Familial Hypohaptoglobinemia
A Genetically Determined Trait Segregating from Glucose-6-Phosphate Dehydrogenase Deficiency

By Arlan Gottlieb, Nathaniel Wisch and John Ross

In recent years genetically determined differences among the haptoglobins of man have been demonstrated. The six more common variants are thought to result from the expression of three haptoglobin alleles, HpF, HpS and Hp2. Three other less common haptoglobin phenotypes have been identified and good evidence has been presented that the level as well as type of this protein is genetically determined. In addition, an apparent absence of serum haptoglobin unrelated to hemolysis, anhaptoglobinemia, has been presumed to result from the expression of either an additional haptoglobin allele Hp, or an independent modifier. Our presentation of a family in whom a genetically controlled depression of serum haptoglobin (Hp) and a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) coexist will include a discussion of the inheritance of G-6-PD deficiency and haptoglobin type with reference to their relationship to familial haptoglobin depression.

Materials and Methods

The family under examination consists of 21 members, 19 of whom were available for study. Six individuals in the F1 and F2 generations are native to the Dominican Republic (I-1, I-2, II-1, II-3, II-6, II-8). With the exception of I-1, now deceased, all have resided in the continental United States for a period exceeding 20 years. The marriages in the second generation are to Americans of Puerto Rican extraction. The third generation offspring and II-9 of the F2 generation were born in the continental United States. All but one of the family were in good health and without a recent history of drug ingestion when studied. One (I-2) suffered from Hodgkin’s disease. Another (III-10), who had undergone mild neonatal hemolysis related to his severe G-6-PD deficiency coupled with normal neonatal glutathione instability, was experiencing no difficulty when examined.

ABO blood typing was performed in all cases. Hemoglobin, packed cell volume, reticulocyte count and peripheral blood smear were obtained on the day of examination. In addition, hemoglobin electrophoresis, sickle cell preparation, gamma and complement antiglobulin tests, plasma methemalbumin and erythrocytic osmotic fragility were checked. Testing
Fig. 1.—Haptoglobin phenotypes. Shown after combination with hemoglobin and vertical starch gel electrophoresis in borate buffer (pH 8.6) (benzidine stain).  

for urinary hemosiderin was carried out in acidified urine by the ferricyanide reaction and was graded from negative to strongly positive.

Erythrocytic G-6-PD was measured according to the modified technic of Zinkham on freshly shed blood.12 Our normal range of values in adults of 150–220 enzyme units (e.u.) / 100 ml. packed red blood cells and in children of 200–400 e.u. / 100 ml. packed red blood cells are in agreement with those published for this technic.11 Normal values for umbilical cord blood are reported as 230 to 420 e.u. / 100 ml. erythrocytes.13

Serum haptoglobin concentration was determined upon serial specimens by the method of Connell and Smithies.14 No significant individual variation was observed. The normal range for this determination in our laboratory is 80–200 mg. per cent. Haptoglobin typing was performed after vertical starch gel electrophoresis in borate buffer at pH 8.6, according to Smithies' technics.15 Haptoglobin genotypes and phenotypes are designated by the nomenclature proposed by Smithies and Walker3 (fig. 1). No attempt to distinguish the Hp1 forms, Hp 1F and Hp 1S, was made in this study. The haptoglobin values obtained by peroxidation were subsequently confirmed by the addition, prior to electrophoresis, of a quantity of hemoglobin sufficient to saturate the serum hemoglobin binding capacity.

RESULTS

A compilation of data is presented in table 1. No evidence for hemolysis was found at the time of study. Hemoglobin, packed cell volume, reticulocyte count and peripheral blood smear were normal as noted. Hemoglobin electrophoresis revealed hemoglobin A except in the newborn, where hemoglobins A and F were found. The sickle cell preparation, gamma and complement antiglobulin tests and plasma methemalbumin were negative. Erythrocytic
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Table 1.—Data

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<th>P.C.V. (%)</th>
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osmotic fragility was normal in all three family members tested (I-2, II-8, II-9). Urinary hemosiderin was present in trace amounts in three individuals with low serum haptoglobin values, whereas in a fourth case (II-9) it was found to be strongly positive.

**Erythrocytic Glucose-6-Phosphate Dehydrogenase Activity**

Assays for erythrocytic glucose-6-phosphate dehydrogenase activity were performed in nineteen family members. In fourteen individuals, G-6-PD activity was normal. Four males (I-1, II-3, II-9, III-10) and a single female (I-2) were found to have a marked enzyme deficiency, the highest value recorded in this group being 22 enzyme units. Despite serial determinations, no enzyme activity could be detected in the hemolysates obtained from I-2 and III-10. In two females (II-6, II-8), one of whom subsequently gave birth to involved child III-10, intermediate values were noted. The results of these examinations are presented graphically in figure 2.

**Serum Haptoglobin Level**

Low haptoglobin values with a mean of 20 mg. per cent and ranging from 6 to 52 mg. per cent were recorded in nine of the 19 individuals tested (II-3, II-8, II-9, III-3, III-4, III-5, III-6, III-8, III-9). This group of four males and five females included six children all over 3 years of age, a single adolescent aged 13, and two adults. Although the value of 52 mg. per cent found in III-5 was considered subnormal in a child 3 years of age, a similar result obtained in III-10 at the age of 5 months fell within the normal range for infants of this age.6,16,17 The persistently elevated haptoglobin value of patient I-2 was associated with her active Hodgkin’s disease.17 The values in the eight remaining patients ranged from 92 to 200 mg. per cent (fig. 3).
Fig. 2.—The inheritance of glucose-6-phosphate dehydrogenase deficiency.

Haptoglobin Phenotype

The inheritance of haptoglobin phenotype is presented in figure 3. The Hp 2-1 phenotype was observed in 12 individuals while Hp 2-2 was seen in seven. In six instances, low serum haptoglobin values were associated with Hp 2-1 patterns while in three cases, Hp 2-2 was found. No Hp 1-1 or Hp 2wu1 phenotypes were observed in the present study.

Relationship of Erythrocytic Glucose-6-Phosphate Dehydrogenase Activity to Serum Haptoglobin Level

Low or intermediate erythrocytic G-6-PD activity was associated with depressed serum haptoglobin values in three individuals (II-3, II-8, II-9). In four, G-6-PD deficiency was found with normal or elevated haptoglobin values (I-2, II-1, II-6, III-10). Six other individuals exhibited normal enzyme activity but low serum haptoglobin (III-3, III-4, III-5, III-6, III-8, III-9). Both G-6-PD and serum haptoglobin concentration were normal in all remaining family members. There was no evidence of serum haptoglobin depression or G-6-PD deficiency outside the blood line established by the I-1/I-2 mating. The segregation of G-6-PD deficiency from the depressed haptoglobin trait is depicted in figure 4.

Discussion

An inborn error of metabolism manifesting itself as a drug-induced hemolysis of the primaquine sensitive type has been attributed to a deficiency of erythrocytic G-6-PD. The metabolic, epidemiologic and biochemical considerations involved have been the subject of a number of recent and extensive reviews.
Fig. 3.—Relationship of haptoglobin phenotype and serum haptoglobin level.

The inheritance of G-6-PD deficiency has been explained by an incompletely dominant sex-linked gene with sexually modified penetrance. Males, more often severely involved than females, show a bimodal inheritance and have either normal or low enzyme activity. In the female, normal, low, or intermediate values are found. The marked phenotypic variation in female heterozygotes has lacked adequate explanation until recently. It had been well noted that markedly depressed enzyme activity as well as normal erythrocytic enzyme levels could be associated with female heterozygosity. Beutler et al. consider that the variability of enzyme level in the female heterozygote results from the action of a mosaic of erythrocytic precursors consisting of cells having either a genetically active maternal or a genetically active paternal X-chromosome. Chromosomal inactivation is presumed to occur at an early embryonic stage resulting in the formation of the Barr sex chromatin body by the inactive chromosome. Evidence supporting the existence of a two-cell population consisting of normal and G-6-PD deficient erythrocyte units in the intermediate female reactor is presented by these authors. The degree of involvement of the female heterozygote would thus become a function of the number of “active” and “inactive” normal or mutant coding units contained in the erythrocytic precursors.

Intermediate enzyme activity has been demonstrated in males on rare occasion. In one study of a Caucasian family, two male subjects were noted to have G-6-PD activity 50 per cent of normal. This unusual circumstance is apparently associated with an enzyme which differs from the normal in having an increased electrophoretic mobility and a decreased affinity for TPN.

Haptoglobin is the principal binding site of plasma hemoglobin. A stable combination of this alpha-2-mucoprotein with the globin moiety of
Fig. 4.—Segregation of hypohaptoglobinemia from glucose-6-phosphate dehydrogenase deficiency.

Hemoglobin may occur independently of variations in heme (methemoglobin, sulfehemoglobin) or deletions or substitutions in the amino acid sequence of globin (Hgb. S, C, F). Unlike free plasma hemoglobin, which is readily excreted in the urine, the larger haptoglobin-hemoglobin complex is presumably destroyed in the reticuloendothelial system. In this manner, the stoichiometric binding of hemoglobin to the extent of 80–200 mg. per cent accounts for the renal threshold for free hemoglobin.

In normal man, haptoglobin levels are rather constant. The protein is first detectable in the umbilical cord blood in only about 10 per cent of the cases, but can be identified during the first week of life in the majority of full term infants. Although normal adult levels are usually attained by the age of 1 year, Galatius-Jensen was not able to demonstrate haptoglobin in 12 of 745 children aged 4 months to 15 years in a population where haptoglobin deficiency was rare among adults. Recently, Whitten, using freeze drying and concentration, has identified haptoglobin in five of six otherwise normal children who had been presumed to be anhaptoglobinemic by more routine methods. Four of these children were phenotypically Hp 2-1 while the fifth was Hp 2-2.

Clinically, haptoglobin values may be depressed due to release of greater than normal amounts of free hemoglobin, as in the hemolytic state. Subsequently, exhaustion of circulating haptoglobin occurs. In our experience, haptoglobin levels in G-6-PD-deficient subjects are invariably normal unless active, clinically obvious hemolysis is present. No evidence for active hemolytic activity could be found in the family presented. Moreover, on the basis of the inheritance patterns discussed, the recently demonstrated reduction in the erythrocyte survival of male but not female G-6-PD-deficient Negro subjects could at most be contributory only in the case of II-3 and II-9. Low haptoglobin levels have also been reported with hepatic disease in man.
Whether this phenomenon results from shortened red cell survival and/or decreased production of haptoglobin, however, requires clarification. Elevated haptoglobin values may be found as part of the nonspecific rise in alpha-2-globulin which accompanies inflammation, tissue destruction or neoplasia.\(^{17,32}\)

Three distinctive haptoglobin patterns commonly emerge when sera are subjected to starch gel electrophoresis, viz., haptoglobin phenotypes 1-1, 2-2, and 2-1.\(^{2}\) On the basis of observations in 18 families, Smithies and Walker proposed that haptoglobin phenotype was determined by the combination of a pair of autosomal incompletely dominant alleles resulting in the corresponding genotypes \(Hp^1 Hp^1, Hp^2 Hp^2, Hp^2 Hp^1\). This hypothesis was subsequently supported by the work of Galatius-Jensen in 106 families and by Harris and his co-workers in their study of 300 families.\(^{7,33}\) Close approximation of the Hardy-Weinberg expectancies have been shown by Sutton et al. and in the review by Harris.\(^{7,34}\) Recently, Smithies and his collaborators have subjected purified haptoglobin to reductive cleavage by mercaptoethenol in the presence of 8 M urea prior to electrophoresis in acidified starch gel.\(^{4,35}\) Using this preparation, previously obscure differences among the haptoglobins appeared, and a group of polypeptides more closely related to their genetic determinants were demonstrated. Following purification, dissociation and electrophoresis, pooled \(Hp\) 1-1 may be resolved into a rapidly migrating polypeptide \(Hp\) 1F, a somewhat slower polypeptide \(Hp\) 1S, and a non-migrating cleavage product common to all haptoglobin types. "Fingerprints" of chymotrypic digests have shown that \(Hp\) 1F and \(Hp\) 1S differ in only a single peptide.\(^{4}\) The \(Hp\) 2 polypeptide migrates as a single zone having less cathodal mobility than \(Hp\) 1S. With this technic, single donor \(Hp\) 1-1 sera have been shown to give either \(Hp\) 1F, \(Hp\) 1S or an equimolar mixture of the two; while \(Hp\) 2-1 resolves into either \(Hp\) 2-1F or \(Hp\) 2-1S. Accordingly, three common haptoglobin alleles, \(Hp\) 1F, \(Hp\) 1S and \(Hp\) 2, and their corresponding six phenotypes, \(Hp\) 1F-1F, \(Hp\) 1S-1S, \(Hp\) 1F-1S, \(Hp\) 2-1F, \(Hp\) 2-1S and \(Hp\) 2-2, have now been proposed. Data on 21 matings involving 55 offspring have been offered in support of this hypothesis.\(^{35}\)

Three other haptoglobin phenotypes have been described. The most common of these, reputedly present in 10 per cent of American Negroes, the so-called 2-1 modified (\(2^m\)-1), differs from the usual 2-1 pattern with regard to the greater protein concentration of its two faster moving components.\(^{5,14}\) The possession of this modified gene (\(Hp\) 2\(^m\)), most particularly as \(Hp\) 2\(^m\)-1, has been associated with a high incidence of apparent anhaptoglobinemia.\(^{36}\) An unusual phenotypic variant exhibiting the morphologic characteristics of both \(Hp\) 2-1 and \(Hp\) 2-2 has now been identified by both Galatius-Jensen and Harris.\(^{6,7}\) Another uncommon haptoglobin phenotype, the so-called Johnson type (\(Hp^j\)), has been noted in eight families.\(^{8,38}\) Both \(Hp^m\) and \(Hp\) 2\(^j\) are now thought to represent \(Hp\) 2 mutations.\(^{4,39}\)

The level of circulating haptoglobin is likewise subject to genetic regulation. In this regard, Bayani-Sioson et al. have demonstrated that random population pairs and dizygotic twins show greater intrapair variability than monozygotic twins in haptoglobin level.\(^{9}\) In addition, normal values were once again
shown to be higher for the Hp 1-1 phenotype than for Hp 2-1 or Hp 2-2.\textsuperscript{9,17} A more marked variation in haptoglobin level\textsuperscript{1} was first noted in a large African population study.\textsuperscript{10} The finding of a presumably congenital “anhaptoglobinemia” in 30 per cent of Nigerian Negroes led Allison, Blumberg and Rees to postulate the existence of the haptoglobin allele, \textit{Hp}\textsuperscript{0}. The homozygous state for this allele would thus result in absence of circulating haptoglobin, while in the heterozygote depressed levels would be found. Since these authors reported a relatively low incidence of Hp 2-1 and Hp 2-2, their data suggest that their proposed new allele had displaced some of the expected incidence of \textit{Hp}\textsuperscript{0}.

This postulation, that anhaptoglobinemia resulted from the homozygous expression of the gene \textit{Hp}\textsuperscript{0}, went unchallenged until the studies of Galatius-Jensen, Sutton, Harris and their co-workers.\textsuperscript{6,7,37} These observers postulated a third suppressor gene at a locus other than the haptoglobin locus. In the otherwise normal Caucasian family reported by Galatius-Jensen, serum haptoglobin was apparently lacking in eight individuals and present in trace quantities in four. Of the latter group, three were phenotypically Hp 2-2 while one was Hp 2-1. Similarly, in the other family reports, both “anhaptoglobinemia” and haptoglobin depression were concomitant findings. In Sutton’s family, three members had no discernible haptoglobin, while one was Hp 2-1. The study of Harris et al. includes two anhaptoglobinemics and a single individual with a weak 2-1 phenotype. Another family furnished by these authors contains a number of their “atypical segregants.” Haptoglobin depression was associated with six 2-2 phenotypes and once with Hp 2-1. Most recently two anhaptoglobinemics and a single hypohaptoglobinemic, who would appear to be Hp 2-2\textsuperscript{i}, have been reported in a Kurdish family in whom the Johnson phenotype was evident.\textsuperscript{38} Analysis of the inheritance patterns reported in all of these families indicates a high probability that any offspring without a readily demonstrable haptoglobin phenotype possesses the \textit{Hp}\textsuperscript{0} allele. In no instance has this possibility been excluded. In nine cases, haptoglobin depression was manifest with Hp 2-2 and on four occasions, Hp 2-1 was the associated phenotype.

Giblett and Steinberg have presented a large American Negro family resulting from the mating of a pair of 2\textsuperscript{mi} phenotypes. The occurrence in the F\textsubscript{2} generation of all haptoglobin phenotypes including anhaptoglobinemia again excludes the possibility that the apparent absence of serum haptoglobin is due to the homozygous state for the recessive allele \textit{Hp}\textsuperscript{0}.\textsuperscript{36} A further mating in this family of Hp 1-1 and \textit{Hp}\textsuperscript{0} phenotypes resulting in offspring which were phenotypically 2\textsuperscript{m}-1, 1-1 and 0 serves as the model for the hypothesis that anhaptoglobinemia is a modification of Hp 2-1. This latter postulation was strengthened by the demonstration that the Hardy-Weinberg expectancies could be approached only if the incidence of Hp 2-1, Hp 2\textsuperscript{m}-1 and anhaptoglobinemia were combined. Noting the absence of Hp 2-1 offspring from matings of Hp 1-1 and Hp 2\textsuperscript{m}-1 individuals and their occurrence after Hp 2\textsuperscript{m}-1 and Hp 2-2 matings, Giblett and Steinberg assumed their third haptoglobin allele to be a genetic modification of \textit{Hp}\textsuperscript{0}. Statistically, in the group of over 500 studied, anhaptoglobinemia was most likely to be \textit{Hp}\textsuperscript{m}\textit{Hp}\textsuperscript{i} geno-
typically. As noted, since a phenotypic difference between the proposed genotypes $Hp^2$ $Hp^2$, $Hp^{sm}Hp^s$ and $Hp^{sm}Hp^s$ could not be distinguished using conventional technics, the possibility that these genotypes could likewise be associated with anhaptoglobinemia could not be excluded. The appearance of a rare anhaptoglobinemic offspring after Hp 1-1 and Hp 2-1 matings, the two normal Hp$^{sm}$-1 issue of Hp 2-1 and Hp$^b$ parents, and four anhaptoglobinemics resulting from Hp 2-1 and Hp 2-1 matings, was less compatible with the postulation that anhaptoglobinemia was invariably an expression of $Hp^{sm}$, and more in accord with previous reports. Moreover, since the $2^m$-1 phenotype is not inconsistent with the presence of normal haptoglobin values, a different genetic action is seemingly implied in phenotype modification than in the determination of the haptoglobin level.$^5,30$

In the family reported herein, depressed but measurable haptoglobin was found. In all instances of haptoglobin depression, normal though faint Hp 2-2 and Hp 2-1 phenotypes were apparent after starch gel electrophoresis. Similarly, in each of the previously reported familial cases with depressed yet discernible haptoglobin, a faint Hp 2-1 or Hp 2-2 phenotype could be identified. In these pedigrees, as in the II-5/II-6 and II-7/II-8 matings of the present study, children of normal parents were found to have depressed or apparently absent haptoglobin or, conversely, parents with low haptoglobin produced normal offspring. Depression or absence of haptoglobin has now been noted in 42 individuals contained in seven pedigrees. Twenty-four were male and 18 were female. Where phenotyping was possible, 10 were Hp 2-1 while 12 were Hp 2-2.

The findings suggest that “anhaptoglobinemia” is not due to the homozygous state for a recessive haptoglobin allele $Hp^a$, nor is invariably associated with the Hp$^{2m}$-1 phenotype, nor is the result of a completely penetrating dominant suppressor. They do suggest, however, that hypohaptoglobinemia might result from the action of an independent gene. The data is as yet insufficient to determine possible linkage and penetrance and whether depression of the haptoglobin level is also dependent on the presence of the $Hp^s$ allele or is linked to the $Hp^s$ locus as an incompletely dominant trait. The relationship between the gene or genes which determine haptoglobin level must also be explored in relation to phenotype modification ($Hp^{2m}$-1) and age.

It is highly probable that the sera of purported anhaptoglobinemics contain a small yet detectable level of haptoglobin. As noted, careful analysis will often demonstrate peroxidase activity or hemoglobin binding capacity. In the present study, haptoglobin phenotypes were demonstrable in nine cases with extremely low values of this protein. It would appear that the less restrictive term hypohaptoglobinemia is more compatible with the genetic and laboratory data available.

**Summary**

1) A family is presented with an inherited deficiency of glucose-6-phosphate dehydrogenase and serum haptoglobin.

2) The inheritance patterns observed are consistent with those postulated for two genetically determined, independently segregating traits.
3) The presence of a benign metabolic defect, familial hypohaptoglobinemia, in individuals with Hp 2-1 and Hp 2-2 phenotypes and the lack of involvement to date of Hp 1-1 phenotypes is consistent with the hypothesis that some modification of the Hp2 allele is responsible for the low levels of haptoglobin observed.

4) The term hypohaptoglobinemia, rather than anhaptoglobinemia, is suggested for individuals who manifest a genetically determined depression in the level of circulating haptoglobin.

**SUMMARIO IN INTERLINGUA**

1. Es presentate un familia con geneticamente transmittite carentias de dishydrogenase de glucosa-6-phosphato e de haptoglobina del sero.

2. Le configurationes de transmission genetic que esseva observate es compatibile con illos postulate pro duo geneticamente determinate characteres de segregation independente.

3. Le presentia de un benigne defecto metabolic, i.e. hypohaptoglobinemia, in subjectos con le phenotypos Hp 2-1 e Hp 2-2 e le absentia, usque nunc, de casos con phenotype Hp 1-1 es in harmonia con le hypothese que le un o le altere modification del allelo Hp2 es responsabile pro le basse observate nivellos de haptoglobina.

4. Es proponite le termino hypohaptoglobinemia plus tosto que anhaptoglobinemia pro designar le condition de individuos qui manifesta un geneticamente determinate depression in le nivello del haptoglobin del circulation.

**REFERENCES**


FAMILIAL HYPOHAPTOGLOBINEMIA


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Familial Hypohaptoglobinemia: A Genetically Determined Trait Segregating from Glucose-6-Phosphate Dehydrogenase Deficiency

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