Acute Hemolytic Anemia in the Newborn Infant due to Naphthalene Poisoning: Report of Two Cases, with Investigations into the Mechanism of the Disease

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Since 1949, at least 18 cases of acute hemolytic anemia following exposure to naphthalene have been reported, including three newborn infants.1-11

It is the purpose of this paper to describe two cases of naphthalene hemolytic anemia occurring in newborns and to report investigations of erythrocyte metabolism in these infants and their families.

METHODS

The peripheral blood was studied as previously described.10 Heinz bodies were stained supravitally with 5% cresyl violet in saline and examined by phase microscopy. Blood glutathione was determined using a modification of the method of Gruenert and Phillips,12 and glutathione stability according to the method of Beutler.13 In addition, glutathione stability was measured upon incubation with known amounts of alpha and beta naphthol.

Methemoglobin reduction was measured in blood collected with heparin or EDTA. Samples were less than three hours old and stored at 8°C, until studied. The whole blood was diluted with 0.85% saline to roughly six times its volume, then centrifuged at 3000 rpm for five minutes and the supernatant removed. To 5 ml of cells an equal volume of 0.25% sodium nitrite in phosphate saline was added, the suspension gently agitated for one minute or less and diluted to approximately 40 ml with 0.85% saline. It was then immediately centrifuged for five minutes at 3000 rpm, the supernatant promptly removed and the cells washed six times with large volumes of 0.85% saline. Great care was taken to minimize the exposure to sodium nitrite in order to avoid release of free pigments into the plasma. After the last washing the supernatant saline was removed and the cells resuspended in 4-5 ml of phosphate saline (M 18 phosphate buffer, pH 7.4, diluted 1:1 with 0.85% saline). One ml aliquots of the cell suspension were then mixed with each of the following substrates: 1 ml each of 0.5% glucose in phosphate saline (2.76 mM of glucose ml-1), racemic lactate in phosphate saline (5.52 mM of lactate ml-1), and phosphate saline alone, and 1 ml of each of these preceding substrates with 0.01 ml of 0.1% methylene blue in 0.85% saline. Methemoglobin concentrations were then determined immediately and at appropriate intervals thereafter, using the method of Evelyn and Malloy.14

Glucose-6-phosphate dehydrogenase activity was measured in hemolysates from blood collected as described above. Whole blood was suspended in 0.85% saline to two to six times its volume, centrifuged once for five minutes at 3000 rpm and the supernatant and

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the buffy coat removed. The packed cells were diluted with an equal volume of distilled water. The resulting hemolysates were dialyzed overnight against distilled water. The sodium salt of glucose-6-phosphate (Sigma) was dissolved in 0.036 molar tris buffer, pH 7.4, to give 15 micromoles/ml. The reaction mixture consisted of 15 micromoles of glucose-6-phosphate, 4 micromoles of TPN (triphosphopyridine nucleotide, Sigma) and hemolysate containing either 3 or 1.5 mg. of hemoglobin in a final volume of 3 ml. The change in optical density at 340 \( \lambda \)WS observed with the Beckman UV Spectrophotometer using a hydrogen lamp light source and silica cells. Since this reflects production of reduced TPN, and since TPN is the hydrogen acceptor for glucose-6-phosphate dehydrogenase, the readings were considered indicative of enzyme activity. Control studies performed with glucose-6-phosphate dehydrogenase obtained from Sigma demonstrated a steady reaction rate for at least 50 minutes and optimal activity when 5-minute increments of optical density up to 0.120 were observed. Reactions were observed for 40 to 50 minutes and 5-minute increments were averaged. Results are expressed as O.D. for "0.1 Gm.% hemoglobin."

Glutathione reductase was measured in a system which contained 1 x 10^-4 molar oxidized glutathione (Nutritional Biochemicals), 1.5 x 10^-4 molar reduced TPN, and hemolysate to a final concentration of 4.25 Gm.% hemoglobin in a total volume of 5 ml with 0.036 molar tris buffer, pH 7.4. The hemolysate used was prepared as described above, the reaction was stopped at exactly 15 minutes by adding 3 ml of 5% metaphosphoric acid and the reduced glutathione produced was measured as described above.

**CASE REPORTS**

**Case 1:** J.S., a 14-year-old Negro female, was admitted to the Boston City Hospital on August 31, 1955, because of progressive icterus of three days' duration. She was the product of a normal full-term pregnancy with a birth weight of 6 lbs., 14 oz. Delivery and neonatal period were uneventful. After returning home she was dressed in clothing heavily impregnated with naphthol. Baby oil had been applied to the skin. Family history was negative for blood dyscrasias, but an older sibling was subsequently found to have an unexplained normochromic, normocytic anemia.

Physical examination revealed slight pallor and marked scleral icterus. There was a grade II apical systolic murmur. The liver was palpable 1 cm. below the right costal margin. The spleen was not palpable.

Laboratory examination of the peripheral blood on September 1, 1955, revealed a hemoglobin concentration of 9.6 Gm.%, erythrocytes 2.64 million/mm.\(^3\), leukocytes 10,600 per mm.\(^3\), and reticulocytes 5.6%. Moderate spherocytosis and polychromatophilia of the erythrocytes were seen on smear. Coombs' test and sickle cell preparation were negative. Both the patient and her mother were Group O Rh positive. Total bilirubin was 19.0 mg.% direct 1.0 mg.%. Urine was yellow and acid with 1-2+ sugar, and there was no albumen, red cells or casts. Occasional white blood cells were seen.

The patient did well in the hospital. By September 22, 1955, the total bilirubin was 8.9 mg.%, direct 0.2 mg.%. The hemoglobin gradually rose to normal levels and the spherocytosis and reticulocytosis subsided within a three-week period. At that time the osmotic fragility was normal.

**Case 2:** D.A., a nine-day-old Negro male, was admitted to the Boston City Hospital on July 22, 1957, because of jaundice of two days' duration. Family history was negative for blood dyscrasias or anemia. He was the first born child of a 19-year-old Negro female whose pregnancy and delivery were uneventful. Birth weight was 5 lbs., 5 oz. Neonatal course was uneventful until his discharge from the hospital at the age of five days, when he was dressed in clothing impregnated with naphthalene mothballs. At home he was given no medication except Castoria and catnip tea for mild constipation. Baby oil had been applied to the skin. Two days prior to admission he was noted to be icteric. One day prior to admission he seemed to cry less than normally and vomited several feedings.

Physical examination was unremarkable except for marked pallor and icterus. The spleen was palpable at the left costal margin and the liver was felt 1 cm. below the right costal margin.
Laboratory data revealed a hemoglobin of 5.8 Gm.%, reticulocytes 5.1%, leucocytes 13,900/mm.³ with 31% polymorphonuclear leucocytes, 3% bands, 9% eosinophils, 42% small lymphocytes, 2% large lymphocytes, 13% monocytes. There were three nucleated red blood cells per hundred white cells, and moderate anisocytosis, poikilocytosis, targeting and stippling of the erythrocytes. Many fragmented erythrocytes were seen on smear. Sickle cell preparation and Coombs' test were negative. Both the infant and his mother were Group A Rh positive. Serum bilirubin was 14.0 mg.% total, 0.99 mg.% direct. Urine was yellow, pH 5.0, with no albumen, sugar, ketones, red cells, white cells or casts. On July 24, 1957, 1-2+ Heinz body formation was seen.

The child did well in the hospital (see fig. 1). The icterus faded, there was a marked reticulocytosis and by August 2, 1957, the hemoglobin had risen to 8.9 Gm.%. He was discharged home on August 2, 1957. On August 4, 1957, he vomited several times. The home atmosphere was found to be "reeking" of mothballs and when seen two days later the hemoglobin was 8.2 Gm.%, reticulocytes 3.6% and many fragmented erythrocytes were seen on smear. He was removed from his home for several days with clearing of symptoms and since then has done well with restoration of his hemoglobin to normal values.

**RESULTS OF BIOCHEMICAL STUDIES**

The glutathione stability of the erythrocytes on incubation with acetyl phenylhydrazine was studied in both of these patients and their families. More than 50 per cent drop of glutathione after two hours incubation was considered evidence of severe glutathione instability while a similar drop upon four hours incubation was termed intermediate glutathione instability. The findings in both families are shown in figure 2. The blood glutathione of the first patient (at age 22 months), her mother and two of her five siblings was severely unstable. The blood glutathione of two additional siblings showed intermediate instability while that of the fifth sibling was normal.
The second patient initially had a normal blood glutathione without instability (fig. 2). This was measured during the period of active hemolysis and the relatively normal results could presumably be due to the previous destruction of older, sensitive cells. At age four months, his blood was retested and showed intermediate glutathione instability. His mother’s glutathione stability curve was similar in configuration while his father’s was within normal limits.

To demonstrate the susceptibility of the blood of these patients to naphthalene, normal and sensitive bloods were incubated with varying concentrations of alpha naphthol (fig. 3). Three mg. of alpha naphthol per ml. of blood resulted in a moderate drop of glutathione in three of four normals at two hours and a marked drop in all four at four hours. When incubated with two mg. of alpha naphthol per ml. of blood there was a less marked drop in the glutathione of three normals at four hours. The decrease of glutathione in the three sensitives was similar. However, the percentage decrement was much greater and the final glutathione level was lower. Duplicate studies in two normal individuals revealed no difference in the effect of similar concentrations of alpha or beta naphthol.

**Fig. 2.**—Familial distribution of glutathione instability upon incubation with 5 mg. of acetyl phenylhydrazine. Open squares or circles represent unaffected subjects; shaded circles, the intermediate unstables; and solid black circles, the severe defect. Case 1 and her family are plotted in A. The propositus (J.S.) is represented by x—x. In B, Case 2 (D.A.) and his family are shown. D.A.-1 indicates the glutathione stability curve during convalescence from naphthalene exposure. D.A.-2 represents the glutathione instability four months later.
The reduction of methemoglobin in vitro was studied in erythrocyte suspensions as a measure of the ability to reduce TPN and DPN. Incubation of the treated cells in presence of lactate allows reduction of methemoglobin through the reduced DPN produced in the presence of lactic dehydrogenase. The reaction is accelerated by methylene blue. This is probably not the usual mechanism of DPN reduction in the erythrocyte, since the direction of the reaction in glycolysis is from pyruvate to lactate with the oxidation of reduced DPN (DPNH₂). The normal mechanism of methemoglobin reduction probably utilizes the two moles of DPNH₂ derived from the breakdown of one mole of glucose to pyruvate via the oxidation of two moles of glyceraldehyde-3-phosphate. In our experiments, the molarity of the lactate was double that of the glucose in order to have physiologically equivalent concentrations of these substrates. Addition of methylene blue to glucose as a substrate results in marked acceleration of the rate of reduction of methemoglobin and is probably related to the action of a methemoglobin reductase which utilizes reduced TPN (TPNH₂) produced via the hexose monophosphate shunt.

Erythrocytes from both patients, their mothers and normal subjects were studied. The results of incubation of erythrocytes for 180 minutes in the pres-
ence of glucose and methylene blue are shown in figure 4A. The deficient reduction of methemoglobin by the red cells of glutathione unstable subjects shown in this figure contrasts with the findings in figure 4B, which demonstrates the normal reduction of methemoglobin by the erythrocytes of our four subjects after incubation for 300 minutes with lactate and methylene blue. There was a similar normal distribution of methemoglobin reduction upon incubation with glucose or lactate without methylene blue. These normal results indicate that there is no abnormality of DPNH2 generation. On the other hand, the deficient reduction in the presence of glucose and methylene blue is consistent with deficiency of either TPNH2 generation or the TPNH2-dependent methemoglobin reductase.

The maintenance of glutathione in the reduced form also depends on a source of TPNH2 as a hydrogen donor. Therefore, observations were made on TPNH2 generation by glucose-6-phosphate dehydrogenase present in hemolysates. Results of these studies are seen in table 1. There was a deficiency of this enzyme in five of six subjects studied. The enzyme activity of the blood of case 1 and her mother was almost normal during a period when

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**Fig. 4.**—Rate of methemoglobin reduction by glutathione unstable (x) and normal (●) erythrocytes. The methemoglobin concentrations at zero hour is plotted on the ordinate and the grams of methemoglobin reduced on the abscissa. ●⇒ represents a normal subject with 100 per cent reduction of methemoglobin at the time measured. A. Represents reduction of methemoglobin in the presence of glucose and methylene blue after 180 minutes incubation and demonstrates a deficiency in the blood of glutathione-unstable subjects when compared to normals with similar initial methemoglobin concentrations. B. Represents methemoglobin reduction after 300 minutes incubation in the presence of lactate and methylene blue. There is no apparent difference between the two groups studied.
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Table 1.—Glucose-6-phosphate Dehydrogenase Activity of Hemolysates Obtained from the Two Patients, Certain Glutathione-unstable Members of their Families and Normal Subjects

<table>
<thead>
<tr>
<th>Subject Tested</th>
<th>Δ O.D. per 5 minutes for 0.1 Gm. % Hgb.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mc.S.</td>
<td>0.020</td>
</tr>
<tr>
<td>2. Al.S.</td>
<td>0.004</td>
</tr>
<tr>
<td>3. J.S.</td>
<td>0.034*</td>
</tr>
<tr>
<td>4. L.S. (a)</td>
<td>0.024*</td>
</tr>
<tr>
<td>L.S. (b)</td>
<td>0.037*</td>
</tr>
<tr>
<td>5. E.A.</td>
<td>0.015</td>
</tr>
<tr>
<td>6. D.A.</td>
<td>0.000</td>
</tr>
<tr>
<td>Normal range</td>
<td>0.040–0.096</td>
</tr>
</tbody>
</table>

*Were hemolyzing when tested.

both were suffering from a hemolytic anemia of unknown etiology and when the erythrocytes were younger and presumably relatively enzyme-rich. At this time the glutathione stability was normal.

Glutathione reductase activity of the blood was also measured in five glutathione unstable subjects in order to determine whether this could be the site of enzymatic deficiency (table 2). The activity of three bloods was within normal limits when compared with the controls. The blood from the remaining two patients showed decreased glutathione reductase activity.

Thus it was found that both of these patients and several members of their families exhibited an instability of blood glutathione upon incubation with acetyl phenylhydrazine and alpha and beta naphthol. TPNH2-dependent methemoglobin reduction was measured and found to be diminished in the four subjects tested. Glucose-6-phosphate dehydrogenase activity was diminished in these patients and their relatives except during periods of active hemolysis. Glutathione reductase activity was normal or decreased.

DISCUSSION

The association of hemolytic anemia with naphthalene poisoning has long been recognized. Six cases were reported between 1920 and 1939.20–22 The first description of this entity in the American literature was that of Zuelzer and Apt in 1949,1 when they reported four Negro infants who had ingested mothballs and developed the characteristic anemia with Heinz body formation, microspherocytosis, fragmentation of the erythrocytes, methemoglobin.

Table 2.—Glutathione reductase activity of hemolysates obtained from the two patients, certain glutathione-unstable members of their families and normal subjects. The enzyme activity was within normal limits in three of the five sensitive subjects and decreased in two.

<table>
<thead>
<tr>
<th>Subject Tested</th>
<th>Mg.% GSH Generated</th>
</tr>
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<tbody>
<tr>
<td>1. L.S.</td>
<td>12.1</td>
</tr>
<tr>
<td>2. Al.S.</td>
<td>5.2</td>
</tr>
<tr>
<td>3. J.S.</td>
<td>11.0</td>
</tr>
<tr>
<td>4. E.A.</td>
<td>11.2</td>
</tr>
<tr>
<td>5. D.A.</td>
<td>6.9</td>
</tr>
<tr>
<td>Normal range</td>
<td>11.1–34.2</td>
</tr>
</tbody>
</table>
binemia and urinary findings with hemoglobinuria. They induced similar findings in dogs fed naphthalene and also remarked on differences in response of individuals, attributing them to variations in intestinal absorption of naphthalene and the detoxifying ability of the liver.

Since 1949, there have been 14 additional cases reported in the British and American literature. Of the 24 cases we have found in the world literature since 1920, 5 were white, fifteen were Negroes or mulattoes and the remaining cases included one each of Puerto Rican (said to be white), Kurdistan Jewish, Chinese and Indian. Thus Negroes and the Eastern races appeared to be far more susceptible to this agent than Western races. Of the three cases reported in newborn period two were Negro and one Chinese.

In 1920, Smillie remarked on the unusual susceptibility of certain individuals to the development of hemolytic anemia when treated with beta naphthol for hookworm infection. In 1948, Earle described the occurrence of hemolytic anemia in 5 to 10 per cent of Negro troops treated with pamaquine. Later primaquine was also implicated. Many other drugs have also been found to produce hemolytic anemia, predominantly in Negroes. Included among these are sulfanilamide, acetanalid, phenylhydrazine, sulfoxone, phenacetin, nitrofurantoin, resorcin and promizole. In a recent report it was also found that the hemolysis of favism is apparently of the same group.

When Beutler et al. incubated the erythrocytes of primaquine-sensitive individuals with primaquine or phenylhydrazine in vitro, Heinz body formation was found. Subsequently they demonstrated low erythrocyte glutathione levels in these patients with a marked drop upon incubation with acetyl phenylhydrazine.

Beutler demonstrated that the drop in reduced glutathione of "sensitive" blood when exposed to acetyl phenylhydrazine was due to oxidation of the glutathione. In normals the effect of acetyl phenylhydrazine is less. The system present in the erythrocyte which maintains glutathione in the reduced form consists of a TPNH$_2$-dependent enzyme, glutathione reductase. There are two reactions which yield reduced TPN in the adult erythrocyte. The first is the dehydrogenation of glucose-6-phosphate with the transfer of hydrogen to TPN, and the second is the oxidation of 6-phosphogluconic acid to pentose phosphate with the evolution of carbon dioxide and the transfer of hydrogen to TPN as follows:

(1) G-6-P + TPN $\rightleftharpoons$ 6-PG + TPNH$_2$

G-6-P dehydrogenase

(2) 6-PG + TPN + H$^+$ $\rightleftharpoons$ Pentose PO$_4$ + CO$_2$ + TPNH$_2$

6-PG dehydrogenase

In the present study a deficiency of glucose-6-phosphate dehydrogenase was found in the propositi and in some members of their families. This would lead to a decrease in available TPNH$_2$ as a source of hydrogen for glutathione reduction. The decreased rate of reduction of methemoglobin by erythrocytes in the presence of glucose and methylene blue was further indirect evidence of this defect. Recently, Carson also has demonstrated a similar defect in the
glucose-6-phosphate dehydrogenase activity in the blood of “sensitive” patients. This defect plus the possible superimposition of diminished glutathione reductase in the newborn period, a common finding in a series of cord blood assays, could certainly lead to the development of hemolytic anemia in these infants on exposure of their red cells to the metabolic products of naphthalene.

More recently Schrier et al. have demonstrated an increase in glutathione reductase in the erythrocytes of adults with this syndrome. This second abnormality was found when more optimal conditions were present for the enzyme than in their earlier studies. Our results were obtained under circumstances similar to those described in Carson’s earlier paper and the low or normal values found in our cases may have been elevated if optimal concentrations had been used.

The two cases presented demonstrate a familial defect. In the first family the mother and all but one of the siblings were affected, with a male and two females markedly sensitive and the mother and two female siblings moderately sensitive. In the second family only the patient and his mother were affected, both moderately unstable and to an equal degree. Such data point to a gene of intermediate dominance. Childs et al. also found the abnormality to be inherited but considered it to be due to a sex-linked gene of intermediate dominance and described cases of intermediate glutathione instability occurring predominantly in females. Our data are consistent with this hypothesis but insufficient numbers do not allow statistical evaluation.

Incubation of erythrocytes with naphthalene derivatives resulted in a drop in glutathione in both normal and sensitive individuals. The results in the present study demonstrate that an in vitro test dose of 2 mg. of alpha naphthol per ml. of whole blood leads to a lower final concentration in the blood of sensitive individuals than in that of normals. Zinkham also has recently described instability of erythrocyte glutathione in patients who had suffered from naphthalene hemolytic anemia and a similar, but transient, defect in the erythrocytes of newborns.

That glutathione is necessary for the integrity of the red cell has been suggested by several investigators. Sheets showed that sulfhydryl inhibitors lead to a striking increase in osmotic fragility of erythrocytes in vitro and suggested that glutathione may function in vivo in maintaining erythrocyte integrity. Fegler also demonstrated that the oxidation of glutathione in the erythrocytes in vitro correlates with an increasing degree of spontaneous hemolysis after the reduced glutathione dropped to about 40 per cent of the initial value.

Glutathione is said to allow activation of many enzyme systems through its reducing or protective action. It is known to protect labile sulfhydryl groups in the erythrocyte and may protect vital enzymes containing this radical. Certain functions of the erythrocyte, such as the movement of sodium across the red cell membrane and the reduction of methemoglobin depend on glycolytic mechanisms, and one could postulate that loss of activity of the sulfhydryl-containing enzymes in this system could lead to hemolysis.

Although the known systems for methemoglobin reduction do not include the GSH →→ GSSG reaction, Mills has presented evidence that there is a factor
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present in the erythrocyte that acts with glutathione to prevent oxidative breakdown of hemoglobin in the presence of peroxide. He has called this factor "glutathione peroxidase." \(^{48}\)

Specifically, glutathione participates in transpeptidation, oxidation-reduction, hydration-dehydration and acyl transfer reactions. How many of these reactions are important to red cell integrity is not yet known, but the red cell viability may depend on one or more of these functions of glutathione. Certainly there is evidence that glutathione is in a dynamic equilibrium in the erythrocyte with a half life of four days, synthesis occurring within the cells from amino acid precursors.\(^{49}\)

Abnormalities of erythrocyte metabolism may not be the only factors that make relatively small amounts of naphthalene toxic to infants. It is known that the skin of infants is thinner than that of adults.\(^{50}\) Toxicity from transcutaneous absorption of other substances has been reported, notably mercury,\(^{51}\) resorcin,\(^{52}\) benzocain\(^{52}\) and aniline dyes.\(^{53-56}\) As a rule these substances are fat soluble and many have been applied as ointments. Thus, the baby oil applied to our patients may have increased absorption.

Another factor that may increase toxicity of naphthalene is the deficient conjugation of glucuronide to substances such as bilirubin by the newborn.\(^{57}\) One of the major pathways of naphthalene detoxification depends on this mechanism.\(^{58}\) Inability of the newborn liver to remove naphthalene and its products from the circulation could lead to an accumulation of toxic levels. This would also explain the severity of the bilirubinemia in the first case in the presence of only moderate anemia.

**SUMMARY**

1. Two cases of naphthalene hemolytic anemia in the newborn period are reported.
2. Both exhibited glutathione instability upon incubation with acetyl phenylhydrazine and naphthol months to years later. Several members of their families exhibited a similar defect with evidence that it is inherited as a simple dominant.
3. In those individuals with glutathione instability there was deficient TPNH\(_2\) generation by their hemolysates in the presence of glucose-6-phosphate and TPN, indicating a deficiency in glucose-6-phosphate dehydrogenase activity. Glutathione reductase activity was normal or decreased.
4. TPNH\(_2\)-linked reduction of methemoglobin by erythrocyte suspensions in the presence of glucose and methylene blue was also decreased in those subjects tested, a finding consistent with the deficiency in glucose-6-phosphate dehydrogenase.

**SUMMARIO IN INTERLINGUA**

1. Es reportate duo casos de anemia hemolytic per naphthalena durante le periodo neonatal.
2. Ambes exhibiva instabilitate de glutathiona post incubation con acetylphenyl-hydrazina e naphthol menses e mesmo annos plus tarde. Plure
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membros del familias in question exhibiva un simile defecto con evidentia que illo es hereditabile como simple dominante.

3. In le individuos con instabilitate de glutathiona, deficientia del generation de TPNH₂ (reducite nucleotido triphosphopyridinic) per lor hemolysatos in le presentia de glucosa-6-phosphato e TPN (nucleotido triphosphopyridinic) esseva notate. Isto indica un deficientia in le activitate de dishydrogenase de glucosa-6-phosphato. Le activitate del reductase de glutathiona esseva normal o reducite.

4. Le reduction, ligate a TPNH₂, effectuate in methemoglobin per suspensiones de erythrocytos in le presentia de glucosa e blau methylenic esseva etiam reducite in le subjectos testate. Iste constatation esseva de accordo con le deficientia in dishydrogenase de glucosa-6-phosphato.

REFERENCES

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Acute Hemolytic Anemia in the Newborn Infant due to Naphthalene Poisoning: Report of Two Cases, with Investigations into the Mechanism of the Disease

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