Hereditary Methemoglobinemia: A New Variant Exhibiting Dominant Inheritance of Methemoglobin A

By Philip L. Townes and George R. Lovell

During recent years, considerable progress has been achieved in our understanding of the clinical entities variously referred to as familial methemoglobinemia, congenital methemoglobinemia, hereditary methemoglobinemia, idiopathic methemoglobinemia, Codounis' disease, hereditary methemoglobinemic cyanosis, methemoglobin M disease or simply methemoglobinemia, depending on apparent or presumed etiology, but all referring to methemoglobinemia of the non-acquired type.

Gibson and Harrison1 described not only the recessive inheritance of methemoglobinemia but demonstrated that it resulted from a deficiency of co-enzyme factor I (diaphorase I).2 More recently3,5 the deficiency has been ascribed to other related enzyme systems. Horlein and Weber5 reported a family exhibiting a dominant pattern of inheritance in which the basic defect proved to be that of an abnormal hemoglobin (globin), subsequently designated hemoglobin M. During the past few years other laboratories7-10 have reported further examples of dominantly inherited methemoglobinemia associated with different subtypes of hemoglobin M.

Through these investigations, it has been established that hereditary methemoglobinemia represents not a single entity but a family of related disorders of two major classes: an enzyme deficiency—recessive type, and a hemoglobinopathy—dominant type (methemoglobin M disease). The present report concerns a family exhibiting dominant inheritance in which the hemoglobin is normal; it thus constitutes an exception to the above generalization.

Materials and Methods

Methemoglobin concentrations were determined by the method of Evelyn and Malloy.11 The recording spectrophotometer (Perkin-Elmer Spectracord), utilized in obtaining the absorption spectra, was standardized against several major bands of the hydrogen arc spectrum (656, 581, 486, and 462 μλ). The patient's hemoglobin and normal (control) hemoglobin were prepared by repeated washing of the red cells with buffered saline (9 parts normal saline to 1 part 0.1 M phosphate buffer, pH 7.4) followed by the addition of 2 volumes of distilled water and 0.4 volumes of toluene to promote hemolysis. The hemolyses were then centrifuged at 4°C for one hour (25,000 x G) to remove the stroma. All filter paper and starch block electrophoretic analyses were run in either veronal buffer pH 8.6, ionic strength 0.05, or phosphate buffer pH 7.05-7.10, ionic strength 0.10, and at 5°C.

Case Report

C. W. is a 28 year old white married male who had enjoyed excellent health except for minor illnesses and an everpresent deep generalized cyanosis. The patient was noted to be...
cyanotic at birth, but was otherwise apparently healthy. No diagnostic evaluation was attempted at the time. Subsequent development was within normal limits. At age 2 years he was hospitalized for bronchopneumonia and at age 4 years was seen by an otolaryngologist for an acute otitis media. On both occasions he was noted to be cyanotic. When 14 years of age, the patient was referred to a local regional cardiac clinic for evaluation but no specific diagnosis was made and he remained asymptomatic. Throughout these years he was able to participate in active sports without exemption. Following graduation from high school, he was refused employment by a major industrial firm because of his cyanosis, although an EKG taken at that time was normal. Throughout his adult years, he performed heavy physical labor without exemption or limitation; the only complication which ensued was a left inguinal hernia in 1956 and a recurrence for which he underwent a second herniorrhaphy in 1959 in an outlying hospital. During the past year he was seen by one of the authors (G. R. L.) at a regional cardiac clinic and referred to this center for evaluation.

The family history is of interest in that the patient's father was grossly cyanotic throughout his lifetime, and that the paternal grandfather was also stated to be cyanotic. The family pedigree is shown (fig. 1) and will be discussed subsequently.

Physical examination revealed a well developed, well nourished white male with marked cyanosis but who otherwise appeared neither acutely nor chronically ill. Vital signs were within normal limits. Significant positive findings included a deep cyanotic discoloration of the external ears, nail beds, lips and oral mucous membranes. The palpebral conjunctivae were of brown hue. Bone conduction was greater than air on left and there was lateralization to the left on Weber test. Lungs were clear to percussion and auscultation. Heart—no enlargement, no murmurs, sounds of good quality with regular rhythm. Except for the presence of a scar in the left inguinal area and the absence of digital clubbing, the remainder of the examination was unremarkable.

Laboratory data. The following laboratory data were obtained and found to be within normal limits: Hct, Wbc, blood smear, reticulocyte count, urinalysis, stool, BUN, FBS, Na, K, Cl, CO2, total protein, icterus index, bilirubin total and direct, alkaline phosphatase, cholesterol, serum electrophoresis, urinary urobilinogen, EKG and chest x-ray.

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![Family Pedigree](https://example.com/family-pedigree.png)

Fig. 1.—Family pedigree. Arrow indicates propositus. Members designated “cyanotic by history-deceased” are presumed to have been methemoglobinemic.
RESULTS

In view of the presenting history and physical findings, which appeared to rule out major cardio-pulmonary pathology, a possible diagnosis of hereditary methemoglobinemia was considered. Examination of the patient's blood revealed a methemoglobin concentration of 19 per cent of the total hemoglobin. The 630 m\(\mu\) absorption maximum characteristic of methemoglobin was noted to disappear on addition of KCN or dilute (1:1000) methylene blue. The middle curve of figure 2A represents the patient's blood showing a peak of 630 m\(\mu\), the lower curve shows the disappearance of this peak on addition of KCN, while the upper curve shows the conversion of oxyhemoglobin to methemoglobin through the addition of potassium ferricyanide. In figure 2B may be seen corresponding changes in spectra of normal blood before and after the addition of these reagents.

In order to determine whether such reduction of methemoglobin could similarly occur in vivo, the patient was requested to breathe room air at a basal rate and, after a period of equilibration, a blood sample was obtained. Methylene blue (1 mg./Kg.) was then administered intravenously and blood samples withdrawn at 5- and 10-minute intervals thereafter. The absorption spectra obtained with these three samples are shown in figure 3. Examination of these curves indicates a gradual reduction of methemoglobin in the immediate postmethylene blue period. Associated with this reduction of methemoglobin was an increase in oxygen capacity of the blood from 12.67 to 14.96 volumes per cent.

More complete spectra of the patient's hemoglobin (fig. 4) showed the hemoglobin containing 16 per cent methemoglobin, the conversion to methemoglobin by addition of potassium ferricyanide, and the cyanmethemoglobin formed by the addition of potassium cyanide. These spectra were typical of hemoglobin A and presented no evidence of a hemoglobin abnormality. Figure 4 is a photograph of the recorded spectra on which has been superimposed a key for the purpose of illustration and identification. Identical spectra were obtained when control mixtures of normal oxyhemoglobin and methemoglobin of equivalent proportion and concentration were examined under the same conditions. The spectra indicate that the hemoglobin investigated is hemoglobin A rather than one of the varieties of hemoglobin M.

Heck and Wolf\(^{12}\) and Pisciotta et al.\(^ {10}\) have demonstrated that spectral differences between subtypes of hemoglobin M and normal methemoglobin are more readily discernible if comparisons are made under conditions of different pH. The patient's hemoglobin was compared to mixtures of oxyhemoglobin and normal methemoglobin of equivalent concentration at pH 6.3 and 7.6 in M/6 phosphate buffer. These acid and alkaline spectra of the patient's hemoglobin were identical with the controls. Further confirmation of the normality of the patient's hemoglobin was obtained by the complete separation of methemoglobin from oxyhemoglobin by means of an IRC-50 chromatographic column, employing the method of Morrison and Cook.\(^ {13}\) The absorption spectra of the chromatographically separated hemoglobins were characteristic of normal methemoglobin and normal oxyhemoglobin individually.\(^ {14}\)
Fig. 2.—Conversion of patient and control blood to methemoglobin and cyanmethemoglobin.

2A—*Middle curve:* patient's blood diluted 1:20, pH 7.3.

*Upper curve:* formation of methemoglobin by addition of potassium ferricyanide (small crystal).

*Lower curve:* formation of cyanmethemoglobin by addition of potassium cyanide.

2B—Corresponding spectra of normal blood under the same conditions.
Fig. 3.—Effect of intravenous methylene blue on reducing methemoglobin in vivo.

3A—Patient’s blood diluted 1:20, pH 7.3.
3B—Same dilution 5 minutes after intravenous methylene blue (1 mg. Kg.).
3C—Same dilution 10 minutes after methylene blue.

Further characterization of the patient’s hemoglobin was obtained by electrophoretic analysis. The patient’s hemoglobin and normal (control) hemoglobins were prepared as described above. Methemoglobins (oxidized hemolyzates) were also prepared by reaction with potassium ferricyanide. Filter paper and starch block electrophoresis at pH 8.6 (veronal buffer, ionic strength 0.05) revealed no differences between unoxidized and oxidized hemoglobins and their corresponding controls. Gerald has shown that more optimal separation of subtypes of M from normal hemoglobin may be accomplished at more neutral pH. The hemoglobins (patient’s and controls) as well as their oxidized hemolyzates were subjected to electrophoretic analysis at pH 7.1 in phosphate...
Fig. 4.—Oxyhemoglobin-methemoglobin, methemoglobin, cyanmethemoglobin spectra. Patient's oxyhemoglobin-methemoglobin, pH 6.5 (phosphate buffer M/6) (———). Patient's methemoglobin formed by reacting with potassium ferricyanide (………). Patient's cyanmethemoglobin formed by reacting with potassium cyanide (- - - -). Hemoglobin concentration as methemoglobin, $2.01 \times 10^{-2}$ mM. L., based on millimolar extinction coefficient of 9.04 at 500 m.$\mu$. (extinction mM. of Fe $\times$ L. for 1 cm. light path).
buffer, ionic strength 0.1. Under these conditions, there were no demonstrable differences in electrophoretic mobility nor in the number of bands present on comparing the patient's hemoglobin or methemoglobin with corresponding simultaneously run controls. In figure 5 may be seen a representative pattern of patient and control oxidized hemolyzates examined at pH 7.05 by the starch block method of Kunkel. The electrophoretic differences described by Gerald in his study of subtypes of hemoglobin M under these conditions were not noted. These findings confirm that the patient has no demonstrable hemoglobin abnormality.

Essentially two different methemoglobin reductases have been reported to be deficient in recessive methemoglobinemia: a TPN linked heme protein and a DPN linked diaphorase. Scott and Griffith recently reported a convenient assay for the latter which they find to be deficient amongst Alaskan Indians and Eskimos having hereditary methemoglobinemia. Employing this method, which is a modification of the procedure reported by Edelhoch et al., the diaphorase activity of hemolyzates of red cells from the patient and controls was assayed. Concentrations of assay components are listed in the legend of figure 6. This figure indicates that the rate of reduction of the dye in two red
Here is a text representation of Figure 6:

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**Fig. 6.** Assay for Diaphorase I. All cuvettes contained tris(hydroxymethyl)aminomethane buffer pH 7.55 (80 µmols), sodium ethylenediaminetetraacetate (3.0 µmols), sodium 2,6-dichlorobenzenoneindophenol (0.34 µmols), DPNH (1.76 µmols). In addition ( ▼--▼) contained 2.0 ml (3.25 mg Hb/ml) nitried hemolyzate of patient's blood, (● - - ●) contained 2.0 ml 3.25 mg Hb/ml nitried hemolyzate of normal blood and (x...x...) contained 2.0 ml tris-hydroxymethylaminomethane buffer pH 7.55 and no hemolyzate added. The original plot (x...x...) is redrawn (......) to have common point of origin. All final volumes 6.0 ml. Optical density readings at 600 μm.
cell hemolyzates is approximately equal, and that this rate is twice that observed in the control in which no hemolyzate was added. The latter represents a measure of the non-enzymatic reduction of the dye by DPNH. Scott and Griffith found that the hemolyzates of their methemoglobinemic patients resulted in activity curves which matched the non-enzymatic controls. This is not the case in our patient whose diaphorase I activity appears to be normal. The original plot of optical density against time for the non-hemolyzate control (...x...) is displaced downward along the ordinate because of the absence of the hemolyzate which contributes to the optical density at 600 m\(\mu\). To facilitate interpretation, this curve is redrawn (...........) while preserving slope, so that the point of origin (optical density at time zero) equals that of the other samples. The TPN linked methemoglobin reductase was isolated and found to be normal.*

Since there was no indication of a hemoglobin abnormality, an attempt was made to evaluate the capacity of the patient's red cells to reduce methemoglobin in the presence and absence of exogenous glucose. Red blood cells (patient's and control) were centrifuged and washed four times with phosphate-saline (normal saline containing 0.01 M phosphate buffer pH 7.4). To an aliquot of washed packed cells was added 1.5 volumes of 0.5 mM sodium nitrite in phosphate-saline (0.4 mg. solium nitrite/ml. packed cells). Nitrition was allowed to proceed for one hour, the cells were again washed four times to remove the excess nitrite and then suspended in either phosphate-saline or phosphate-saline to which glucose had been added to give final concentration of 180 mg. per cent. Aliquots of each suspension were treated with potassium ferricyanide or potassium cyanide to determine the optical density values at 630 m\(\mu\) for zero and 100 per cent methemoglobin. Methemoglobin determinations were then made on aliquots of each suspension after specified periods of incubation at 37 C. The latter values are plotted in figure 7 as per cent methemoglobin as a function of time.

Examination of figure 7 reveals that while the normal cells reduced methemoglobin at a given rate, the rate was markedly increased in the presence of glucose. The patient's cells reduced methemoglobin at approximately the same rate as the phosphate-saline normal controls, but did not exhibit any significant increase in the presence of glucose. In the patient's cells, the rate of reduction with or without added glucose was essentially the same as that of the normal cells in the absence of glucose. These findings are in agreement with results of Gibson and Harrison and reflect an inability of the patient's cells to utilize normal glucose-dependent metabolic pathways for reduction of methemoglobin. The reduction that did occur was probably mediated by some non-specific reductant such as ascorbate or glutathione. Since the patient's cells do respond rapidly to methylene blue, one may conclude that the hexosemonophosphate shunt is intact and that the defect is in the glycolytic pathway, probably involving one of the DPN dependent dehydrogenases. Although the

*We are indebted to Dr. Martin Morrison of the Department of Biochemistry, University of Rochester School of Medicine, Rochester, N. Y., who isolated and assayed the TPN methemoglobin reductase in this patient.
specific defect remains to be defined, it does not involve either of the two recognized methemoglobin reductases, for these have been found to be normal. Notwithstanding our incomplete knowledge of the nature of the specific defect, it was deemed advisable, in view of the patient's known response to methylene blue, to attempt a therapeutic trial with ascorbic acid, 400 mg. daily by mouth. The methemoglobin level was 15 per cent prior to treatment on the day therapy was initiated, 11 per cent the following day, 5.6 per cent the fourth day and 6 per cent after four weeks of treatment. This degree of methemoglobinemia, while still significant, represents a major reduction from the pre-treatment status. That ascorbic acid can completely reduce the patient's methemoglobin in vitro was demonstrated by adding a 0.3 ml. aliquot of the
patient's hemoglobin (4 Gm. per cent) to 2.7 ml. of 0.3 M phosphate buffer pH 7.4 and recording the spectral changes which followed the addition of 0.05 mM. ascorbic acid in 0.3 ml. of buffer. Final pH remained at 7.4. Under these conditions 80 per cent of the methemoglobin was reduced in 90 minutes and complete reduction was achieved in 120 minutes. The less complete reduction of methemoglobin observed in vivo probably reflects a lower intracellular ascorbate level than was achieved in vitro.

The available family data are presented in pedigree form (fig. 1). While not directly examined, the patient's father is presumed to have been an affected individual. The patient, the patient's mother and paternal aunt describe him as always having been markedly cyanotic but otherwise well until his terminal illness and death at home from a "strep throat". The patient's grandfather, who died at age 79, is said by these informants to have been similarly affected. The grandfather and his siblings all lived at a considerable distance and we have not had an opportunity thus far to investigate any of the siblings or their descendants. It is stated that the patient's father was aware of, and impressed by, the presence of the cyanosis in the three successive generations.

The patient's first two children were males which aborted spontaneously at gestation age 6 months. The third child, a three year old daughter, is not cyanotic and her methemoglobin is within normal limits. The methemoglobin content of the cord blood of a son born since this study was begun was normal. On re-examination at age 6 months, the blood was again found to contain less than 1 per cent methemoglobin.

Discussion

There are now an adequate number of sufficiently detailed family pedigrees to establish that hereditary methemoglobinemia may be transmitted as an autosomal recessive trait. The specific defect has been studied in a few instances and shown to involve a deficiency of a reductase which normally functions to reduce methemoglobin. The precise nature of the deficient reductase is somewhat uncertain. Gibson proposed that hereditary methemoglobinemia resulted from a deficiency of diaphorase I. Huennekens et al. on the other hand concluded that methemoglobin reductase was not a diaphorase, but that it was a heme protein which functioned as a TPNH oxidase. Eder, Finch and McKee supported this conclusion in an indirect way by showing that flavin adenine dinucleotide, an essential component of the diaphorase, was present in normal amounts in methemoglobinemic individuals. Scott and Hoskins suggested that the primary defect involved "some unidentified reductase which was mediated through the pyridine nucleotides." In a more recent report, Scott and Griffith concluded that the deficiency does involve diaphorase I, as had been originally proposed by Gibson.

It is possible that the ultimate resolution of this problem will reveal that the recessive type of methemoglobinemia can result from more than one specific enzyme deficiency, for it is otherwise difficult to reconcile the above findings. That not all cases of recessive methemoglobinemia are identical is suggested by differences in oxygen dissociation curves; some have shown a shift to the
left while others have not. Some cases have associated symptoms, others not; an environmental effect as well as a predeliction for certain ethnic groups has also been proposed. The latter may represent sampling bias imposed by geographic locale of the investigators. In none of the recessive pedigrees have there been reported any studies of the hemoglobins, and they were assumed to be normal.

The first pedigree of dominant methemoglobinemia was provided by Hörlein and Weber. Through the ingenious method of hemoglobin dissociation and recombination, a globin abnormality was demonstrated. The absorption spectrum of the abnormal hemoglobin was unique in that the 630 nm peak of methemoglobin was supplanted by a new maximum at 600 nm and reduction by methylene blue did not occur. Like normal methemoglobin, a cyanmethemoglobin was formed on addition of KCN. Precisely how many of the previously reported cases of methemoglobinemia may have involved an abnormal hemoglobin is problematical; however, they were probably few, because none of the earlier examples evidenced dominant inheritance.

Gerald and co-workers described a second family with methemoglobinemia of the Hörlein and Weber type, showing dominant inheritance in a family of German extraction in New England. Although this hemoglobin was spectrally similar to that reported by Hörlein and Weber, it subsequently proved to differ in reactivity to various ligands. Recognizing these differences, and adopting the nomenclature of Singer, this new abnormal hemoglobin was designated \( \text{MB} \) (Boston). In the same publication, Gerald and George reported a study of the hemoglobin obtained from the family originally described by Baltzan and Sugarman. This methemoglobin differed electrophoretically from \( \text{MB} \) and was found to be measurable by the Evelyn-Malloy method, although a distinct 630 nm peak was not demonstrable. The reactivity of this hemoglobin \( \text{MB} \) (Saskatoon) also differed from \( \text{MB} \) and was considered by Gerald and George to bear striking resemblance if not identity to that of Hörlein and Weber.

Heck and Wolf reported a patient with a cardiac disorder which did not account for the cyanosis. Although the family history was negative, in that only normal levels of methemoglobin were found among immediate family members, the patient was found to have an abnormal hemoglobin by the hemoglobin dissociation and recombination method of Hörlein and Weber. Kiese, Kurze and Schneider described further metabolic studies on the erythrocytes of this patient.

Pisciotta, et al. reported a family exhibiting dominantly inherited cyanosis with an associated hemolytic anemia. By electrophoretic examination of the blood of various family members, it was established that the hemolytic anemia was associated with a "C"-like hemoglobin, while the cyanosis was correlated with the presence of a hemoglobin electrophoretically like A but of brown color. This methemoglobin differed from A in that it was not measurable by the Evelyn-Malloy method and cyanmethemoglobin was not formed on reacting with KCN. It was considered to be identical with \( \text{Mn} \). Pisciotta and co-workers reported another family with dominant methemoglobinemia. The methemo-
globin was measurable with the Evelyn-Malloy method and its spectrum bore a resemblance to methemoglobin A, but differed from the latter in that it had an absorption maximum at 625 m\(\mu\) rather than at 630 m\(\mu\). This new hemoglobin designated M\(_M\) (Milwaukee) was subsequently shown to differ from normal methemoglobin electrophoretically.\(^28\)

It is apparent, in comparing the various M types of hemoglobin, that some show remarkable similarities and possible identity, while others are clearly different. It would appear that the various subtypes of M differ from one another in either spectral characteristics, reactivity to ligands or electrophoretic behavior. Presumably this portends that with further study still other hemoglobin abnormalities will be found. The case reported herein is still another type of hereditary methemoglobinemia in that it shows dominant inheritance, as do all of the above with the possible exception of the case reported by Heck and Wolf,\(^26\) and yet the hemoglobin is type A. It is conceivable that the patient described by Heck and Wolf represents either a new mutation, a lack of expression in one parent, or an instance of illegitimacy. In our patient, not only is the hemoglobin normal, but there is no demonstrable deficiency of either of the two methemoglobin reductases. In short, all of the mechanisms heretofore reported to be of causal significance in hereditary methemoglobinemia are normal. More recent investigations clearly indicate that the specific defect involves a previously undescribed abnormality of glutathione metabolism.\(^14\)

Although it is now clearly established that methemoglobinemia of the non-acquired type is a hereditary disorder, the precise pattern of inheritance is not fully elucidated. The fact that the present case does not conform to either of the two basic types, (enzyme deficiency—recessive, hemoglobinopathy—dominant) makes a brief review of the available genetic data regarding this entity of some relevance.

It is apparent that many of the early sporadic cases of methemoglobinemia, while originally considered to be idiopathic, may have been idiopathic only in that there were insufficient family data to substantiate a pattern of inheritance. This is one of the intrinsic difficulties of human genetics. Notwithstanding these difficulties, there are now a sufficient number of well documented pedigrees to establish the hereditary nature of this pathologic state. To this end, the pedigree of Gibson and Harrison\(^1\) is sufficient in itself, for one finds that five-ninths of the siblings in one generation have demonstrable methemoglobinemia. For this to occur on a random (non-genetic) basis is quite unlikely. The probability would be the incidence of the disorder (not known, but very low) to the fifth power. Gibson and Harrison\(^1\) appropriately interpreted their pedigree as one of autosomal recessive inheritance. Not excluded however, is the possibility that the pedigree is consistent with dominant inheritance because one of the parents (mother) was dead and thus not subject to direct examination. Although the mother was not known to be cyanotic, it is conceivable that she had methemoglobinemia in a low degree of expression such that it might have escaped detection by the laity (family) who described her as acyanotic. If this were the case, the pedigree would be quite consistent with autosomal dominant inheritance. One feature of the pedigree which is sugges-
tive of dominance is the fact that five-ninths of the children were affected. This approximates the 1:2 ratio of affected to non-affected more closely than the 1:4 expectations of recessive inheritance. Admittedly, the small population concerned with in this single family invalidates any conclusion regarding dominance versus recessivity purely on the basis of such ratios. The pedigree of Barcroft et al.29 in which the father was dead and presumed to be normal may be considered in a similar manner.

More recently4,14,15 there have been reported other pedigrees in which recessive inheritance appears to be more firmly established. In all of these the hemoglobin spectra are consistent with normal methemoglobin and in the few instances in which enzyme activity was assayed a specific deficiency was found. It is questionable, however, whether all previous cases of methemoglobinemia involving normal hemoglobin are in fact recessive as has been presumed. It is somewhat equivocal in the pedigrees of Gibson and Harrison1 and Barcroft et al.29 and is clearly dominant in the present case report. That different interpretations may result from the same family data is well demonstrated in the Melaniarides pedigree of Codounis,18 who at the time claimed to be the first to demonstrate the hereditary nature of this disorder and concluded that it was one of recessive inheritance, only to conclude at a later date19 from the same pedigree that it featured dominant inheritance. Codounis19 proposed that all instances of hereditary methemoglobinemia follow a dominant pattern of inheritance. The pedigree data unfortunately extend retrospectively to 1845 and are consequently without good documentation. The nature of the defect in these families is not described; however, it is assumed they are of the enzyme deficiency type. Except for Codounis no other workers have proposed dominant inheritance of the normal hemoglobin type of methemoglobinemia; the preponderant evidence is clearly for recessive inheritance.

To date, all claims for dominant inheritance, with the exception of Codounis, have stemmed from family studies in which an abnormal hemoglobin was shown to be present, and conversely every instance in which an abnormal hemoglobin was demonstrated proved to be transmitted as an autosomal dominant trait. The only exception to the latter generalization is the patient reported by Heck and Wolf23,24 in which the family history is negative. This pedigree is still consistent with dominance if one assumes non-expression in a parent, a new mutation in the patient or illegitimacy. It is also consistent with recessive inheritance in the absence of these assumptions.

In conclusion, it would seem that despite these exceptions, hereditary methemoglobinemia is generally of two types: a recessive—enzyme deficiency type and a dominant—hemoglobinopathy type. This conclusion is in agreement with that recently advanced by Gerald.28 The present case is an exception in that it involves the dominant transmission of a normal hemoglobin. It is further unusual in that neither of the two recognized enzyme deficiencies associated with methemoglobinemia of normal hemoglobin appear to be involved in the defect. That this may well not be the first such case is inferred in our consideration of our inadequate knowledge of both the inheritance and the specific defect in these related disorders. From a semantic point of view, one may even question whether certain types of hemoglobin M disease are truly
examples of methemoglobinemia, for methemoglobin is a specific hemoglobin which is well characterized in terms of spectra, chemical reactivity and state of oxidation of iron in the heme moiety. The M hemoglobins have different spectra and reactivity and the primary abnormality is in the globin component. It is evident that hereditary methemoglobinemia is not a single entity but several distinct entities having different metabolic defects and different patterns of inheritance.

**SUMMARY**

1. A case of dominantly inherited methemoglobinemia is described.
2. Despite the pattern of autosomal dominant inheritance, the hemoglobin is thus far indistinguishable from methemoglobin A and is considered to be normal rather than one of the subtypes of hemoglobin M.
3. The primary defect is one in which there is a decreased capacity to reduce methemoglobin via the normal glucose dependent pathway.
4. The nature of the specific defect remains to be more completely elucidated but is considered not to result from a deficiency of TPN or DPN methemoglobin reductase.
5. Hereditary methemoglobinemia and hemoglobin M disease are reviewed.

**SUMMARY IN INTERLINGUA**

1. Es describite un caso de methemoglobinemia a hereditate dominante.
2. In despecto del configuration de hereditage autosomal dominante, le hemoglobina (usque nunc) es indistinguibile ab methemoglobina A. Illo es considerate como normal plus tosto que como un del subtypos de hemoglobina M.
3. Le defecto primari es characterisate per le redticite capacitate de reducer methemoglobin via le circuito normal a dependentia de glucosa.
4. Le natura del defecto specific remane a elucidar pltis completemente, sed il es opinate que illo non resulta de un carentia del reductases de methemoglobin que es ligate a TPN o a DPN.
5. Es revistate le mcrhos hereditari de methemoglobinemia e de hemoglobina M.

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