METHAEMOGLOBINAEMIA AND ANAESTHESIA

BY

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Any disease that has the power to interfere with the normal oxygen-carrying capacity of the blood is of interest and importance to anaesthetists, particularly so when a technique involving the use of nitrous oxide and oxygen relies upon an adequate amount of oxyhaemoglobin as one important factor for the proper oxygenation of the tissues.

Methaemoglobinaemia is such a disease and, because it is eminently treatable, is worthy of the attention of the anaesthetist who may well save himself a good deal of unnecessary worry because of the colour of the blood if, on his pre-operative visit, he can diagnose and treat this complaint, which is probably more common than we suspect.

BIOCHEMISTRY

The biochemistry and pharmacology of methaemoglobinaemia was reviewed in detail by Bodansky in 1951. Methaemoglobin is a normal oxidation product of the blood pigment haemoglobin; a compound of iron and protoporphyrin. In haemoglobin the iron is in the ferrous state, and in its role as an oxygen carrier it is oxygenated and does not change its valency, but in methaemoglobin the iron has been oxidized to the ferric form. This change is a reversible one and is not accompanied by red cell damage or destruction (Eder, Finch and McKee, 1949) but, of course, the methaemoglobin is unable to transport oxygen.

Reconversion mechanisms.

Human blood contains various enzymatic oxidizing and reducing systems which establish an equilibrium between haemoglobin and methaemoglobin which, under normal circumstances, is shifted predominantly in favour of haemoglobin (Van Slyke et al., 1946). Normally the red cell contains only 1 to 2 per cent of methaemoglobin (Paul and Kemp, 1944).

The continuous conversion of methaemoglobin to haemoglobin in the red cell is accomplished by one or more enzymatic reduction mechanisms. Various workers have shown that these consist of methaemoglobin reductase together with coenzymes I and II. These coenzymes are nucleotides present in the intact red cell. Coenzyme I, diphosphopyridine nucleotide (DPN) is converted to its active state by the glycolysis of glucose; coenzyme II, triphosphopyridine nucleotide (TPN) by the oxidation of glucose-6-phosphate or 6 phosphogluconic acid (Gibson, 1943; Gutmann, Jandorf and Bodansky, 1947; Huennekens et al., 1957a; Huennekens et al., 1957b).

Excess amounts of methaemoglobin will be formed by:

1. Interference with or absence of necessary factors for the normal reconversion mechanisms (idiopathic methaemoglobinaemia) (fig. 1).
2. Oxidation of haemoglobin in amounts which exceed the capacity of the normal red cell reconstruction mechanisms (secondary methaemoglobinaemia) (fig. 1).

Oxygen dissociation curve.

Darling and Roughton (1942) showed that in haemoglobin solutions containing methaemoglobin produced in vivo or in vitro, the oxygen dissociation curve is shifted to the left as the methaemoglobin concentration increases, and that the typical “S” shape becomes progressively more hyperbolic. They also demonstrated that this effect is qualitatively similar to, but quantitatively less than, that produced by carboxyhaemoglobin; this effect of methaemoglobin is likewise reversible. Although there is agreement in the changes produced in the oxygen dissociation curve of blood from patients with secondary methaemoglobinaemia, conflicting reports have arisen from studies on cases of idiopathic methaemoglobinaemia.
Gibson and Harrison (1947) studied the oxygen dissociation curve of one of their patients suffering from familial idiopathic methaemoglobinemia and found it shifted to the left, and quote Hitzenberger (1932) as eliciting the same result. However, Eder, Finch and McKee (1949) reported no change in the curve of blood from a patient with congenital methaemoglobinemia.

In secondary methaemoglobinemia the shift in the dissociation curve and its change of shape is of considerable importance because the tissues are liable to anoxia, not only because of the loss of oxygen-carrying capacity of the blood but also because the residual oxyhaemoglobin is less able to unload its oxygen to the tissues.

CLASSIFICATION AND CAUSATIVE FACTORS

Doctor (1953) classified methaemoglobinemia into extracellular and intracellular types; the latter may be primary or secondary.

**Extracellular.**

Extracellular or plasma methaemoglobinemia is associated with diseases in which there is haemolysis, such as eclampsia, blackwater fever, paroxysmal haemoglobinuria, sepsis due to anaerobic organisms where the haemoglobin released into the plasma is changed to methaemoglobin.

**Intracellular.**

(a) **Primary or idiopathic haemoglobinemia** is believed to be congenital. Over 100 cases have been reported, but the mode of inheritance is debatable; most favour a recessive trait but it is suggested that different modes may operate with differing biochemical defects. Deficiencies of factors involved in normal reconversion mechanisms are thought to be responsible, probably DPN (coenzyme I) (Gibson, 1948) and possibly TPN (coenzyme II) (Kiese, 1944).

Finch (1948) states that the ascorbic acid level in the serum of these patients is lowered despite a normal intake, suggesting that reducing substances (ascorbic acid and glutathione) act as a secondary line of defence. Clinically these patients show a persistent lavender cyanosis from birth or early life. They usually reach an equilibrium at about 40 per cent methaemoglobin (Finch, 1948).

(b) **Secondary intracellular methaemoglobinemia** has an exogenous origin and is commonly caused by drugs or chemicals which in themselves, or through their degradation products, convert haemoglobin to methaemoglobin. The amino and nitro compounds are the worst offenders, and nitrites, aniline derivatives and sulphonamides are the drugs most commonly implicated in the aetiology of secondary methaemoglobinemia.

Because of the heavy ingestion of phenacetin in the modern population, a much higher incidence of methaemoglobinemia may exist than is suspected. The commonest haematological abnormality produced by acute or chronic ingestion of this drug is methaemoglobinemia, but occasionally in chronic habitués haemolytic anaemia is seen, although on rare occasions this has been reported with acute intoxication. The formation of methaemoglobin has been attributed to the action of normal degradation products of phenacetin, but recent reports suggest that acetic-4-chloranilide, a common contaminant of available phenacetin preparations, is involved.

Ingested nitrates may cause methaemoglobinaemia in the presence of gastro-intestinal upsets. Aromatic nitro and amino compounds are particularly dangerous and may penetrate the skin and lead to a very severe and acute form of methaemoglobinemia in which the patients may become comatose (Mangelsdorff, 1952).

There may be associated red cell destruction with these drugs and this may vary considerably in degree. Generally methaemoglobinemia can be regarded as a fairly mild and reversible form of cell injury but, depending on the drug that causes it, there may well be severe accompanying cell damage—even haemolysis.

The degree of methaemoglobinemia caused by any particular substance will depend upon a number of factors, the most important amongst which are the duration and mode of administration, its rate of absorption, the rapidity of formation of degradation products, the rate of their excretion, and the functional capacity of the methaemoglobin-reducing mechanisms of the patient.
NORMAL RED CELL

Oxidation

Haemoglobin → Methaemoglobin

Methaemoglobin Reductase + Coenzyme 1 (D.P.N.)
Coenzyme II (T.P.N.)

Secondary Reduction: Ascorbic Acid, Glutathione

PRIMARY (IDIOPATHIC) METHAEMOGLOBINAEMIA

Oxidation

Haemoglobin → Methaemoglobin Accumulation

Methaemoglobin Reductase + Coenzyme II deficiency
?? Coenzyme II deficiency

Secondary Reduction: Ascorbic Acid, Glutathione

SECONDARY METHAEMOGLOBINAEMIA

Drug, Chemical, Oxidation

Haemoglobin → Methaemoglobin

Reducing mechanisms normal but capacity exceeded.

SIGNS AND SYMPTOMS

Cyanosis is the outstanding sign in methaemoglobinemia especially in the absence of any respiratory distress or cardiovascular signs. In the author’s experience the cyanosis is often typical, being of a lavender hue in the less severe cases, and in these the discoloration is usually limited to the fingers, ears and lips. In the last-mentioned it is often confined to the cutaneous section and does not extend beyond the mucocutaneous junction. In the more severe cases the cyanosis is generalized and more marked.

Finch (1948) reported that although 5 g of reduced haemoglobin per 100 ml of blood is required to produce cyanosis, only 1.5 g of methaemoglobin or 0.5 g of sulphaemoglobin per 100 ml need be present to produce comparable signs. He also stated that the symptoms of methaemoglobinemia are attributable to the decreased oxygen capacity of the blood, or to the side effects of the agent producing the disease. At a concentration of 20 per cent methaemoglobin, working subjects complained of fatigue and showed high blood lactic acid levels. Resting subjects may have 30 per cent methaemoglobin without any symptoms.

Apparently very severe symptoms do not become manifest until 50 to 60 per cent of the haemoglobin has been oxidized and above this level ataxia, excessive salivation and vomiting
occurs. Prostration and unconsciousness supervene when 80 per cent conversion has taken place and 90 per cent proves fatal (Doctor, 1953).

In the idiopathic variety the symptoms at rest may be minimal.

**DIAGNOSIS**

When methaemoglobinaemia is suspected, blood for examination should be collected and placed in a tube containing anticoagulant and centrifuged. If the plasma is clear then haemolysis and abnormal pigments derived therefrom are excluded from the cause of cyanosis. The whole blood may then be shaken in air. If the blood remains dark, intracellular pigments are present. It should then be diluted with water, approximately fivefold, so that when placed in a spectrograph (preferably reversion) only the red end of the spectrum is visible. A dark band at 630 m\(\mu\) is characteristic of methaemoglobin.

Sulphaemoglobin shows a band at 618 m\(\mu\) which may be confusing, but if a few milligrams of potassium cyanide are added the methaemoglobin band disappears quickly whilst the sulphaemoglobin band remains fixed for 24 hours. Methaemoglobin can be estimated quantitatively by gasometric or spectrophotometric methods, but these techniques are more complicated. At the bedside or in the operating theatre a very simple test is to place a drop of the patient's blood on to blotting paper beside another drop of normal blood—perhaps the anaesthetist's—and compare the colour. If methaemoglobinaemia or sulphaemoglobinaemia is present the patient's blood exhibits a typical brownish coloration on the blotting paper. If the cyanosis is due to a low oxygen saturation in the arterial blood, the blood will become red on exposure to air.

**TREATMENT**

The normal reconversion mechanisms convert methaemoglobin to haemoglobin at the rate of 0.5 g of methaemoglobin per hour (Finch, 1947). In secondary methaemoglobinaemia, if the causative agent is ascertained and withdrawn, these normal mechanisms will suffice in the treatment of most patients. However, in anaesthesia there is need for speedy reduction of the abnormal blood pigment, and this is best achieved by elimination of the offending agent and by the use of intravenous methylene blue which catalyzes the normal mechanisms and results in rapid restoration of the normal pigment. If the diagnosis is confirmed on a pre-operative visit then treatment should be instituted immediately. If methaemoglobinaemia is suspected at operation and there are no means available to confirm the diagnosis, methylene blue should be given intravenously, as no harm can be done even if sulphaemoglobin is present, providing the therapeutic dosage is not exceeded.

The usual dose is 1 to 2 mg/kg of body weight given intravenously over a 5-minute period. If cyanosis does not disappear within 1 hour, a second dose of 2 mg/kg can be given to adults. In infants, however, Goluboff and Wheaton (1961) have reported the occurrence of cyanosis and acute haemolytic anaemia complicating the treatment of secondary methaemoglobinaemia with large doses of methylene blue.

Ascorbic acid is effective as a direct reducing agent of methaemoglobin (Gibson, 1943), but its action is much slower than the rapid reconversion accomplished by the catalytic action of intravenously administered methylene blue. It reacts with methaemoglobin yielding haemoglobin and dehydroascorbic acid which is then reduced back to ascorbic acid. Since its reconversion rate is much slower than the normal mechanisms of methaemoglobin reduction (Finch, 1948) it has no place in the pre-operative or operative treatment of secondary methaemoglobinaemia and should be used only in the therapy of the idiopathic variety (fig. 2).

**SULPHAEMOglobinaemia**

No discussion of methaemoglobinaemia could be complete without mention of sulphaemoglobinaemia. Many of the drugs which will cause the former, will also produce the latter, and in some patients both pigments are present.

Clinical conditions necessary to produce sulphaemoglobin include an oxidizing agent (often in the presence of some bowel upset) or a sulphur-containing medication (Harrop and Waterfield, 1930).

Sulphaemoglobin cannot be reverted and does not indicate red cell damage, but rather an irreversible change in the normal blood pigment and it stays in the cell for the remainder of its...
life span, which is not altered. There is no specific treatment except to remove the causative drug and attend to the bowel upset if present.

CASE HISTORIES
Examination of the records in the Biochemistry Department of Sydney Hospital showed that over a three-year period 115 patients were referred for spectroscopic examination for abnormal pigments in their blood; twenty-four patients had positive tests for methaemoglobin and, of these, ten came to surgery. In addition some of these patients had positive tests for sulphaemoglobin also, but those with sulphaemoglobin alone are not included in this survey.

Of the ten patients who came to surgery, methaemoglobinemia was diagnosed pre-operatively in two, during operation in two, and post-operatively in six. Thus it is obvious that too many patients were not diagnosed until after the anaesthetic was over, although one did not develop methaemoglobinemia until postoperative sulphonamides and aspirin had been administered.

CASE 1. A male aged 57 years, suffering from a chronic duodenal ulcer, was to undergo gastrectomy. He gave a long history of salicylate intake and had typical lavender coloration of the skin and mucous membranes. On spectroscopic examination of his blood both methaemoglobin and sulphaemoglobin were identified. Administration of 100 mg of methylene blue intravenously resulted in slight improvement of his cyanosis.

**Fig. 2** Rate of methaemoglobin reversion.
Ordinate represents the percentage of the initial level of methaemoglobin, usually between 2 and 5 g per 100 ml in the patients studied. (From Finch, C. A. (1948), *New Engl. J. Med.*, 239, 470, by kind permission of the author and editors.)
CASE 2. An unmarried female aged 27 years was found disorientated and wandering in the streets, complaining of severe headaches. On admission she was 38 weeks pregnant, febrile and exhibiting signs of cerebral irritation. Despite a thorough investigation no definite diagnosis could be established. She was given sodium salicylate (1 g daily for 8 days) with little effect. Three weeks after admission she became deeply cyanosed and had epileptiform fits. It was decided to perform an urgent Caesarean section and pre-operatively the anaesthetist suspected the presence of methaemoglobinaemia. However, the operation was in progress and the baby just delivered before spectroscopic examination was performed and methylene blue administered. The baby which was cyanosed at birth died 1 hour later. The mother's colour improved considerably following the methylene blue, and she left the theatre in a satisfactory condition. Postoperatively, however, she had several episodes of cyanosis which were relieved by intravenous methylene blue. It was discovered subsequently that she had a supply of A.P.C. powders and phenacetin in her handbag. Psychiatric consultation was advised, but she refused treatment and left hospital a normal colour but with symptoms of hysteria still present.

In retrospect, it was considered that had the methylene blue been administered before the delivery of the baby its outcome may have been different.

CASES 3 AND 4. These two cases were diagnosed as having methaemoglobinaemia during operation. One was a female aged 62 who was suffering from a carcinoma of the breast and also had a painful cervical spondylitis for which she took A.P.C. powders. During operation, as her blood was noticed to be a "dusky" colour, a sample was taken for spectroscopic examination and methaemoglobin was found. Intravenous methylene blue was administered resulting in a dramatic return to the normal appearance of the blood.

The other case was a female of 29 years with a perforated gastric ulcer. One year previously she had had a perforated gastric ulcer and on that occasion was diagnosed as having methaemoglobininaemia. A bluish tinge of her blood again led to the diagnosis of this condition which was confirmed spectroscopically during operation. Eighty milligrams of methylene blue given intravenously returned the colour of the blood to normal. She later admitted to a continued large A.P.C. intake since her previous operation.

CASE 5. A female patient aged 46, undergoing a partial gastrectomy for duodenal ulcer, was noted to be "a little cyanosed" on arrival in the theatre. The anaesthetist reported that the blood appeared "dusky" colour throughout operation. Methaemoglobin was identified in her blood in the early postoperative period, whereupon 100 mg of methylene blue was administered intravenously and the patient rapidly returned to a normal colour. This patient gave a history of phenacetin intake.

CASE 6. A female aged 62 had a spinal cord tumour removed, but cyanosis was not detected until the postoperative period. Methaemoglobin was identified in her blood and 100 mg of methylene blue were administered intravenously with consequent return to a normal colour. No history of drug intake could be elicited from her.

CASE 7. A female aged 49 was admitted to hospital at night suffering from a perforated gastric ulcer, which was oversewn. The following day a lavender cyanosis was noticed and methaemoglobin identified spectroscopically. Again the dose of methylene blue administered was 100 mg, which led to reconversion of the cyanosis. This patient admitted to a long history of A.P.C. intake.

CASE 8. A critically ill female of 71 entered hospital with an incarcerated umbilical hernia, which reduced spontaneously soon after admission. She was suffering from moderately severe chronic bronchitis and congestive cardiac failure, and exhibited a marked cyanosis. Operation was delayed in order to digitalize her and treat her bronchitis, and a week later it was performed under local anaesthesia. Postoperatively it was considered that her cyanosis was not due entirely to the bronchitis and cardiac failure. Her blood was examined spectroscopically and methaemoglobin and a trace of sulphaemoglobin were detected. Intravenous administration of methylene blue produced considerable improvement in the degree of her cyanosis. The patient admitted to A.P.C. intake.

CASE 9. A female of 58 years had undergone hypophysectomy for a pituitary tumour. Fourteen days postoperatively she complained of dizziness and nausea and developed a cyanotic tinge. She had no abnormal respiratory or cardiovascular signs, but as she had been taking Trisulpha and aspirin tablets for an infected wound and headaches, her blood was examined for methaemoglobin and sulphhaemoglobin, both of which were present. The drugs were suspended and methylene blue 100 mg was administered intravenously. She soon became symptom-free and within two weeks her cyanosis had improved greatly.

CASE 10. A male aged 63, suffering from carcinoma of the oesophagus, had an oesophagoscopy with insertion of a Souttar's tube. Postoperatively, because of the cyanosis of the lips and a history of phenacetin intake, his blood was examined spectroscopically. Sulphaemoglobin and a trace of methaemoglobin were detected, but in this case no methylene blue was administered. He was advised to discontinue the phenacetin.

SUMMARY
The formation, biochemistry, causative factors, diagnosis and treatment of methaemoglobinaemia have been discussed. It is again stressed that this disorder of the blood pigment is probably more common than is usually thought, and the anaesthetist should suspect it when a patient presents with cyanosis without comparable respiratory or cardiovascular signs. Even when these are present, however, and a history of relevant drug intake is also ascertained, the blood should be spectroscopically examined for abnormal pigments.

Methaemoglobinemia can be a danger during anaesthesia due to the diminished oxygen-carrying capacity of the blood, and when diag-
nosed it is eminently treatable with intravenous administration of methylene blue which results in speedy reversion of methaemoglobin to normal haemoglobin.

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REFERENCES

SUMMARY
La formation, la biochimie, les facteurs favorisants, le diagnostic et le traitement de la méthémoglobinémie sont discutés. On insiste de nouveau sur le fait que ce trouble de pigment sanguin est probablement plus courant qu'on ne l'a prétendu, et l'anesthésiste doit le suspecter lorsqu'un malade présente une cyanose sans signes respiratoires ou cardiovasculaires comparables. Cependant, même si ceux-ci sont présents, et une anamnèse de prise importante de médicaments est aussi établie, le sang doit être examiné au spectroscopie pour rechercher des pigments anormaux.
La méthémoglobinémie peut devenir un danger pendant l'anesthésie à cause de pouvoir réduit du sang de fixer l'oxygène; et lorsque le diagnostic a été posé, elle est facile à traiter par l'administration de bleu de méthylène, qui résulte en une réversion rapide de la méthémoglobiné en hémoglobiné normale.

ZUSAMMENFASSUNG
Wegen der vergrößerten Sauerstofftransportkapazität kann die Methämoglobinämie während der Narkose zur Gefahr werden. Wird sie aber diagnostiziert, so lässt sie sich leicht mit intravenöser Applikation von Methyleneblau behandeln, das das Methämoglobin rasch in normales Hämoglobin umwandelt.