data are presented with respect to seven male infants with red-cell glucose-6-phosphate dehydrogenase (G-6-PD) deficiency who presented with severe neonatal jaundice. Their racial origins were Chinese (four), Greek (two) and Italian (one). In five of the seven cases, hemolysis was probably triggered by exposure to the vapour of mothballs in the home. Six infants developed kernicterus and four of these died. Only one child is alive and well.

The general subject of G-6-PD deficiency is reviewed briefly, with special emphasis on the problem of neonatal jaundice. Recommendations are made for the detection of such cases before the onset of jaundice, in order that proper measures may be instituted to avoid the serious consequences seen in the present group of infants.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE GENERAL PRACTITIONER AND RESEARCH

Coming from one, himself once a general practitioner, who has probably done as much as any other physician of our time to apply scientific methods to the elucidation of important practical questions, James Mackenzie's words (*British Medical Journal*, January 3, 1914) are worthy of our earnest attention. He says, "The general practitioner must be recognized as an essential adjunct in research. To him especially we should look to find out the early stage of disease and its progress. Hitherto the lack of this assistance has been the cause of the tardy advance of medicine."

There is no essential reason for lack of harmony, in work or aim, among the different branches of our profession. Friction means dissipation of energy and lessened efficiency. Mutual support, sympathy and co-operation are essential to success. In the fight against disease, we represent different sections of one great organization, each with all-important duties—the laboratory worker and the experimenter devising and proving new implements and methods, the hospital clinicians and specialists bringing forward that which is new and best withstands the test of application—thus keeping open the communications with the men on the firing line, the great body of practitioners, on whose training and efficiency, after all, victory ultimately depends. Our students are the recruits who must be imbued with the proper spirit and trained to take their places in the ranks depleted by the casualties of service and by the falling out of the veterans.—H. B. Anderson, Presidential Address to the Academy of Medicine, Toronto; *Canad. Med. Ass. J.*, 4: 1036, 1914.