FAMILIAL IDIOPATHIC METHAEMOGLOBINAEMIA

ASSOCIATED WITH MENTAL DEFICIENCY AND NEUROLOGICAL ABNORMALITIES

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The idiopathic form of methaemoglobinaemia is a rare condition, and Finch (1948) found only 16 examples recorded in the literature. All cases had been cyanosed from birth or from an early age. Litarczek *et al.* (1930), Miller (1930), and Dieckmann (1932) described the manifestations of the disorder and emphasized its differentiation from the toxic form of methaemoglobinemia, which may result from such substances as bis-muth subnitrate, aniline and its derivatives, acetanilide, sulphonamide preparations, nitrophenol, and various nitrites, including drinking-water contaminated by nitrates, which are converted into nitrites in the intestine (Ewing and Mayon-White, 1951).

A familial incidence has been reported by several observers, including Baltzan and Sugarman (1950) (15 cases in a family-tree extending over four generations); Barcroft *et al.* (1949) (seven cases in two families); Bensley *et al.* (1938) (brother and sister); Breakey *et al.* (1951) (brother and sister); Codounis *et al.* (1947) (14 cases in a family of several generations); Deeny *et al.* (1943) (two brothers); Hitzengerger (1942) (three brothers); Lian *et al.* (1939) (a mother and five children—three brothers and two sisters); and Lutembacher (1949) (six cases in four generations).

Codounis *et al.* (1947) as well as Baltzan and Sugarman (1950) considered that familial methaemoglobinaemia was inherited as a Mendelian dominant. The evidence from earlier records, however, indicated that the inheritance was of a recessive character, a view supported by the more recent report of Breakey *et al.* (1951).

The outstanding clinical feature of idiopathic methaemoglobinaemia is that of cyanosis of lavender hue, especially of the lips, cheeks, nose, and buccal mucosa, dating from birth or very early life, remaining constant apart from treatment, and persisting throughout life. The general condition is usually good; the heart and blood vessels are normal and most patients do not complain of symptoms. In some examples, however, headache, vertigo, muscular cramps, asthenia, tachycardia, and mild dyspnoea have been described; such symptoms have been attributed to an insufficiency of blood oxygenation. Mild polycythaemia (5,500,000 to 6,000,000 red corpuscles per c.mm.) with increase in the mean corpuscular diameter, and slight leucocytosis, polymorphs predominating, have also been recorded (Lian *et al.*, 1939).

Expectation of life is apparently normal, and cases are mentioned at 70, 75, and 80 years of age.

The three siblings we describe with idiopathic methaemoglobinaemia were all mentally defective and each had the same type of strabismus. They also showed abnormalities of the tendon reflexes; in two of the cases both the knee- and ankle-jerks were absent as well as the deep reflexes of both arms; in the third case one ankle-jerk and all arm reflexes were absent. Abnormalities of the tendon reflexes do not appear to have been recorded in association with methaemoglobinaemia, and mental deficiency is very unusual, only Hitzengerger's case being mentally defective as well as physically undersized, and van den Berg's (1905) patient being described as "a not very intelligent man."

Two of the children were observed to be "blue" at birth, and cyanosis was first noticed in the other child at the age of three months.

Case 1

A girl aged 8 years and 10 months was first seen in December, 1948. She is the second child of the family. Her elder sister, aged 11, is free from cyanosis, is of normal intelligence, and is in good health. The patient was blue when born; the labour had been normal. The infant sucked poorly and moved very little; her mother stated that "she lay like a doll in the pram." She did not walk until she was 3 years old, nor did she make any attempt to speak until about the same age.

On examination the child showed generalized cyanosis, especially of the cheeks, lips, ears, roof of mouth, and hands, together with the brownish tinge of the skin characteristic of methaemoglobinaemia. She had an internal concomitant strabismus; apart from scanty retinal pigment the fundi were normal. Her speech was an almost unintelligible drawl. All four limbs showed normal movement and power. The radial, supinator, biceps, and triceps jerks were all absent; both knee- and ankle-jerks were also absent. The plantar responses were equivocal and the abdominal reflexes were very sluggish but equal. Co-ordination was normal. The heart and other systems were normal; the pulse rate was 80; and blood pressure 115/75. Intelligence tests showed that the child's mental age was only 3 years with an I.Q. of 34, indicating middle-grade imbecility. She could count numbers only up to 3, had no idea of letters, and no drawing capacity. Her speech was mainly a babble, with a few clear words and phrases emerging as at a 2-years level. In manipulation she was very awkward and had great difficulty in using a pencil.

Investigations.—X-ray examination of the chest showed no abnormality; electrocardiograms were normal. Cerebro-spinal fluid was normal, with negative Wassermann and Lange reactions. Blood count: red cells, 5,250,000; packed cell volume, 46%; reticulocytes, 1.7%; total pigment 84%; colour index 0.8; white cells, 8,400 (polymorphs 65%, lymphocytes 25%, monocytes 4%, eosinophils 5%, basophils 1%); W.R. negative.

Methaemoglobin was estimated with a hand-spectroscope. On December 30, 26% of the total blood pigment consisted of methaemoglobin. An intravenous injection of 7 ml. of a 1% solution of methylene blue was given that day; within half an hour of the injection the cyanosis had disappeared, the child was looking pink and healthy, and investigation revealed no methaemoglobin in the blood. For the next 12 days the child was given 200 mg. of ascorbic acid twice daily by mouth; nevertheless, four days after starting the ascorbic acid she was again cyanosed and the blood methaemoglobin had risen, but to a lower level than before the injection of methylene blue—11% as compared with 26%. After 12 days ascorbic acid was discontinued and the percentage of blood methaemoglobin gradually rose, to reach 20% in nine days. Ascorbic acid (400 mg.

FIG. 1.—Case 1. Idiopathic methaemoglobinaemia. Effect of injecting 7 ml. of a 1% solution of methylene blue intravenously, and of giving ascorbic acid and methylene blue by mouth.

daily) was then resumed and the blood methaemoglobin gradually fell to 17% in five days. Next, 4 gr. (0.26 g.) of methylene blue in tablet form was given twice daily by mouth for two days. Within an hour of the first dose the cyanosis had disappeared, and for five days there was only a faint trace of methaemoglobin in the blood; on the following day it had risen to 5% and next day to 7%. A further dose of 4 gr. (0.26 g.) of methylene blue again caused the methaemoglobin to disappear from the blood (see Fig. 1).

Case 2

A boy aged 7, and next in the family to Case 1, was first seen on February 24, 1949. He is said to have been normal at birth, but was noticed to be "blue" at the age of 3 months; the cyanosis has persisted. He did not sit up until 12 months old, and did not walk or talk until the age of 3½ years.

On examination the child showed the same generalized cyanosis as his sister, especially of the cheeks, lips, and buccal mucosa. He also had an internal strabismus. The pupils and fundi were normal. Speech was confined to a few simple words. All deep reflexes in both arms were absent, but the knee-jerks were present and equal; the right ankle-jerk was absent and the left sluggish. Both plantar reflexes were flexor. Co-ordination was very poor.

Intelligence tests showed his mental age to be 3 years and 10 months, giving an I.Q. of 47. His vocabulary was very limited and approximated to that of a child of 3 to 4 years, but most of his speech was intelligible. He could count up to 12 and was fairly good at space and form relations in recognition tests, but at less than a 4-years level.

Investigations.—X-ray examination of chest, and the electrocardiogram, revealed nothing abnormal. Cerebrospinal fluid was normal, with negative Wassermann and Lange reactions. Blood count: red cells, 5,560,000; packed cell volume, 45%; reticulocytes, 1.8%; total pigments, 86%; colour index, 0.78; white cells, 10,000 (polymorphs 71.5%, lymphocytes 22%, monocytes 5.5%, eosinophils 0.5%); W.R. negative.

Investigation of the blood daily for eleven days showed that the amount of methaemoglobin varied from 12 to 18% of the total blood pigment. At 11.30 a.m. on March 7 he was given 4 gr. (0.26 g.) of methylene blue by the mouth; by 12.15 p.m. his cyanosis was replaced by a healthy pink

colour: at 12.30 a sample of blood showed no trace of methaemoglobin. Three further doses of 4 gr. (0.26 g.) of methylene blue were given at 12-hour intervals. No methaemoglobin was detected in his blood until March 10, when a slight trace was found; on the 11th there was 6%, and it had risen to 16% by the 14th. He was then given 4 gr. (0.26 g.) of methylene blue twice daily by mouth for two days, which again abolished the cyanosis and reduced methaemoglobin in the blood to nil; by March 21, however, it had risen to 8% (see Fig. 2). Subsequently it was ascertained that 4 gr. (0.26 g.) of methylene blue by mouth twice a day for two days kept him free from clinical cyanosis and from detectable methaemoglobin in the blood for about five days.

Case 3

A younger brother of Cases 1 and 2, aged 3 years and 5 months, was first seen in March, 1949. He was "blue" at birth and labour had been normal. His progress has been very slow and he has always been backward; he sat up at 10 months and has not yet spoken.

On examination the child showed about the same degree and distribution of cyanosis as his sister and brother, and also an internal strabismus. He was only just beginning to walk on a widened base. Co-ordination both of arms and of legs was very poor, although showing a full range of movement. The knee- and ankle-jerks, as well as all deep reflexes in the arms, were absent. The plantar reflexes were flexor and the abdominal reflexes present and equal. The heart showed a faint apical systolic murmur, but the other systems were normal.

On attempting intelligence tests (Dr. Ruth Griffiths) it was necessary to resort to tests for an infant of 6 months. His development age was approximately 9 months, with a developmental quotient of 20. The child had no speech, could stand alone for only a short period, and walked on

FIG. 2.—Case 2. Idiopathic methaemoglobinaemia. Effect of giving methylene blue, 4 gr. (0.26 g.) twice daily for two days by mouth.

a widened base when led. He was not very interested in materials, and his manipulative skill was poor. He was unable to feed himself, and had not acquired control of his excretory functions.

Investigations.—X-ray examination of the chest was normal. The cerebrospinal fluid was normal with negative Wassermann and Lange reactions. Blood count: red cells, 5,050,000 per c.mm.; packed cell volume, 38%, reticulocytes, 1%; total pigments 76%; colour index, 0.75; white cells, 4,400 (polymorphs 38%, lymphocytes 51%, monocytes 5%, eosinophils 6%).

Estimation of the blood over a period of one week showed the methaemoglobin to average 20% of the total blood pigments. The child was put on methylene blue, 2 gr. (0.13 g.) twice daily, on April 10 for two consecutive days. As with his sister and elder brother, after the first dose the cyanosis disappeared and no methaemoglobin could be detected in the blood (see Fig. 3). Without further methylene blue, the blood methaemoglobin had returned to its former level of 20% by April 21. By taking 2 gr. (0.13 g.) of methylene blue twice daily for two consecutive days of each week he remained relatively free from cyanosis.

FIG. 3.—Case 3. Idiopathic methaemoglobinaemia. Effect of giving methylene blue, 2 gr. (0.13 g.) twice daily for two days by mouth.

form of plain tablets each of 2 gr. (0.13 g.). Sugar-coated tablets of methylene blue were tried, but these appeared relatively inert as regards effect both on the cyanosis and on the blood methaemoglobin, the coating of the tablets probably interfering with absorption.

After some months Case 3 refused to take methylene blue tablets. Consequently, he was put on the following:

Methylene blue 1 gr. (65 mg.)
Syrup of tolu 10 min. (0.6 ml.)
Chloroform water to ½ oz. (14 ml.)
One tablespoonful twice daily on three consecutive days of each week.

Although the reduced amount of methylene blue did not abolish the cyanosis, this was rendered less apparent, with considerably reduced blood methaemoglobin.

The morphological haematology of the three affected children's blood was essentially normal. Mean corpuscular volumes were normal, and the mean corpuscular concentrations of total pigment, measured as alkaline haematin, were 30–31%. Reticulocyte percentages in all three fluctuated from less than 0.1 to 2.4%, but the observations were spread over periods with and without treatment. The aspirated marrows were not significantly different from normal. The overall picture did not therefore suggest any acceleration of formation and destruction of erythrocytes.

The methaemoglobin in the blood was entirely intracorporeal, and the plasma was also free from methaemoglobin and was not icteric.

The blood of the mother and of the eldest child was normal, and methaemoglobin was not detected with the Hartridge reversion spectroscop.

The excretion of coproporphyrin was measured in Cases 1 and 2, but the daily average was only of the order of 15 µg. in the urine and 50 µg. in the faeces (White and Ventura, 1951). These figures are well below those reported by Dobriner *et al.* (1937) for a normal 12-year-old child. Brownlee (1939) and Rimington and Hemmings (1939) found that increased coproporphyrin III excretion occurs in the methaemoglobinaemia due to various aromatic compounds and sulphonamides, and suggested an increased rate of breakdown of the methaemoglobin through paths leading to porphyrin formation. This does not appear to be so in the present cases, although the possibility of imbalance between excretion of coproporphyrins I and III was not investigated.

The effect of ascorbic acid and methylene blue therapy on the haemoglobin and methaemoglobin content of the venous blood of Cases 1 and 2 was examined on a number of occasions. The principal results are given in Fig. 4. The methods and reference frame are those adopted by King *et al.* (1951). On the Haldane scale 100% = 14.8 g. of Hb per 100 ml.; using the Huffer factors, the iron content is 0.34%, and 1 g. Hb = 1.34 ml. of O₂ or CO. The total pigment findings agree well when determined by iron content, as alkaline haematin or cyanhaematin, or by carbon monoxide capacity after reduction, but the oxygen capacity decreases in proportion to the amount of methaemoglobin present. Grateful acknowledgment is made to Dr. R. J. Bartholomew and Miss M. Geiser for their co-operation in these observations, and to Mr. A. H. Latham.

The methaemoglobin was directly measured as a percentage of the total blood pigment by use of the Klett spectro-colorimeter (King *et al.*, 1947). It was also measured photocolometrically; the decrease in absorption at 630 µ on conversion of the methaemoglobin to cyanmethaemoglobin was compared with the absorption when all the pigment dilution of the sample was converted to methaemoglobin with ferricyanide (King and White, 1949, unpublished observations).

In-vitro experiments on the reduction of methaemoglobin were carried out with cells from Cases 1 and 2, and from a further case of idiopathic methaemoglobinaemia (Dresner, Tay, and White, 1951, unpublished observations), and are summarized in Tables I, II, and III. Ascorbic acid may have a relatively great effect *in vivo*, despite the limited concentrations which can be reached in the plasma, by lessening the gap between the rates of production and reduction of

FIG. 4.—Blood pigments of normal and affected members of the family. 1.—Mother's blood. Methaemoglobin absent. 2.—Case 1. 2A: Blood after six weeks without treatment. 2B: Five days later, after 300 mg. of ascorbic acid a day. 2C: Blood taken after one month of treatment by methylene blue, 4 gr. (0.26 g.) twice daily on two days a week. 2D: Eighteen days later, no methylene blue being given during this time. 2E: Ditto, 22 days from 2C. 3.—Blood of normal eldest child (girl aged 11). Methaemoglobin absent. 4.—Case 2. 4A–E: Conditions as for 2A–E.

a: Total blood pigment in grammes per 100 ml., estimated by iron content. b: Ditto, estimated by CO capacity after reduction. c: Ditto, estimated by oxygen capacity. d: Grammes of methaemoglobin per 100 ml. of blood, estimated in Klett spectro-colorimeter. e: Ditto, estimated in the photo-electric colorimeter. f: Total pigment by alkaline haematin.

TABLE I.—*In-vitro* Experiment on the Reduction of Methaemoglobin in the Red Cells from Cases 1 and 2 by Ascorbic Acid and Methylene Blue

Case No.	Total Pigment Concentration in g./100 ml. and Millimols*	Unincubated Cells	Methaemoglobin as % of Total Pigment Cells Incubated for 2 hours at 37° C. in Isotonic Sodium Chloride with:		
			No addition (Control)	2.5 mg./100 ml. Ascorbic Acid (0.14 mM)	0.25 mg./100 ml. Methylene Blue (0.0067 mM)
1	7.8 g. 1.14 mM	19	11.1	12.8	6.1
2	6.5 g. 0.96 mM	16.6	14.8	12.0	5.4

* Mol. Wt. of Hb, 68,000.

TABLE II.—*Further Experiment on the Reduction of Methaemoglobin in the Red Cells of Case 1 by Increasing Concentrations of Ascorbic Acid*

Total Pigment Concentration in g./100 ml. and Millimols	Unincubated Cells	Methaemoglobin as % of Total Pigment Cells Incubated for 2 hours at 37° C. in Isotonic Phosphate Buffer with:			
		No addition (Control)	50 mg./100 ml. (2.8 mM) Ascorbic Acid	500 mg./100 ml. (29 mM) Ascorbic Acid	2.5 g./100 ml. (0.144 mM) Ascorbic Acid
7.8 g. 1.14 mM	115	14	11.3	5	Haemolysis and destruction of haemoglobin

TABLE III.—*In-vitro* Experiments on the Reduction of Methaemoglobin in the Red Cells of a Further Case of Idiopathic Methaemoglobinaemia (female, aged 21) by Anaerobic Incubation with Ascorbic Acid and by Methylene Blue. Administration of 300 mg. of Ascorbic Acid Daily by Mouth Subsequently Reduced the Methaemoglobin from 26% to 7% of the Total Blood Pigment in Seven Days

Total Pigment Concentration in g./100 ml. and Millimols	Unincubated Cells	Methaemoglobin as % of Total Pigment Cells Incubated for 12 hours at 37° C. in Isotonic Sodium Chloride with:					
		No addition (Control)	5 mg./100 ml. Ascorbic Acid (0.28 mM)	50 mg./100 ml. Ascorbic Acid (2.8 mM)	100 mg./100 ml. Ascorbic Acid (5.6 mM)	Methylene Blue added. 0.27 mg./100 ml. (0.0073 mM)	
						Anaerobic	Aerobic
11.3 g. 1.67 mM	29	26	15.4	9.2	3.5	18.5	12

methaemoglobin. *In vitro*, however, it is not as active as methylene blue; Barcroft *et al.* (1945) often found slow and incomplete reduction, but with increased activity when the ascorbic acid was protected under anaerobic conditions.

Discussion

In none of these three cases was there any history of diarrhoea, drug-taking, or haemolysis.

Their mother stated that one of her female cousins had blue cheeks "like the children." The paternal grandfather was invalided from the Army during the 1914-18 war on account of "blueness," although it was stated that he showed no disease of the heart or lungs. No further information regarding these relatives could be obtained. If

these vague histories, however, can be accepted as evidence of methaemoglobinaemia, we may construct a family tree as shown at the foot of the previous column.

The oxidative change from haemoglobin to methaemoglobin, and the reverse, take place readily in plasma until a point of equilibrium is reached. In the intact red blood corpuscle, however, an enzyme system reconverts the methaemoglobin as rapidly as it is formed, and under normal conditions there is never more than 1 or 2% in the cell. Idiopathic methaemoglobinaemia is an inborn error of metabolism probably due to a congenital defect of a component of this enzyme system—co-enzyme factor 1 (Gibson, 1948; Eder *et al.*, 1949), so that haemoglobin is largely converted into methaemoglobin, and the concentrations of the two pigments are nearly equal in amount. This occurs also in those cases of methaemoglobinaemia with haemolysis—for example, blackwater fever. In poisoning with substances such as acetanilide and dinitrotoluene, methaemoglobin is formed too rapidly for the cell enzyme system to cope with its reconversion. Methylene blue facilitates the reconversion of methaemoglobin, not by direct chemical reaction with the pigments, but by accelerating the normal enzyme process in the red blood cell (Finch, 1948).

It is tempting to regard persistent anoxia as the cause of the mental deficiency and areflexia in our cases, but it is more probable that both the methaemoglobinaemia and the mental defect are inherited separately, possibly as recessive characters from heterozygous parents (Penrose, 1950). In Huntington's chorea, for instance, the dementia and the chorea are transmitted by separate genes. As stated previously, only two other cases of the association of mental deficiency with methaemoglobinaemia appear to have been reported—those of Hitzenger and van den Berg. Consequently, the coincidence of mental deficiency, abnormalities of the tendon reflexes and methaemoglobinaemia in our three cases in one family is a striking one. A point in favour of the argument that anoxia is the cause of the mental deficiency in these cases is the high percentage of low-grade defectives in one family in this particular social stratum. The common finding is that when mental deficiency occurs in a professional-class family one of the children is a low-grade defective and the others of average or above-average intelligence; but if mental deficiency appears in a lower-class family all the children tend to be high-grade defectives, with an I.Q. of about 75.

As regards the possible association of mental deficiency with other inborn errors of metabolism—in the porphyrias, for instance—we have not encountered mental deficiency, nor are we aware of any reports of such an association. Mania may supervene during the attacks of "acute" porphyria, but it seems to be secondary to the metabolic condition and is not constant. On the other hand, in the rare condition of phenylketonuric or phenylpyruvic amentia (Penrose, 1935; Folling *et al.*, 1945) the metabolic disorder is definitely associated with mental deficiency and is inherited as a Mendelian recessive character.

The symptoms in all reported cases are surprisingly mild considering the degree of anoxia present. For instance, one of the two brothers examined by Deeny *et al.* was able to play a strenuous game of hockey. The three children we describe were no exceptions. Although there was usually a deepening of the cyanosis on crying or on undue exertion, they did not appear to be handicapped so far as their physical condition was concerned. The mildness of symptoms is probably to be explained by the chronicity of the condition. The mild compensatory polycythaemia which was present in all of our patients, as stated previously, is usual.

Lian *et al.* (1939) demonstrated the beneficial action of ascorbic acid in methaemoglobinaemia both *in vivo* and *in vitro*, an observation subsequently confirmed by Deeny *et al.* (1943), Sievers and Ryon (1945), and King *et al.* (1947). Lian and his co-workers showed that, *in vitro*, using a laked blood containing 39% methaemoglobin, 0.05 g. of ascorbic

acid caused the abnormal pigment to disappear in six hours, but it reappeared after 24 hours. *In vivo*, 0.1 g. of ascorbic acid, taken over a period of three weeks, reduced a 45% methaemoglobinaemia to one of 25%; after six days without ascorbic acid, however, the methaemoglobin in the blood was found to have reached its former level.

Hartmann *et al.* (1938) and Cox and Wendel (1942) obtained beneficial results with methylene blue in the treatment of methaemoglobinaemia caused by sulphonamides, while Schwartz and Rector (1940), Sievers and Ryon (1945), and King *et al.* (1947) demonstrated its value in reducing the blood methaemoglobin, and consequently the cyanosis, in cases of idiopathic methaemoglobinaemia.

Lian and his co-workers considered that the effect of ascorbic acid was superior to that of methylene blue in diminishing the methaemoglobinaemia, while King *et al.* (1947) regarded both substances as effective. In our Case 1, however, methylene blue was more effective than large doses of ascorbic acid in diminishing the percentage of blood methaemoglobin (Fig. 1) and reducing the cyanosis. It was for this reason that Cases 2 and 3 were treated solely with methylene blue. Nevertheless, the improvement in our patients was only temporary, and in order to maintain the beneficial effect it was necessary to repeat the dosage of methylene blue each week. Except for the rapidity of the changes in the cyanosis and the blood methaemoglobin level, administration by the mouth was quite as satisfactory as by the intravenous route. In any case, repetition of intravenous injections would be impracticable in a restless child and difficult to arrange under home conditions. No toxic effects from the methylene blue were seen over a period of two and a half years' observation, thus confirming the opinion of King *et al.* (1947) that methylene blue can be continued to be given orally without ill effect. The only drawback is that, in hospital, the nursing staff dislike the bright-blue stains on the bed-sheets from the urine of ill-controlled bladders.

Over a period of two and a half years' observation the three children described have remained free from noteworthy cyanosis provided they take the methylene blue on two days of each week. In the case of the two elder children, the dosage is 4 gr. (0.26 g.) twice daily for two days and in the younger child 2 gr. (0.13 g.) on each of the two days of treatment. No demonstrable improvement has occurred in the mental condition of any one of the three children, each showing approximately the same I.Q. as formerly. The state of the tendon reflexes, however, has improved to a slight extent in Cases 1 and 2. In Case 1, who originally showed total areflexia, a very slight left knee-jerk and right ankle-jerk can now be obtained on reinforcement; the other tendon reflexes are still absent. Case 2 shows supinator jerks, but they are unequal, the left being brisker than the right, and also a sluggish right ankle-jerk, previously absent. All tendon reflexes are still absent in Case 3.

Summary

The cases of three siblings suffering from familial idiopathic methaemoglobinaemia are described.

In each of the three children, the inborn error of metabolism was associated with mental deficiency and abnormalities of the tendon reflexes, two of the children showing total areflexia.

Records of other familial examples are mentioned and the literature of the condition briefly reviewed.

Large doses of ascorbic acid (400 mg. daily) were found to be efficacious in reducing the percentage of methaemoglobin in the blood and consequently the cyanosis, confirming the results of other observers. Methylene blue, both intravenously and by the mouth, was found to be even more efficacious, and was continued on two days a week without ill effect over a period of more than two years' observation.

No beneficial effect on the mental condition of the children was noted as a result of treatment, but slight improvement (reappearance) in some of the tendon reflexes occurred in the two elder children.

Acknowledgments are due to Dr. L. Osler, Dr. W. Leese, and Mr. Charles Wyatt for their considerable help in the investigations, and to Dr. P. H. R. Anderson, Divisional Medical Officer, Surrey County Council, for drawing our attention to the cases.

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