THE SUCCESSFUL TREATMENT OF TWO RECENT CASES OF CYANIDE POISONING

BY

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It has long been recognized that hydrogen cyanide with its sodium and potassium salts is one of the most potent and rapidly acting poisons. In spite of this, the cyanide salts have been used industrially, especially in gold mines to extract gold from the ore, for very many years. The case hardening of metals and electroplating processes also depend on the use of cyanide salts in considerable quantities, and during the past 30 years hydrogen cyanide itself, which was hitherto only regarded as a laboratory chemical, has come into prominence industrially, first as a fumigant, and later in relatively large quantities in chemical processes for the manufacture of plastics. The acid is very much more dangerous than its salts, owing to its high volatility and the extreme toxicity of small amounts when inhaled in the form of vapour. An atmosphere containing less than 500 parts per million can be breathed by man for only one minute without fatal results, and breathing apparatus is necessary whenever the concentration of the gas is likely to exceed 100 parts per million (Occupation and Health, 1930).

The number of accidents from hydrogen cyanide poisoning in factories in Britain is surprisingly small, and it is to the credit of the safety organizations in industry that only 19 such accidents were reported between the years 1921 and 1948, four of which were fatal (Merewether, 1949). It has to be remembered that these figures refer only to accidents in factories, and reference to the Registrar General's return for England and Wales for the years 1933-47 shows that there were, during that period, 18 deaths from cyanide gassing and 38 deaths due to other accidental cyanide absorptions. The 18 deaths from gassing probably contain several which were due to the use of hydrogen cyanide as a fumigant, and it is, therefore, interesting to note that a considerable number of such deaths occurs in places where the Factories Act does not apply.

United States figures indicate, as would be expected, that the majority of deaths from cyanide poisoning have been suicidal, but that fatalities from hydrogen cyanide are more frequently accidental than suicidal. One hundred and twenty deaths of an accidental nature are reported between the years 1933 and 1941 from gaseous hydrocyanic acid (Chen, Rose, and Clowes, 1944). It is obvious that the opportunity to try newer methods of treatment of cyanide casualties has been much greater in the United States than in Britain, and a search of the available literature confirms the fact that this opportunity has not been disregarded.

Routes of Entry and Action

The possible routes of entry of any poison into the human body are by ingestion, by inhalation, and through the skin. With cyanide salts the main risk is of accidental ingestion, although it is well known that there is a grave risk of absorption through the skin where the latter is damaged by hot cyanide salts falling on it, or by simple mechanical cuts and abrasions. The evidence suggests that in the stomach the cyanide salts react with hydrochloric acid to liberate hydrocyanic acid. Failure to poison the notorious Rasputin has, in fact, been attributed to his being achlorhydric.

With hydrogen cyanide the risk is largely one of inhalation, but it can also be absorbed through the unbroken skin (Walton and Witherspoon, 1926; Fairley, Linton, and Wild, 1934). One of the cases described later in this paper confirms the importance of this observation.

Whatever the route of entry, the effect of the cyanide radicle is the same. There is a local action, slight but constant, on the peripheral nerve endings, and a much stronger action on the central nervous system, leading to a transitory irritation followed by paralysis. In the stricter sense of the word it is a bulbar poison, and death is usually due to paralysis of the respiratory centre and consequent asphyxia.

In the blood stream, where cyanide can be detected within 40 seconds of placing a little pure acid on the tongue of an animal (Dixon, 1929), it affects the respiratory function and prevents the liberation of oxygen from the hemoglobin. It combines readily
with methæmoglobin to form cyanmethæmoglobin, which, according to some observers, accounts for the bright red colouring of the skin sometimes described in cyanide poisoning. It is eliminated partly by the lungs in the form of unchanged acid, in traces in the sweat, and in the urine as a thiocyanate. Lang (1933) claims that the latter reaction is due to an enzyme, present in all tissues except blood and muscle, which he has named rhodanese.

**Methods of Treatment**

The affinity of the cyanides for methæmoglobin forms the basis of the various types of treatment which have been formulated by a number of authors during the past few years. Hug (1933) demonstrated that a number of compounds found to have some effect in combating cyanides owed their activity to transformation of hæmoglobin into methæmoglobin. The majority which he describes were themselves toxic to animals, because of the formation of methæmoglobin, but the production of this compound retards the action of cyanide and permits time for its complete detoxication by the tissue cells. He investigated, amongst other substances, methylene blue, sodium nitrite, and phenyl hydrazine. Geiger (1932) had already reported methylene blue to be efficacious in clinical practice.

Later results obtained in animal experiments by other authors (Buzzo and Carratala, 1933; Chen and others, 1934; Hanzlik and Richardson, 1934; Etteldorf, 1939), as well as by Hug (1933, 1934), suggested that the combination of sodium nitrite and sodium thiosulphate provided the best method of treatment for cyanide intoxication. Table 1 indicates the relative efficiency of the reagents tested by Chen and others (1934) in their experiments on animals.

With the exception of amyl nitrite, which was given by inhalation, all the antidotes in Table 1 were given intravenously at the same time as the cyanide was injected subcutaneously.

The authors observe that the best antitodal action was obtained with successive injections of sodium nitrite and sodium thiosulphate, and point out that in their experiments four out of seven dogs were saved from 20 minimum lethal doses of sodium cyanide by this method. In the dogs which did not survive death was delayed for several hours. They demonstrated that the action of the sodium nitrite was prompt and often relieved symptoms within a few minutes, whereas sodium thiosulphate was comparatively slow in its effect.

One feature of the treatment was the conversion of a rapidly fatal course of cyanide poisoning to one of prolonged remission, with occasional reappearance of toxic signs. They considered that the nitrite and thiosulphate should be repeated when there was a recurrence of vomiting, hyperexcitability, tremor, dyspæa, or tachycardia, but emphasized that the dosage should not be repeated more than once an hour, since the rapid accumulation of sodium nitrite is just as serious as cyanide poisoning as it increases the degree of asphyxia.

It was considered that these animal experiments warranted a trial of the treatment in human cases, and, in fact, two cases at that time had already been successfully treated (Viana, Cagnoli, and Cendan, 1934). The suggested dosage in human beings, according to the authors, was 6–10 mg. sodium nitrite per kg. and 0.5 g. sodium thiosulphate per kg.; that is, in an average individual weighing 50 kg. an initial dosage would be 0.3–0.5 mg. sodium nitrite and 25 g. sodium thiosulphate.

In a later communication Chen and others (1944) reviewed the literature and reported that in 15 human cases, in whom treatment with the sodium nitrite–sodium thiosulphate antidote had been given, 14 had recovered.

**Table 1**

**Efficiency of reagents tested by Chen and others (1934)**

<table>
<thead>
<tr>
<th>Antidote</th>
<th>None</th>
<th>Nitroglycerin</th>
<th>Methylene blue</th>
<th>Sodium thiosulphate</th>
<th>Sodium tetraionate</th>
<th>Amyl nitrite</th>
<th>Sodium nitrite</th>
<th>Methylene blue and sodium tetraionate</th>
<th>Amyl nitrite and sodium thiosulphate</th>
<th>Sodium nitrite and sodium tetraionate</th>
<th>Sodium nitrite and sodium thiosulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of minimum lethal doses of sodium cyanide required to kill a dog</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>14</td>
<td>21</td>
</tr>
</tbody>
</table>
Mechanism of Cyanide Detoxification

The probable mode of action, and that suggested by Chen and others (1934, 1944), is that the nitrite ions react with haemoglobin to form methaemoglobin, and the cyanide radicle combines with this to form cyanmethaemoglobin, which is much less toxic than cyanide. The addition of sodium thiosulphate aids in the conversion of the cyanide to thiocyanate, which is the normal mechanism of excretion of non-fatal doses of cyanide salts. Thiocyanate, which is relatively harmless, is formed slowly by the reaction of cyanmethaemoglobin with the sulphur constituents of the body when sodium nitrite is given alone. Sodium thiosulphate accelerates this reaction so that the speed of conversion from cyanide to thiocyanate is greatly increased. It must be emphasized that the reaction is reversible and, therefore, signs of cyanide poisoning may reappear. This explains the need for repetition of the treatment in severe cases of poisoning, and for maintaining careful observation of a patient for at least 48 hours.

Instructions for the Use of Antidotes

In a group of factories in Britain where cyanide salts and hydrocyanic acid are manufactured on a large scale, it was decided, after studying the report of the experimental work already described, to have in readiness an emergency kit containing the necessary doses of sodium nitrite and sodium thiosulphate in ampoule form, and appropriate syringes and needles in sterile containers, as well as amyl nitrite capsules, and the usual first aid material required in cyanide poisoning. The emergency box is kept close to the process building, and the following instructions are pasted within its lid.

First Aid in H.C.N. or Cyanide Poisoning

1. Remove the patient to a pure atmosphere.
2. Place in a recumbent position. Do not in any circumstances walk him about.
3. If breathing shows signs of failing or has ceased, apply artificial respiration, (Schafer's method) and continue without interruption.
4. When assistance is available instruct assistants to (a) administer oxygen, carbon dioxide mixture; (b) cut away any clothing splashed with cyanide solution or H.C.N.; (c) wrap the patient warmly in blankets and apply hot water bottles.

As soon as possible after the alarm is given a doctor must be summoned. Artificial respiration must be continued until breathing is restored or until the doctor has pronounced life extinct.

Nitrite—Thiosulphate Therapy.—The following method of treatment by the medical officer has been devised.

(1) Immediately administer by inhalation amyl nitrate for 15-30 seconds, the inhalation being repeated every two to three minutes until the syringes are filled with the antidotal solutions.

(2) Give an intravenous injection of sodium nitrite at the rate of 2·5-5 ml. per minute. (The correct dose of sodium nitrite for an adult weighing 50 kg., i.e. 0·3 g. in 10 ml. sterile distilled water, will be found in the ampoule in the kit.)

(3) Immediately follow by intravenous injection of sodium thiosulphate at the same rate, taking great care to avoid extravasation. The correct dose of sodium thiosulphate for a 50 kg. man, i.e. 25 g. dissolved in sterile distilled water to make a 50% solution, will be found in the ampoule in the kit.

(4) Gastric lavage should then be performed if cyanide has been taken by mouth.

(5) The patient must not be moved but must be kept under observation for 24-48 hours. Temporary improvement after initial medication does not ensure ultimate recovery. When signs of poisoning persist or reappear one hour after the initial dose, the nitrite and thiosulphate may be repeated. If there is no indication for repeating the antidote, a second injection may be given two hours after the first for prophylactic purposes.

Fortunately, although the emergency kit has been available for many years, the safety precautions have been of such a high standard, that, until a few months ago, no serious case of hydrocyanic acid gassing had occurred. Two accidents, which occurred within three weeks of each other in September, 1949, however, presented an opportunity of observing the effect of the intravenous therapy and of confirming the claims made for it by American authors.

Case Reports

Case 1.—T. C., aged 41 years, process worker, had been employed on a hydrogen cyanide process for eight years.

On September 2, 1949, he entered the H.C.N. chamber at 11·30 a.m., to take the routine weekly sample of liquid hydrocyanic acid. He was equipped with rubber boots and gloves, and was wearing a fresh air respirator. Some difficulty was experienced in obtaining the sample because of a blockage in the pipeline, and the man removed one glove in order to deal with this more easily. An observer outside the chamber then noticed that some liquid hydrocyanic acid ran over the operator's bare hand, and he was seen to wave his hand about to aid evaporation, and then replace his glove. A few minutes later he came out of the chamber and proceeded to wash his gloves before
removing them. He complained of dizziness and difficulty in breathing, shouted for help, and was assisted to the plant first-aid room. Two minutes later, i.e. about five minutes after contaminating his hand, he became deeply unconscious. The first-aid attendant immediately instituted the routine treatment already described and rang the alarm bell to obtain medical assistance. He arrived on the scene within a few minutes accompanied by the consultant physician, who happened to be visiting the factory at that time.

The patient was being treated by inhalation of an oxygen/carbon dioxide mixture through a B.L.B. mask, and had already inhaled the contents of one capsule of amyl nitrite. He was deeply unconscious, his breathing was stertorous and his face rather flushed. The pulse rate was 100 and was bounding in quality. His tongue had been bitten, but no other history of a convulsion could be obtained. His limbs were flaccid and deep reflexes were not present, except in the case of the plantar, which showed an extensor response on the left side. The pupils were dilated and equal, and showed no reaction to light.

No smell of hydrogen cyanide could be detected, nor were there any cuts or abrasions on his hand, but in view of the history it was assumed that the man was suffering from cyanide poisoning. Two further capsules of amyl nitrite were broken and given by inhalation, and an intramuscular injection of cocaine, 3 ml., was given. His condition became rapidly worse, respirations were stertorous and of Cheyne-Stokes variety, the pulse rate increased to 140 and became thready, and the face showed a greyish pallor with some cyanosis of mucous membranes.

It was decided, in view of the patient's condition, to give the experimental intravenous therapy, and accordingly 0·3 g. sodium nitrite in 10 ml. sterile water was given intravenously at the rate of 2·5 ml. per minute. The patient became a little cyanosed during this injection, but no other change could be discerned. Through the same needle 50 ml. of 50% solution of sodium thiosulphate was then given at the rate of 5 ml. per minute. Towards the end of this injection respiration lost its Cheyne-Stokes character, and became less stertorous, and the patient began to move his lips and moisten them with the tip of his tongue. Before withdrawing the needle from the vein a sample of blood was taken for chemical and spectroscopic examination.

Five minutes after completing the injection therapy the patient began to move his arms and legs and muttered incoherently. He then vomited copiously. At this stage his respiration had returned to normal, his pulse rate was 90 and the rhythm was irregular. His skin remained pale with a tendency to cyanosis of mucous membranes and extremities. After two further attacks of vomiting, he felt much better and wanted to sit up, but was prevented from doing so. The total period of unconsciousness was 55 minutes. He was kept under observation in the works surgery for two hours, and, as there was no evidence of recurrence of symptoms, he was then transferred by ambulance to hospital, where the physician who had observed him throughout and had assisted in his treatment, investigated him to exclude any possibility of constitutional illness which might have caused his collapse. On arrival at the hospital about 5 p.m. he complained of weakness, nausea, and soreness across both loins. He was quite conscious and well orientated. His temperature was 98° F. and pulse rate 80.

No abnormality could be detected in the cardiovascular or respiratory system. His blood pressure was 100/80. No abnormality was present in the abdomen. The pupils were dilated and equal, and reacted to light and convergence. The right plantar response was extensor, but otherwise the nervous system was normal.

At 10 p.m. the patient stated that he felt perfectly well, and examination revealed no departure from normal.

The urine did not contain albumin or sugar; its reaction was acid and the deposit contained scanty leucocytes. The blood urea on September 3, 1949, was 20 mg. %. The blood count on September 3, 1949, was normal. The Wassermann reaction was negative.

No abnormality was detected in radiographs of the skull. The lung fields were clear and the cardiovascular shadows within normal limits. The electroencephalograph was perfectly normal in all respects.

The specimen of blood had, unfortunately, not been covered with a layer of oil, and qualitative examination, using the copper guaiacum test, did not reveal the presence of cyanide.

The man returned to work after an absence of 32 days, and has continued his work on the same process since without further trouble.

Case 2.—F. B., aged 52 years, a process worker employed in a hydrogen cyanide process for two years, on September 21, 1949, equipped with rubber boots and gloves and wearing a fresh air respirator, entered an H.C.N. chamber to clear a blocked pipe and to take a sample. In order to reach the pipe easily it was necessary for him to lie on his side on the floor of the cubicle, and in doing so the line to his air mask kinked and cut off his air supply. He experienced dizziness and dyspnoea, and stated that his head began to throb and his legs "turned to jelly". He staggered from the chamber and collapsed outside at 3.55 p.m., when his mate carried him forthwith to the first-aid room attached to the plant.

The first-aid attendant immediately gave him oxygen/carbon dioxide mixture through a B.L.B. mask and stripped him of his protective clothing. A capsule of amyl nitrite was crushed and he was allowed to inhale the vapour. I saw him at 4 p.m., when he was deeply unconscious. The respiration was stertorous, the pulse rate 110 and bounding in quality. The pupils were equally contracted and did not react to light. His limbs were flaccid and the deep reflexes absent, both plantar responses being flexor. There was an odour of hydrogen cyanide about the patient, and in view of the history and our previous experience it was decided that the intravenous therapy should be instituted without delay. While the syringes were being filled, it was noted that the patient developed fine convulsive movements in his legs and these rapidly extended over the whole body with intermissions of a few seconds. During the convulsive movements his breathing became irregular and often ceased for a short time, but began again spontaneously.
TREATMENT FOR CYANIDE POISONING

His pupils were now widely dilated and his pulse was rapid and less bounding in quality. His face was pale and he was sweating profusely. A second capsule of amyl nitrite was crushed and given by inhalation, and, at the same time, intravenous injection was begun. The same dose as in Case 1 was used, i.e. 0·3 g. sodium nitrite in 10 ml. sterile water at a rate of 2.5 ml. per minute, followed by 50 ml. of 50% solution sodium thiosulphate at the rate of 5 ml. per minute.

During the final 45 seconds of the latter injection breathing became more regular, and there were signs of recovery in the form of voluntary movements of the face and limbs and incoherent muttering. The pupils at this stage reacted to light and the conjunctival reflex had returned. Within 10 minutes of completing the injection consciousness had returned entirely, and the patient was able to tell us his early symptoms.

A specimen of blood was withdrawn for chemical and spectroscopic examination, and on this occasion the surface of the blood was covered with a protective film of oil. Qualitative analysis, using the copper guaiacum test, was positive and indicated the presence of cyanide. The total period of unconsciousness was 25 minutes and no relapse occurred after the first evidence of recovery. The patient was kept at rest for two hours, and was then transferred by ambulance to hospital for observation.

On arrival at the hospital the patient stated that he felt quite well and had no complaints. His pulse and temperature were normal, and his blood pressure 140/80. No abnormality could be found on clinical examination.

He was examined again at 10 p.m. when he said he felt perfectly well and no abnormal physical signs were discovered.

He remained in hospital until September 26, 1949, when he was discharged.

No abnormal clinical findings were discovered at any time. The urine was normal. The blood count was normal.

The man returned to work on the same job after an absence of five days and has had no trouble since his accident.

Discussion

To be certain that one is dealing with a case of cyanide poisoning, positive proof of the presence of cyanide in the blood is essential, but circumstantial evidence must be accepted in the case of a sudden accident. In the first of these two cases the positive evidence was not obtained, but the absence of constitutional disease and the circumstances leading up to the initial collapse, namely, that the man had just come out of the chamber in which he had been observed with liquid hydrogen cyanide on his bare hand, seemed to be indisputable evidence of cyanide intoxication. The absence of cyanide in chemical tests of the blood was difficult to understand, but it is suggested that as examination was delayed for 24 hours and the blood specimen was not covered with an oil film, the cyanide had volatilized. In the second case the circumstantial evidence of collapse after leaving the H.C.N. chamber, where the airline to the patient's fresh air mask had been kinked, warranted intravenous therapy, and the positive evidence of cyanide in the specimen of the blood was ultimately obtained without difficulty, as a film of oil had been spread on the surface and no volatilization had occurred.

The prolonged period of absence from work in Case 1 was due entirely to our desire for a complete hospital investigation to exclude any possibility of constitutional disease which might have caused collapse. The man had recovered completely from the ill-effects of his accident within 48 hours, and in the ordinary course of events would have returned to work in three days.

In both cases the effect of the nitrite-thiosulphate antidote was dramatic and confirmed all the claims made for it by American authors. There is no doubt that its use prevented at least one fatality. Hydrogen cyanide is so rapid in its action that it is essential to have the antidote readily available wherever human beings are likely to come in contact with hydrocyanic acid or its salts. There is no time to prepare solutions and sterilize apparatus once the patient is overcome. Speed in diagnosis and in treatment is then essential. First aid measures, including the administration of amyl nitrite by inhalation, the giving of oxygen, and the performance of artificial respiration, should be initiated by other workmen on the plant, or by a first-aid attendant who is constantly in attendance and aware of the particular hazard. The emergency kit already described must be kept in or near the process building, and must be inspected at frequent intervals to ensure that syringes are intact and in working order.

The experience gained in the two cases which have been described suggests that if a patient suffering from cyanide poisoning can receive this treatment immediately or can be brought to a medical department or hospital still alive, and then receive the intravenous therapy, the chances of a fatal outcome will be reduced to a minimum.

Summary

The experimental work leading to the use of sodium nitrite and sodium thiosulphate by intravenous injection in the treatment of cyanide poisoning is discussed, and reference is made to the treatment of human casualties in the United States.

Two cases which occurred in September, 1949, in a chemical factory in England and were treated successfully by this method, are described and details of the treatment are included.

The importance of speed in diagnosis and treatment is emphasized and the provision of an emergency kit close to the plant is suggested.
I am indebted to Dr. Thelwall Jones for notes on the hospital investigations of both cases, and for his helpful advice and criticism in the preparation of this paper; also to Dr. Winston Evans for analytical reports on the specimens of blood.

REFERENCES
