SULPHAEMOGLOBINAEMIA DUE TO ANILINE DERIVATIVES

BY

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The continued use of aniline compounds may produce a marked and persistent cyanosis due to the formation of sulphaemoglobin in the red blood corpuscles. Attention has been directed in recent years to the frequency with which sulphonamide therapy is associated with sulphaemoglobinaemia, but the power of the humbler aniline antipyretics in this direction does not appear to be so well appreciated. Snapper (1925) described two cases of sulphaemoglobinaemia which were due to the continued use of aniline antipyretics. Similar cases have been described by Harrop and Waterfield (1930), Healy (1933), and Morgan and Anderson (1940), among others.

The toxicity of the different members of the aniline antipyretic group varies. The relative toxicity of acetanilide is high, and most of the reported cases of sulphaemoglobinaemia precipitated by aniline antipyretics have been due to that drug. Addiction to it has been observed, and this danger has been emphasized by a number of observers. Acetanilide is now included in Part I of the Poisons List (1937), is not easily available to the public, and hence widespread abuse of it is not to be expected.

Phenacetin presents a quite different problem. It is a component of numerous proprietary headache powders and can be obtained without difficulty. Its chemical structure is similar to that of acetanilide; it is less toxic, however, and cases of chronic poisoning by phenacetin are therefore seldom encountered. In large doses it can, as might be expected, produce poisoning, with effects, including sulphaemoglobinaemia, very much like those seen with acetanilide. Snapper's (1925) two cases of sulphaemoglobinaemia were due to chronic poisoning with phenacetin, and Coxon and Crawford (1940) have reported another. Two cases of sulphaemoglobinaemia have been seen recently, and are described here.

Case I

On April 6, 1943, a housewife aged 42 was admitted to hospital on account of severe headache, weakness, and cyanosis. She had been subject to attacks of severe headache since childhood. These attacks occurred at least once a week and each lasted one to two days. Since the menopause in 1941 the severity and duration of the headaches had increased. The pain began in the crown of the head and then spread to one or other side. The patient could not account for the headaches; she read avidly without ill effect, and was free of nausea and photophobia during the attacks. She shunned company and crowded places, as she feared that an attack might be precipitated in these circumstances. In 1930 she received numerous injections of morphine to ease the headaches. Eighteen months before admission she had noted that her lips were blue, and she stated that her skin had been blue for about a year. This blueness was more pronounced during attacks of headache, and the patient's relatives had remarked on the blue colour of her face. She had taken many brands of analgesic powders for her headaches, but two years before admission she resorted to a proprietary tablet (phensic) which contains approximately 3.6 gr. of acetylsalicylic acid and 2.1 gr. of phenacetin. She took between "4 and 10 tablets daily," according to the severity of the headache. During an attack of pain she had had as many as 30 tablets in a day (=63 gr. of phenacetin).

Her husband stated that in the last attack, which persisted for four days before admission, his wife had taken over 100 tablets. He said that the patient had become very irritable and depressed during the past few months. She was confused when the headaches were severe and kept swallowing tablets without regard to their number. During the past year she had been given $4\frac{1}{2}$ gr. of ferrous sulphate daily and monthly injections of anahaemin, presumably to improve her general condition.

On admission the patient was greatly distressed with headache, but not confused. She was thin and poorly nourished. There was no dyspnoea, but cyanosis was very marked. The skin was a slate-grey colour, which was especially noticeable in the lips, ears, nose, and beds of the nails. The temperature was 99° F., the pulse rate 100, and the respiratory rate 20 a minute. The pulse was regular and of good volume: the arterial wall was not palpable. The area of cardiac dullness was not increased and the heart sounds were well heard. A systolic murmur audible at the mitral area was not conducted. The chest was symmetrical and moved equally on both sides. Further examination did not reveal any abnormality of the

lungs. There was no evidence of any mediastinal abnormality. The abdomen was tense, but moved freely with respiration. The liver and spleen were not palpable. Examination of the nervous system did not reveal any abnormality. The optic fundi were normal. The urine was free of albumin, sugar, and blood, but showed the "diacetic acid fallacy" with ferric chloride solution.

Blood examination showed: Hb, 105% (Sahli); red cells, 4,800,000 per c.mm.; white cells, 4,200 per c.mm. The blood films were normal. The venous blood was darker than normal and remained so despite shaking in air. On spectroscopic examination of lysed blood an absorption band was seen in the red portion (612-620 μ) of the spectrum. This band was not affected by the addition of potassium cyanide solution and was presumed to be due to sulphaemoglobin. It was visible in a 1 in 100 dilution of blood in water two days after admission (April 8). No specific treatment was given. The headaches were considered to be psychogenic in type.

Progress.—The acute headache passed off after three days, but the cyanosis remained. Analgesics were withheld, and so far as is known the patient did not have a secret supply. Despite this, it was 16 days before there was any obvious diminution in the cyanosis. Three weeks after admission the cyanosis had lessened considerably, but the sulphaemoglobin absorption band was still present in a 1 in 18 dilution of venous blood. The patient was discharged after four weeks.

Six weeks after admission (May 21) the cyanosis had almost disappeared, although the sulphaemoglobin band was still detectable in a 1 in 12 dilution of the blood. Blood examination showed: Hb, 70% (Sahli); red cells, 4,800,000; white cells, 6,500 per c.mm. On June 11—i.e., just over eight weeks after withdrawal of the tablets—spectroscopic examination of the blood failed to reveal a sulphaemoglobin band. The general skin cyanosis had gone, but the lips were still dusky. Reviewing this case, we may conclude that the regular ingestion of phenacetin (8-20 gr. daily) over a period of two years had led to the formation of sulphaemoglobin in the blood.

Case II

A baker aged 57 was seen as an out-patient on July 10, 1943. He had had severe pain in the left shoulder during the previous three weeks. The onset of the pain had been sudden and some improvement had occurred with local counterirritant measures and analgesic powders. There was no dyspnoea.

The patient was a cheerful well-built man. Marked cyanosis, of blue-grey colour, was seen in the lips, face, ears, and especially in the nail-beds. Systemic examination did not show any further abnormality. In particular, there was no evidence of any upset of the respiratory and cardiovascular systems. Blood films were normal: Hb, 95% (Sahli); red cells, 4,250,000 per c.mm.; white cells, 7,800 per c.mm. The urine appeared to be normal on chemical examination. Rheumatic myalgia of the left deltoid muscle was found to be responsible for the pain; it responded to massage.

The analgesic powders prescribed by the patient's doctor contained 10 gr. of phenacetin and 5 gr. of acetanilide. Twelve powders were taken each week. Thus when first seen he had had a total of 240 gr. of phenacetin and 120 gr. of acetanilide in two weeks.

On being questioned he stated that the blue colour of his face had been noted by his relatives for a week and that it had caused them some concern, as they feared it was due to "heart trouble." The venous blood was darker than normal, having a chocolate tinge, and an absorption band in the red was found on spectroscopic examination. This band was not affected by potassium cyanide solution, and it was thought to be due to sulphaemoglobin. The band was easily detected in a 1 in 65 dilution of the blood.

No more powders were given, and the patient made an uninterrupted recovery. As is usual in sulphaemoglobinaemia, the cyanosis lifted slowly. Thus, one week later (July 17) cyanosis was still present and the sulphaemoglobin band was detected spectroscopically in a 1 in 30 dilution of venous blood. Two weeks later (July 24) the cyanosis was definitely less marked. The patient resumed his employment and did not return for further observation.

Both acetanilide and phenacetin had been taken in this case, and both may have contributed to the formation of the sulphaemoglobin. However, acetanilide, because of its greater toxicity, must be held largely responsible. No treatment of the cyanosis was given apart from withdrawal of the drugs. Long and Spriggs (1918) noted that inhalations of carbon dioxide and oxygen improved their cases of sulphaemoglobinaemia. Healy (1933) gave carbon dioxide and oxygen inhalations, together with a high-fat diet and ammonium chloride, to two cases of sulphaemoglobinaemia, and reported that the cyanosis disappeared within a week.

Discussion

Apart from the different drugs involved, these two cases of sulphaemoglobinaemia may be taken as examples of two clinical types in which cyanosis due to aniline antipyretics can occur. Case I is an example of the entity called "enterogenous

cyanosis." The salient features here are psychological instability, weakness, chronic headache, and cyanosis without associated dyspnoea, occurring almost exclusively in women. While it is just possible that some of these cases may be idiopathic, it is now recognized that the majority are due to the ingestion of aniline antipyretics. The self-administration of drugs is often denied by these patients, and careful search may be necessary to find the actual cause of the sulphaemoglobinaemia. Case I suffered a relapse some months after dismissal. This patient was admitted to another hospital and a normal ventricular system was demonstrated by cisternal encephalography. She was then examined by a psychologist, who reported that the symptoms were psychological in origin. Case II presents many different features. Here the drugs were taken to obtain relief from pain caused by an organic condition. The pain of rheumatoid arthritis, as in the case reported by Coxon and Crawford (1940), or of rheumatic myalgia as in the case here described, may be the prime factor. Both sexes may be affected, psychological instability is not present, and the tendency to habit formation is not marked.

The mode of formation of sulphaemoglobin is the same whether it is produced by aniline itself or one of its derivatives. According to Snapper (1925), the circulating haemoglobin is sensitized by aniline derivatives and can thus unite with traces of sulphide absorbed from the intestine. Snapper induced sulphaemoglobinaemia in men by administering aniline compounds and sulphur. Outside the body, however, aniline and its related compounds have no effect on haemoglobin. It appears that aniline compounds are oxidized to the corresponding phenyl-hydroxyl amines and *p*-aminophenols in the blood stream and that these substances affect haemoglobin. Gley (1937) and Morgan and Anderson (1940) have demonstrated that both these substances, when added to blood, lead to the rapid formation of sulphaemoglobin if a trace of sulphide be present, and to methaemoglobin if sulphide be absent. Methaemoglobin can be produced only with difficulty by giving aniline antipyretics alone (Harrop and Waterfield, 1930). Further, methaemoglobin is highly unstable in the blood stream, being rapidly converted to haemoglobin (Stadie, 1921), and large quantities are required to produce cyanosis. Such cyanosis lifts within 24 to 48 hours after withdrawal of the drug, and is more likely to appear in acute than in chronic poisoning.

Finally, there is some evidence in favour of the view that coloured oxidation products of *p*-aminophenol are present in the blood after the ingestion of aniline compounds and that these are partly responsible for the cyanosis. Leslie (1939) described a case of acute acetanilide poisoning in which marked cyanosis was not associated with any change in the blood pigment and was considered to be due to the presence of some coloured derivative of acetanilide in the blood. Lundsteen, Meulengracht, and Rischel (1938) described 11 cases of chronic acetanilide poisoning with cyanosis, and were able to demonstrate a chocolate-coloured derivative of *p*-aminophenol in the blood of one of their cases which was specially investigated. It is difficult, at present, to assess the importance of this coloured *p*-aminophenol derivative in the production of cyanosis. In the majority of cases of chronic poisoning with aniline antipyretics, including the two described here, the cyanosis has been adequately, if not completely, accounted for by the presence of sulphaemoglobin in the blood.

Summary

The clinical and laboratory findings in two cases of sulphaemoglobinaemia due to aniline antipyretics are described. The method of formation of the abnormal pigment and other factors which may contribute to the cyanosis are discussed.

I wish to express my indebtedness to Dr. John Gracie for permission to investigate cases under his care, and to Drs. S. V. Telfer and G. H. Bell for their advice and help.

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THE CHILD WITH FREQUENT COLDS

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In this article are given the results of a comprehensive investigation of 100 school-children suffering from frequent colds. At the invitation of the County Medical Officer, the children were referred by the school medical inspectors in the area of South-West Essex to a special clinic established at the hospital for the purpose of investigating this prevalent condition. The children were mostly drawn from middle-class and artisan families. The main part of the investigation consisted of clinical, x-ray, and laboratory examinations, and note was also taken of the environment and development of the children. While our chief purpose was to establish the clinical characteristics of the child with frequent colds, we also considered the problem of which department in a hospital should be responsible for their examination and should advise on their treatment.

It was inevitable that a number of children suffering from asthma and hay-fever should be referred to such a clinic. If these are excluded the history of the disorder is a typical one. The children usually began to suffer from frequent colds when they started attendance at school. They complained at first of blockage of the nasal passages followed by a mucous discharge which after a few days became muco-purulent. Often there was also a mild upper respiratory infection, with slight cough but little sputum. The general constitutional disturbances always found in an adult suffering from coryza were absent. The cold will last about two weeks, and then the child may be free for a few weeks until the next attack. This cycle will continue right through the winter and may often be present during the summer months, though the colds are usually less severe in the warm weather. In a small number of cases there was continuous muco-purulent nasal discharge between the attacks. Many of these children had had these frequent colds for as long as three years. While the children remain fairly well in spite of these frequent attacks, both the parents and the education authorities show concern at the amount of schooling lost. Some parents are also anxious lest the frequency of the attacks denotes some constitutional deficiency or even serious organic disease—e.g., tuberculosis.

We have examined 130 children, the findings in the first 100 of which are given below. There were 59 boys and 41 girls in this series. Four children were between the ages of 1 and 5, 69 between 6 and 10, and 27 between 11 and 15 years.

History

Their birth weights were all within normal limits, and they all developed normally from birth, reaching the usual milestones at the expected ages; 88 had been breast-fed and 12 bottle-fed; and 95 were given cod-liver oil and orange juice or other additional vitamins to supplement a normal diet. Only 2 children were in the habit of going to bed late. We analysed this series with regard to previous infectious diseases and found that 84 had had measles, 59 whooping-cough, 3 diphtheria, 59 bronchitis, 23 tonsillitis, and 14 otitis media. The majority of them had been vaccinated and immunized against diphtheria. No definite relation was found between any of these infectious diseases and the onset of colds. In 33 cases the mothers complained that their children snored at night and were mouth-breathers. Twenty-one children had had their tonsils and adenoids removed before being seen by us, mainly for the relief of frequent colds, and of these 18 were not improved. A near relative of 26 children had suffered from tuberculosis and of 22 from an allergic condition.

Clinical Examination

These children all showed normal weights and heights for their age and sex, and appeared to be well developed and of normal intelligence, with the exception of 3 who were slightly