Hemoglobin Zürich. I. A New Hemoglobin Anomaly Associated with Acute Hemolytic Episodes with Inclusion Bodies after Sulfonamide Therapy

By PAUL G. FRICK, WALTER H. HITZIG AND KLAUS BETKE

HEMOLOGIC SYNDROMES with the appearance of erythrocyte inclusion bodies (Heinz-Ehrlich bodies) after exposure to certain chemicals and drugs have been well documented in man and in animals. Some chemicals, like phenylhydrazine, induce hemolysis in all humans, while others (sulfonamides, primaquine, phenacetin, etc.) are effective only in certain individuals who are susceptible to one or more compounds. The latter type of response is not necessarily an "all or none" type of reaction; various factors may influence it—the dose, the degree of absorption and excretion, and maybe the metabolism of the drug. The cause of the individual susceptibility has been determined only in a minority of patients. A deficiency of glucose-6-phosphate dehydrogenase (G-6PD) accounts for the hemolytic episodes induced by primaquine and related compounds. An immunological mechanism has been described in hemolytic anemia induced by Fuadin.

This paper is a report on a new hemoglobin anomaly discovered during the search for an intrinsic red cell defect which could account for a severe hemolytic anemia after sulfonamide therapy in two members of the same family. According to the directives given at the VIII International Congress of Hematology in Tokyo, the new abnormal pigment was called hemoglobin Zürich, because it was first observed in the town of Zürich, Switzerland. The anomaly is harmless, unless the red cells are challenged by sulfonamides or related compounds. The severe hemolytic episodes are characterized by the appearance of unusually large inclusion bodies visible both with supravital and Giemsa stains.

CASE REPORTS

Case 1

U. Sch., a 2-9/12 year old girl, daughter of Case 2. At the age of 7 months the first episode of hemolysis occurred during treatment of an otitis with Elkosin (sulfisomidine) with fall of the hemoglobin to 6.7 Gm./100 ml. in 5 days and spontaneous recovery. A more severe, life-threatening episode of hemolysis led to hospitalization on the Pediatric Service on March 20, 1960, after the girl received Madribon drops (sulfadimethoxine) over a period of 5 days for a fever of unknown origin. The child was extremely pale; liver and spleen were palpable just below the rib margin.
Laboratory examinations (fig. 1, table 1): The laboratory examination showed: Hgb 3.4 Gm./100 ml.; erythrocytes 1,790,000/cu.mm.; hematocrit 14 per cent; reticulocytes 1.2 per cent. The erythrocytes showed marked anisocytosis and fragmentation. Eighty-four per cent of the red cells contained inclusion bodies. The leukocyte count showed 52,000/cu.mm. with 11 per cent immature forms, 50 per cent neutrophils, 0.5 per cent eosinophils, 16.5 per cent monocytes, 20.5 per cent lymphocytes and 1 per cent plasmacells. Platelets were normal on smear. Erythropoiesis was increased in the bone marrow preparations. The myeloid:erythroid ratio was 0.6:1. Plasma and urine were dark brown. Serum bilirubin was 1.8 mg./100 ml.; serum iron 107 gamma/100 ml. The direct and indirect Coombs tests were negative.

Subsequent course: After two transfusions of 120 ml. of blood, the patient quickly recovered. The erythrocytic inclusion bodies disappeared within 2 days. The reticulocyte peak reached 43.7 per cent. Fifteen months later the Hgb was 11.2 Gm./100 ml., the reticulocytes 5.4 per cent and the leukocytes 5,500 with a normal differential count.

Case 2

L. Sch., a 27 year old white male of Swiss origin who experienced occasional mild episodes of jaundice with dark urine since childhood. These were not necessarily related to the intake of medications. The patient noticed, however, that after taking certain drugs for colds and other minor ailments, he frequently was tired and pale for a few weeks. His general health was good and he was able to perform his duties in military and civil life without unusual fatigue.

From June 3 to 6 he took Lederkyn (sulfamethoxypyridazine), 1 Gm. daily, for disuria. On the 4th day of treatment the urine turned black and the patient was referred to the
HEMOGLOBIN ZUERICH I

Table 1.—Summary of Laboratory Findings in the Hemoglobin Zurich Syndrome

<table>
<thead>
<tr>
<th>Case 1</th>
<th>During hemolytic crisis</th>
<th>After recovery</th>
<th>Case 2</th>
<th>During hemolytic crisis</th>
<th>After recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb Gm./100 ml.</td>
<td>3.4</td>
<td>11.2</td>
<td>6.9</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Erythrocytes/10⁶/cu.mm.</td>
<td>1.7</td>
<td>3.5</td>
<td>1.9</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>14</td>
<td>35</td>
<td>21</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes %</td>
<td>43.7</td>
<td>3.2-5.4</td>
<td>27.7</td>
<td>2.4-7.4</td>
<td></td>
</tr>
<tr>
<td>RBC inclusion %</td>
<td>84</td>
<td>0</td>
<td>99</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Normoblasts/100 WBC</td>
<td>44</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Siderocytes</td>
<td>4.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte morphology</td>
<td>anisocytosis, fragmentation</td>
<td>normal</td>
<td>anisocytosis, fragmentation</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Osmotic fragility</td>
<td>% saline beginning-complete</td>
<td>0.52-0.25</td>
<td>0.66-0.20</td>
<td>0.48-0.35</td>
<td></td>
</tr>
<tr>
<td>Mechanical fragility</td>
<td>absent</td>
<td>normal</td>
<td>diminished</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>present</td>
<td>1%</td>
<td>11-13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb Zurich in % of total Hgb</td>
<td>22</td>
<td>0</td>
<td>present</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>Hgb spectroscopy</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin, total mg.%</td>
<td>3.5</td>
<td>0.6</td>
<td>2.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>RBC G-6-P-dehydrogenase</td>
<td>elevated</td>
<td>normal</td>
<td>elevated</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>RBC catalase</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>RBC glutathione concentration</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>RBC glutathione stability</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>RBC methemoglobin reductase</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
</tbody>
</table>

Medical Service of the University Hospital of Zurich. He was pale, slightly icteric and cyanotic. The spleen was temporarily palpable 2 cm. below the rib margin and was tender. There were no other positive physical findings.

Laboratory examinations (fig. 1, table 1): The laboratory examination showed: Hgb 12.4 Gm./100 ml.; erythrocytes 3,350,000/cu.mm.; hematocrit 33.5 per cent; reticulocytes 4.8 per cent. The erythrocytes showed a marked degree of anisocytosis and fragmentation; on supravital stains 99 per cent of the red cells contained an unusually large single inclusion body (fig. 2). The majority of these inclusions bodies was also visible on Giemsa stain as polychromic discs in a niche on the surface of the cell. Some of them were free outside the cells, others were phagocytized by monocytes. The inclusion bodies were iron negative by Prussian blue stain. Siderocytes were 4.6 per cent. The leukocyte count showed 22,600/cu.mm. with 75.5 per cent neutrophils, 3.5 per cent eosinophils, 1 per cent basophils, 6.5 per cent monocytes, and 13.5 per cent lymphocytes. Platelet count was 304,000/cu.mm.

The bone marrow showed moderate normoblastic hyperplasia. Plasma and urine were dark brown and contained methemoglobin. Total serum bilirubin was 2.2 mg./100 ml. The direct and indirect Coombs tests were negative, screening tests for warm and cold agglutinins at physiologic pH were negative. Serology was negative. The hemolytic episode was accompanied by a temporary rise of the NPN to 73 mg./100 ml. with a fall of the bicarbonate to 16 mEq./100 ml.; the other serum electrolytes remained within normal limits.

Subsequent course: Within 3 days the Hgb fell to 6.9 Gm./100 ml. The administration of 4 units of blood was just sufficient to prevent a further drop. The erythrocytes with inclusion bodies disappeared by the 6th day of hospitalization; during the recovery phase the reticulocytes attained a maximum of 27.7 per cent.

Five months after the hemolytic episode, the Hgb was 14.7 Gm./100 ml., the erythrocytes 4,500,000/cu.mm., and the hematocrit 43 per cent. The reticulocytes varied between 2.4 and 7.8 per cent. On smears the red cells were unremarkable. At no time on subsequent studies were any inclusion bodies detectable, except during a minor hemolytic episode.
after intake of Causyth [8-(dimethylaminoantipyrin) oxyquinoline sulfonic acid for pain. This time the erythrocytic inclusions were small and demonstrable only with supravital stain.

**Special Studies**

**Hemoglobin Studies**

The results obtained in both patients were identical; therefore only the results obtained with the father’s hemoglobin will be presented. On starch block electrophoresis (barbital buffer pH 8.6) the patient’s hemoglobin showed two distinct components: one with the mobility of the normal hemoglobin A and a second one of slower anodal motility which appeared between Hgb F and Hgb S (fig. 3). By chromatography with carboxymethylcellulose, 22 to 28 per cent of the total hemoglobin could be separated as abnormal moiety. On the basis of extensive additional physicochemical investigations reported previously7-8 and in a companion paper,9 the electrophoretic hemoglobin anomaly is not identical with any of the previously described forms. It was therefore named hemoglobin Zürich.

**Erythrocyte Metabolism**

The osmotic and mechanical fragility were decreased during the acute hemolytic phase after sulfonamide therapy. Five and twelve months after recovery they were normal. The activity of glucose-6-phosphate dehydrogenase, of catalase and of methemoglobin reductase, the concentration of glutathione and the glutathione stability in the presence of acetylphenylhydrazine were determined only after recovery; they were all within normal limits except for an elevated G-6PD activity secondary to the reticulocytosis. After incubation with 333 mg. per cent acetylphenylhydrazine at 37 C., pH
7.4 in the presence of glucose, the patient's erythrocytes revealed more Heinz bodies than did normal controls.

**Determination of the Erythrocyte Survival Rate with Cr⁵¹**

During the acute hemolytic episode of Case 2, the Cr⁵¹ T₁/₂ of the patient's erythrocytes was only 1½ days (fig. 4). Five and twelve months later it was 13 and 11 days respectively (normal 30 ± 3 days). These values, together with a persistent mild elevation of the reticulocyte count, are proof of a constant degree of increased hemolysis despite normal erythrocyte morphology and hemoglobin levels. Surface scanning over liver, spleen and sacrum during the acute hemolytic phase and 5 months later failed to disclose any increased counts over the spleen.

Cr⁵¹ T₁/₂ of the patient's erythrocytes transfused to hematologically normal individuals varied between 9 and 12 days, a value which is virtually identical with the survival of autotransfused cells. Normal erythrocytes infused into a recipient with hemoglobin Zürich had a normal survival time.

**Studies of Ferrokinetics with Fe⁵⁹**

Ferrokinetics were determined in Case 1 after recovery with slightly modified standard technics originally described by Huff et al. T₁/₂ of the disappearance rate of injected Fe⁵⁹ was reduced to 42 min. The plasma iron turnover was increased to 64.8 mg./day. The iron uptake by the marrow and the release as erythrocyte iron was extremely rapid (fig. 5). Maximal iron in-

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**Fig. 3.**—Hemoglobin electrophoresis.
corporation in the erythrocytes was already attained on the 2nd day after injection of Fe\textsuperscript{59} (fig. 6). It remained constant up to the 5th day. Later there was a progressive fall of erythrocyte iron activity without any simultaneous rise of counts over the spleen. As a result of the increased rate of erythrocyte destruction, the per cent of Fe\textsuperscript{59} present in the circulating red cells attained only 45 per cent (normal range 77–94 per cent). This kinetic pattern is typical of a hemolytic process without predominant sequestration and destruction of red cells in the spleen.
Study of the Effect of Other Drugs

Extensive and systematic efforts to devise a simple and reliable in vitro test, which would separate the drugs affecting the erythrocytes with hemoglobin Zürich from inert compounds, failed. An in vivo test was therefore devised which gave excellent information. The patient’s blood was tagged in vitro with Cr\(^{51}\) and divided into aliquots of 60 ml. Each aliquot was transfused to a compatible, hematologically normal recipient. One of the aliquots was reinfused in the patient. The Cr\(^{51}\) T\(^1/2\) was determined in all recipients and compared with the survival of autotransfused cells. A certain period after infusion of the labeled cells (varying from 4 to 14 days), the hematologically normal recipients were started on one of the drugs to be tested. In two instances the medication was started simultaneously with the infusion of the cells. This type of experiment was repeated various times with a new group of recipients. The autotransfusion of tagged cells was performed only twice in order to avoid excessive exposure of the patient to Cr\(^{51}\). A typical experiment applying Elkosin (sulfisomidine) is illustrated in figure 7. Before administration of the drug the Cr\(^{51}\) T\(^1/2\) was 11 days, a value which is identical with the Cr\(^{51}\) T\(^1/2\) of the autotransfused cells. After administration of Elkosin, the labeled cells disappeared from the recipient’s circulation within 3 days. Because of the small volume of transfused erythrocytes, no ill effects ensued and the serum bilirubin and hemoglobin remained unchanged. A large number of drugs was tested with this method. The results are summarized in table 2. All types of sulfonamides (short and long acting) and two oxyquinoline compounds (primaquine and Causyth) promptly induced hemolysis. Compounds with steroid structure like digitoxin, dianabol and dienestrol had no effect. The same was true for phenobarbital, acetylsalicylic acid, marcoumar, nicotinic acid, amyl nitrite, atropin and insulin.

The time interval between infusion of the tagged red cells and the adminis-
Fig. 7.—Effect of Elkosin on survival of labeled cells from Case 2 in normal recipient.

...tration of the drug had no influence on the rate of disappearance of the abnormal cells. The Cr\textsuperscript{11} T\textsubscript{1/2} of disappearance varied between 1 and 4 days.

**Family Studies**

The presence of an abnormal hemoglobin in two members of the same family led to the investigation of 65 relatives over four generations. The erythrocytes of 15 members contained hemoglobin Zürich. The quantitative ratio of hemoglobin Zürich to total hemoglobin was 1:4 in all positive carriers. The anomaly was present in males and females. Figure 8 illustrates only a section of the family tree. Details of the complete family study are reported elsewhere.\textsuperscript{5} The anomaly is inherited as a dominant autosomal character. All positive individuals tested thus far were heterozygous. Some carriers of hemo-

**Table 2.—Susceptibility of Erythrocytes with Hemoglobin Zürich to Various Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hemolysis</th>
<th>No Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting sulfonamides:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elkosin (sulfasomidine, Ciba)</td>
<td>Digitoxin</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Gantrisin (sulfamoxazole, Roche)</td>
<td>Dianabol (methandrostenolone, Ciba)</td>
<td></td>
</tr>
<tr>
<td>Long acting sulfonamides:</td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Lederkyn (sulfamethoxypyridazine, Lederle)</td>
<td>Acetylsalicylic acid</td>
<td></td>
</tr>
<tr>
<td>Madribon (sulfadimethoxine, Roche)</td>
<td>Roniacol (β-pyr:dy-carbinol, Roche)</td>
<td></td>
</tr>
<tr>
<td>Doxulfon (sulfaphoxyline + Sulfamerazine, Geigy)</td>
<td>Marcoumar (phenylpropyl 4-hydroxyocumarin, Roche)</td>
<td></td>
</tr>
<tr>
<td><strong>Oxyquinolines:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primaquine 8-(4-amino 1-methylbutylamino)-6-methoxyquinoline.</td>
<td>Atropin</td>
<td></td>
</tr>
<tr>
<td>Causyth 8-(dimethylaminoantipyrin) oxyquinoline sulfonic acid.</td>
<td>Insulin</td>
<td></td>
</tr>
</tbody>
</table>
globin Zürich had histories of anemia and episodes of slight jaundice, others have always been perfectly well. No body ever suffered from a peracute hemolytic episode like Cases 1 and 2, reported above because the asymptomatic relatives were fortunate enough not to have taken any offending drugs. The activity of glucose-6-phosphate dehydrogenase, the concentration of glutathione and the glutathione stability in the presence of acetylpheynylhydrazine was tested in the majority of the individuals with hemoglobin Zürich. All results were within normal limits except for increased G-6PD activity in the presence of reticulocytosis.

**Discussion**

The most unusual feature of the new familial hemoglobin anomaly is the development of peracute, life-threatening hemolytic crises after sulfonamide therapy. Both patients described above would probably have succumbed, had they not been given blood transfusions during their acute hemolytic episode. The severity of the acute hemolytic phase may be due to the fact that both individuals received long acting sulfonamides. The hemolytic episode experienced by the child at the age of 7 months during treatment with a short acting compound (Elkosin) was not as severe: the hemoglobin fell only to 7 Gm. per cent and recovery occurred spontaneously; the administration of the long acting Madribon over exactly the same period of time like Elkosin induced a life-threatening fall of the hemoglobin to 3.4 Gm. per cent. Hemolysis was mainly intravascular with the release of hemoglobin and methemoglobin in the plasma with consequent hemoglobinuria and methemoglobinuria. Virtually all erythrocytes and reticulocytes contained a single large Heinz body. These inclusion bodies should only be visible on supravital staining; in our case they were also demonstrable by Giemsa stains as polychromatic discs. It
is possible that this unusual behavior is a peculiarity of the denaturation of hemoglobin Zürich under the influence of certain drugs.

The survival of the erythrocytes with hemoglobin Zürich after administration of a noxious compound varies between 2 and 6 days. Even when the carriers of hemoglobin Zürich are not exposed to any drugs and chemicals, they have a mild degree of asymptomatic compensated hemolysis as demonstrated by red cell survival studies, ferrokinetics and a constant reticulocytosis. Erythrocyte morphology is absolutely nonrevealing. Catalase and methemoglobin reductase activity, the concentration of glutathione and glutathione stability after incubation with acetyiphenylhydrazine were all within normal limits. The slightly elevated values of the glucose-6-phosphate dehydrogenase activity are a consequence of the persistent reticulocytosis. The physicochemical characteristics of the new hemoglobin permit a clear-cut distinction from any previously described forms. Despite some similarities with other hemolytic anemias with inclusion bodies, the syndrome of hemoglobin Zürich—that is, the association of a hemoglobin anomaly with a drug-induced peracute hemolytic anemia with Heinz bodies—remains unique. The congenital hemolytic disease described by Schmid et al., Lange and Akeroyd and by Scott et al. is associated with red cell inclusion bodies independent of any drug effect; hemolysis is unremitting, there is no methemoglobinemia, but an abnormal pigment metabolism with excretion of a dipyrrol in the urine. The separation from hemoglobin H disease is simple because of the very rapid anodal mobility of hemoglobin H beyond that of hemoglobin A at pH 8.6. Hemoglobin Zürich moves more slowly than hemoglobin A. Furthermore, there is spontaneous denaturation of hemoglobin H within intact cells in vitro with the formation of multiple small inclusion bodies.

The mechanism of action of the sulfonamides and primaquine on the erythrocytes with hemoglobin Zürich is still unknown. Unlike red cells deficient in glucose-6-phosphate dehydrogenase which are only affected by primaquine when they reach the age of approximately 60 days, the drugs affecting hemoglobin Zürich containing erythrocytes induce the formation of Heinz bodies and consequent hemolysis of the cells of all ages, including the reticulocytes.

SUMMARY

A new abnormal hemoglobin was observed in 15 members over four generations of a large Swiss family and has been termed “Hemoglobin Zürich.” The discovery of this hemoglobin was prompted by a severe hemolytic crisis in two members of the family after sulfonamide therapy. During this episode, virtually all erythrocytes and reticulocytes contained a single large inclusion body which was visible with Giemsa and brilliant cresyl blue stains. Outside the hemolytic episode, the erythrocytes revealed no morphologic abnormalities. The results of enzyme studies were all within normal limits. The association of a hemoglobinopathy with a drug-induced inclusion body anemia without any demonstrable enzyme defect is a new entity. The anomalous hemoglobin is inherited as a dominant character and affects both sexes. Thus far, only the heterozygous form has been observed.

SUMMARIO IN INTERLINGUA

Un nove hemoglobina anormal esseva observate in 15 membros de quatro
HEMOGLOBIN ZUERICH I

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generationes de un grande familia switze. Illo es designate con le nomine
"Hemoglobina Zürich." Le discoperta de iste hemoglobina esseva occasionate
per un sever crise hemolytic in duo membros del familia post therapia sulfon-
amidic. Durante iste episodio, virtualmente omne erythrocyto e reticulocyto
del patientes contineva un sol grande corpore de inclusion que esseva visible
post tincturation Giemsa e con brillante blau cresylic. A parte le episodio
hemolytic, le erythrocytos revelava nulle anormalitates morphologic. Le re-
sultatos del studios del enzymas esseva omnes intra le limites normal. Un
hemoglobinopathia in association con un anemia pharmacogenic a corpores
de inclusion es un nove entitate. Le hemoglobina anormal es hereditate como
character dominante e affice ambe sexos. Usque nunc solmente le forma
heterozygotic ha essite observe.

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   in erythrocytes, a review. Blood 4:
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    erythrocyte inclusion bodies and a
    defect in pigment metabolism. Blood
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genital hemolytic anemia with abnor-
    mal pigment metabolism and red cell
    inclusion bodies: A new clinical syn-
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    E., and Wintrobe, M. M.: Congenital
    hemolytic disease associated with red
cell inclusion bodies, abnormal pig-
    ment metabolism and an electrophoretic
    hemoglobin abnormality. Blood

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