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THE ABSORPTION OF HYDROCYANIC ACID VAPOUR THROUGH THE SKIN

WITH NOTES ON OTHER MATTERS RELATING TO ACUTE CYANIDE POISONING

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(With 2 Figures and 20 Charts in the Text)

CONTENTS

INTRODUCTION

THE original scope of this investigation was the study of the passage of hydrocyanic acid vapour through the skin. We have partly repeated and confirmed the results of Walton and Witherspoon (1926). In view of the extensive use of hydrocyanic acid vapour in the destruction of vermin in ships the subject is of considerable practical interest. In the course of our work certain other matters were considered and these are referred to in the text.

I. THE EFFECTS OF EXPOSURE OF A SMALL AREA OF THE SKIN OF GUINEA-PIGS TO AN ATMOSPHERE SATURATED WITH HYDROCYANIC ACID VAPOUR

Apparatus

The apparatus (Fig. 1) consisted of a Buchner flask, containing liquid HCN, standing on a thick sorbo rubber base, and enclosed, for safety, in a tin filled with lumps of calcium oxide. The side tube of the flask was led downwards into the CaO, to ensure the maintenance of atmospheric pressure in the flask. The animal was fastened by tapes to a wooden lid which had a central aperture through which the neck of the flask projected slightly. By means of the slight spring in the sorbo rubber pad, the skin of the abdomen could be maintained in close apposition to the mouth of the flask. The hair on the abdomen was clipped close in preference to shaving, as it was desirable to avoid even the smallest skin abrasion. The animal's back was covered with cotton-wool, and a hot-water bottle was placed over that to avoid any effects from chilling.

The internal area of the mouth of the flask was 1·23 sq. in. and, as the average surface area of the guinea-pigs used was about 60 sq. in., approximately 0·02 of the animal's body surface was exposed to the vapour of HCN.

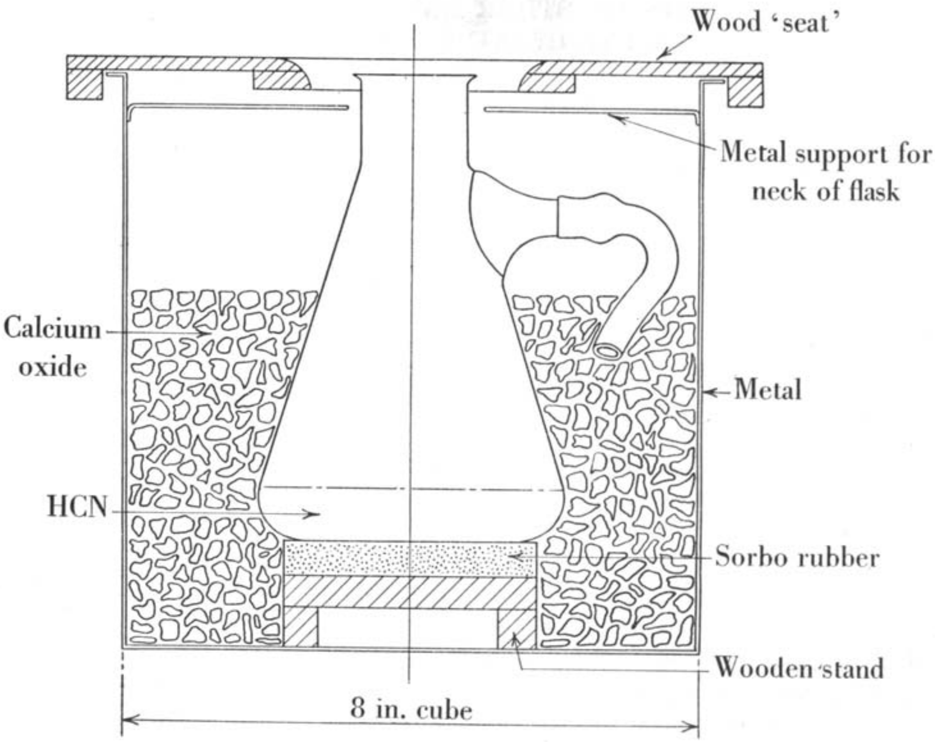

Fig. 1. Apparatus used for exposure of a small area of animal's skin to a saturated atmosphere of HCN.

Experiment I

The results of this experiment are shown in Table I. Five guinea-pigs were used, each weighing approximately 24 oz. The air temperature during the experiment varied from -2° C. in No. 2 to 6° C. in Nos. 3, 4 and 5, therefore the theoretical maximal concentrations of HCN in air in contact with the skin ranged between 1 in 3·2 and 1 in 2·2.

The onset of symptoms in the animals used in this experiment was considerably later than that reported by Walton and Witherspoon (1926), although the exposed area of skin was slightly less in their experiments. It is not known whether precautions were taken by them to avoid the effects of cold and exposure as was done in the series now under consideration. The temperatures at which their experiments were carried out, and the consequent concentrations of HCN in contact with the skin, are not stated.

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It will be noted that the animals showed signs of oxygen deficiency during exposure, and the post-mortem findings are those of asphyxia. It is suggested that the gastric distension that was noted in three of the animals was the result of air-swallowing.

Table I. *Exposure of small area of skin to atmosphere saturated with hydrocyanic acid vapour.*

Guinea-pig No.	Exposure min.	Result	Post-mortem appearances	Microscopic examination of exposed skin
1	97	Violent sudden convulsions at 55 min. Between 55 and 97 min. animal was partly comatose, breathing in shallow gasps, and had several minor convulsions. Removed at 97 min. and killed with $CHCl_3$	All organs normal. Venous blood rather dark	Slight vascular congestion, with some degree of deficiency in the normal staining reaction of the epithelial cells
2	60	Breathing became laboured and animal was gasping at 30 min. No convulsions, but deepening coma. Death at 60 min.	All blood dark and venous. Submucous haemorrhages in stomach, which was dilated with air. Other organs normal	Normal except for some swelling of connective tissue fibres
3	35	Collapsed suddenly, and with gasping breathing, became comatose at 35 min. No convulsions. Removed, and died at 45 min.	Stomach distended with air and showed submucous haemorrhages. All blood dark. Other organs normal	—
4	15	At 15 min. animal began to lose muscular tone, and partially collapsed. Removed and had recovered completely by 60 min., when it was killed by $CHCl_3$	No obvious abnormality	Slight vascular congestion, and the epithelial cells stained poorly
5	65	Coma gradually developed, starting at about 26 min. No convulsions. Died at 65 min.	Stomach distended with air, and showed submucous haemorrhages. Blood dark. Other organs normal	As for No. 4

Experiment II

The next experiment had as its object the study of the effects of repeated short exposures. One guinea-pig, 20 oz. in weight, was used, and exposures were given as shown in Table II.

The theoretical concentrations of HCN in air, in contact with the skin, ranged between 1 in 1·8 and 1 in 2·5.

II. The effects of exposure of the entire body surface of rabbits (head excluded) to measured concentrations of hydrocyanic acid vapour

Drinker (1932) reports three cases of men who developed serious symptoms after exposure to an atmosphere containing approximately 2 per cent. HCN vapour, although they were protected by masks which gave excellent respiratory protection.

The dangers from the absorption of HCN vapour through the skin are also referred to by Williams (1931) and by Flury and Zernik (1931).

The subject has a very practical application in the cyanide processes of ship fumigation, and fairly accurate knowledge of the concentrations encountered in these processes would seem to be of importance.

The literature consulted does not contain much information on this point. Ross and Larmouth (1933), working at Durban, mention "a standard 60 gramme dosage and a two hour exposure," and from the subsequent condition of the rats, they assess the resulting concentration at about 1 : 11,000.

Hamer (1933), writing of the Orient Line, says that the maintenance of a 0·4 per cent. concentration for at least 6 hours is necessary in dealing with insect vermin. But, in such manoeuvres as the manual emptying of Galardi

Table II. *Effect of repeated exposures.*

Guinea-pig No. 6

Day	Air temp. °C.	Exposure min.	Results
1	6	15	Loss of equilibrium; breathing distressed; recovered in 2 hours
2	3	10	No symptoms
5	9	10	
6	9	10	
7	11	15	Symptoms as at first exposure, but rather less in degree
8	10	10	No symptoms
9	8	10	
10	3	10	
12	6	10	
14	4	15	
15	3	78	Symptoms at 15 min. similar to those at first exposure in nature and degree, increasing to coma without convulsions. Recovered partially on removal, but collapsed 1½ hours later and died with signs of air hunger and slight repeated convulsions. Post-mortem: macroscopically all organs appeared normal. Blood dark

bottles, it is obvious that the operator must encounter much higher concentrations, at least momentarily. The Ministry of Health's *Memorandum* (1928) makes no mention of concentrations.

As will be shown later, the attainment and maintenance of a given concentration of HCN vapour is not a simple matter of space to be dealt with and the amount of gas generated, but is dependent on many factors, of which the presence of moisture is one.

Apparently the method of fumigation, and the concentrations aimed at, vary with different shipping companies and at different ports, and it appears probable that, in some cases at least, the concentrations employed are of an unknown degree.

The apparatus used in this series of experiments and shown in detail in Fig. 2 consisted of the following essentials:

(*a*) A stout glass cylinder, which acted as the animal chamber. One end of this was closed by a rubber diaphragm which closely embraced the neck of the animal. The other end was closed by a board seated on rubber, and perforated by an inlet and an exit tube.

(*b*) A small fan connected with the inlet of (*a*) and the exit of (*c*). This fan

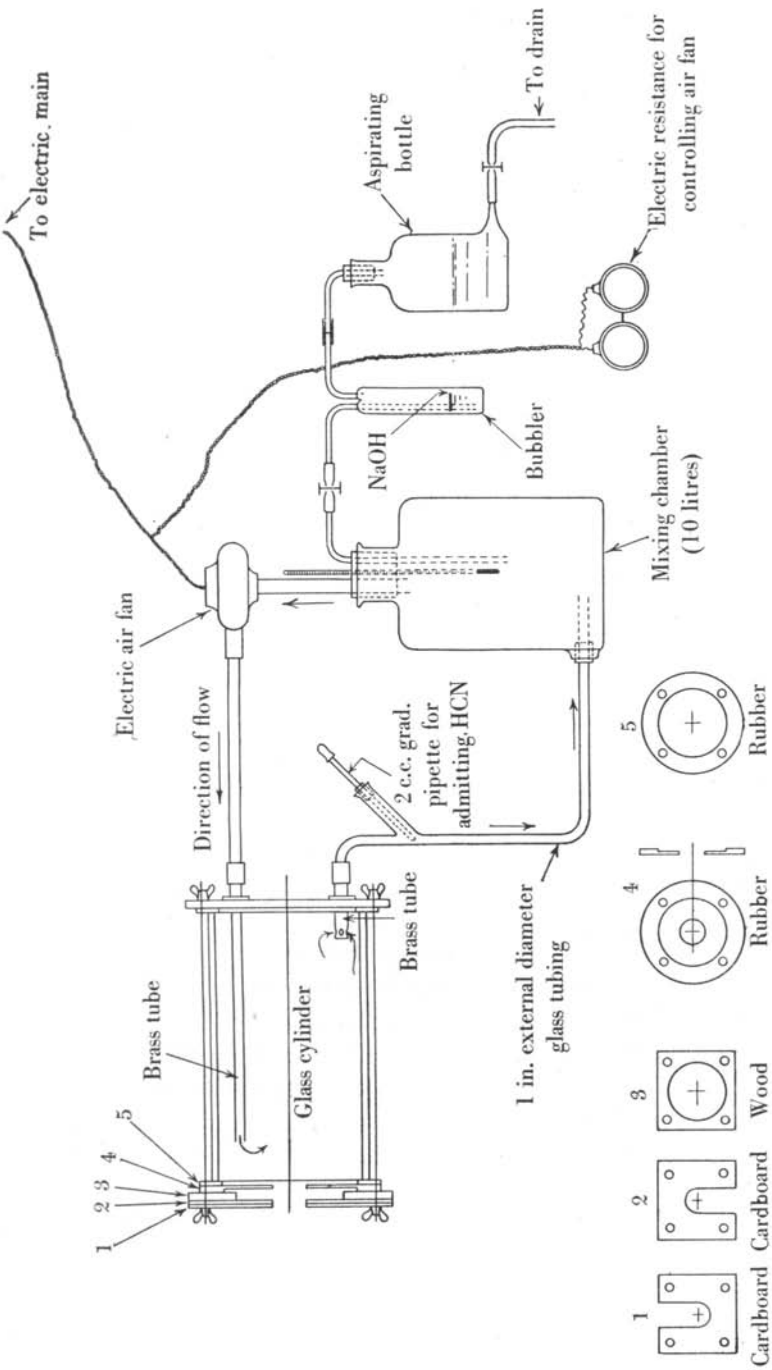

Fig. 2. Apparatus for exposure of skin (rabbit) to measured concentrations of HCN vapour.

was improvised from a hairdresser's drying fan, cased in with aluminium sheeting, and with all external joints sealed with plasticine. A resistance was interposed between the fan and the electric main.

(*c*) A mixing chamber, made from a 10-litre bottle connected with the inlet to (*b*) and the exit from (*a*). An aspirating bottle and bubbler were attached for the convenient removal of samples.

(*d*) The device for inserting liquid HCN consisted of a graduated pipette let into a by-pass in the tube connecting (*a*) and (*c*). When in use, with an animal *in situ*, the apparatus was, for practical purposes, gas-tight.

Its volume was approximately as follows:

Animal chamber ... 5·64 litres,
Mixing chamber ... 10·00 litres,
Tubing, fan, etc., about 0·36 litre,

giving a total of 16 litres, and, as the flow of the fan was 90 litres per minute, the atmosphere of the apparatus was completely circulated rather more than five times in 1 min.

A rabbit, accustomed to handling, would crouch comfortably in the apparatus, eating normally.

The concentrations of HCN vapour were estimated by the withdrawal of a 200 c.c. sample through 10 per cent. NaOH, and titrating the resulting cyanide with $N/50$ $AgNO_3$ (Liebig's method).

Physical signs

The physical signs observed coincided closely with those arising from acute poisoning by HCN either inhaled or ingested. But, as absorption through the skin appears to be a more gradual process, the onset of these signs was slower.

For the sake of clearness in the charts, signs have been used as follows:

Premonitory symptoms indicated by †
Convulsion symptoms indicated by §
Collapse symptoms indicated by ‡

The premonitory symptoms were as follows:

(1) *An appearance of alarm.* This sign is difficult to describe, but was quite definite when seen, and took the form of an expression on the animal's face as though it thought something was wrong.

(2) *Lateral swaying movements of the head.* This was noticed in nearly every case.

(3) *Expiratory effort.* The breathing quickened, and expiration instead of remaining as a muscular relaxation became a definite effort, and was often accompanied by a slight grunt.

Before describing the animal experiments, under this heading, it is advisable to mention some practical difficulties that emerged during preliminary work with the apparatus.

(*a*) *Fall in concentration after a single introduction:* 0·2 c.c. HCN was introduced and the proportion of HCN to air at the end of 7 min. was found to be 1 in 175. At the end of an hour this proportion had fallen to 1 in 425, although no leak could be detected by the most careful examination. Repeated introductions of HCN were obviously necessary to maintain a level concentration.

(*b*) *Absorption of* HCN *by moisture:* In another case, an initial concentration of 1 in 60 was obtained. Early in the experiment the animal passed urine, and an immediate fall to 1 in 90 occurred, and it was found impossible to increase this concentration by any reasonable addition of HCN. The same effect was produced by immersing animals in water and drying them roughly with a towel before placing them in the apparatus.

(*c*) *Effect of clean apparatus:* After a series of preliminary trials, it became necessary to clean out the glass cylinder and its connections. This was done thoroughly with acetone. It took 1·8 c.c. of HCN, introduced during 20 min., to raise the concentration above 1 in 80. Presumably a considerable quantity of HCN vapour had to be absorbed by the apparatus itself.

In the charts which illustrate this part of the work the abscissae indicate time in minutes, while the ordinates show concentrations of HCN in air within the apparatus. All the rabbits used ranged from $3\frac{1}{2}$ to 4 lb. in weight. (The number of each rabbit coincides with that of the chart throughout.)

Charts 1 and 2 show the effect of medium concentrations of the order of 1 in 120 to 1 in 140.

Chart 3 illustrates an attempt to find a concentration that would be just tolerable to a rabbit for 90 min. This appears to be in the region of 1 in 210.

Charts 4–8 show the effects of somewhat higher concentrations.

For comparison with a series to be considered under the next heading, it was decided to standardise a 33-min. exposure as nearly as possible. The resulting concentrations of HCN in air were between 1 in 50 and 1 in 70 and are illustrated by Charts 9–12. It will be noticed that, in three cases, the animals were removed at 33 min. completely collapsed, while in the fourth case death ended the experiment at 27 min.

III. Attempts at protection against hydrocyanic acid poisoning, absorbed through the skin, by the intravenous injection of sodium thiosulphate

The technique employed was as follows:

A 5 per cent. solution was employed, *i.e.* 5 g. of anhydrous $Na_2S_2O_3$ in 100 c.c. of distilled water. This was injected into the marginal ear vein of rabbits in a proportion of 4 c.c. per kg. of body weight, 3 min. before the exposure to HCN was started.

The rabbits used again ranged from $3\frac{1}{2}$ to 4 lb. in weight.

As far as possible, the exact condition, in which Charts 9–12 were produced, were now duplicated, in order to obtain comparable concentration curves.

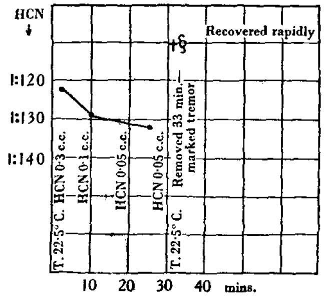

Chart 1.

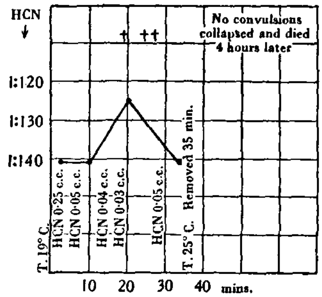

Chart 2.

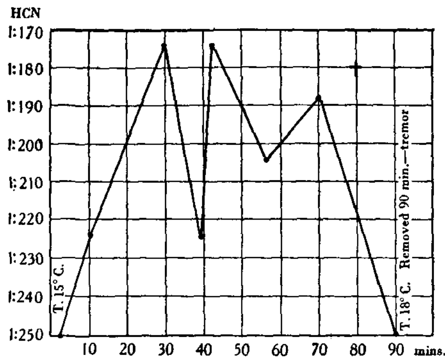

Chart 3.

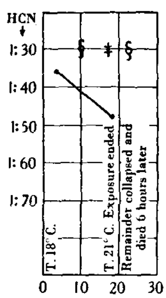

Chart 4.

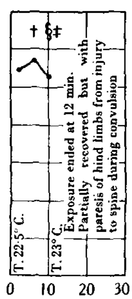

Chart 5.

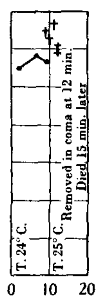

Chart 6.

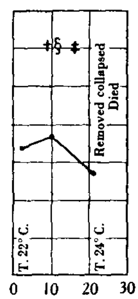

Chart 7.

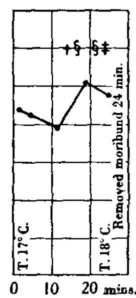

Chart 8.

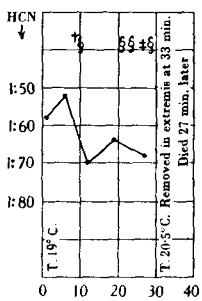

Chart 9.

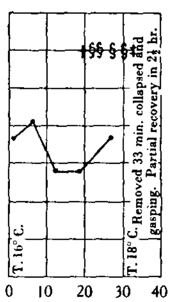

Chart 10.

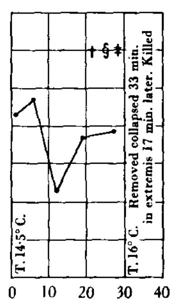

Chart 11.

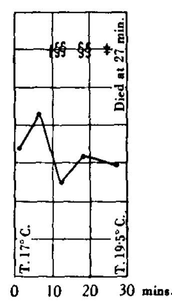

Chart 12.

(Compare with Charts 13–15.)

Absorption of HCN vapour through the skin of rabbits.

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The results are shown on Charts 13, 14 and 15.

Although the general level of the concentrations of HCN in air, in the latter series, tended, for some reason, to be slightly higher, it will be seen that all three animals survived their 33-min. exposure without showing any signs of poisoning at all, and were perfectly normal on release.

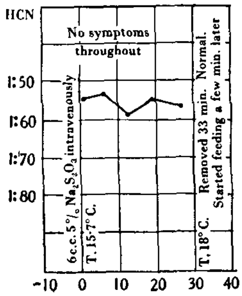

Chart 13.

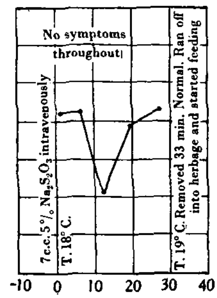

Chart 14.

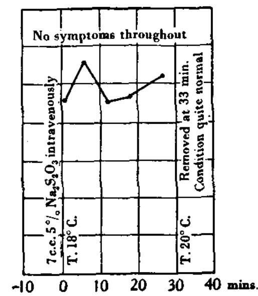

Chart 15.

(Compare with Charts 9–12.)

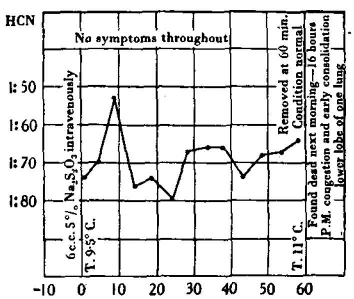

Chart 16.

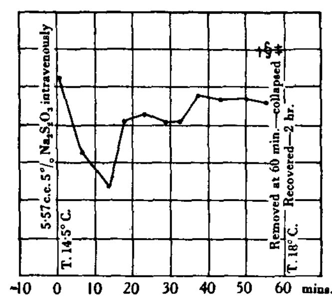

Chart 17.

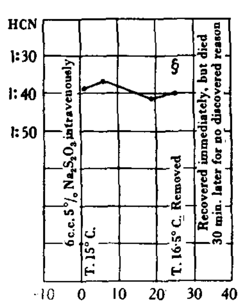

Chart 18.

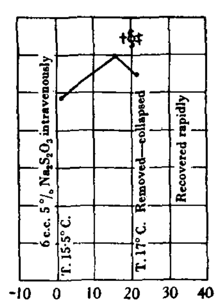

Chart 19.

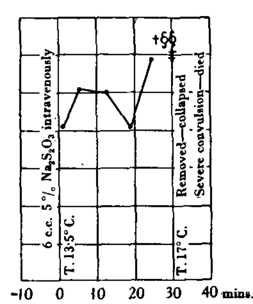

Chart 20.

Protection against the effects of HCN vapour, absorbed through the skin, by intravenous injection of sodium thiosulphate.

Charts 16 and 17 show exposures to similar concentrations prolonged up to 60 min. As recorded in Chart 16 the animal showed no symptoms, but died the following day with signs of early pneumonia at the base of one lung. In Chart 17 the animal had its first symptoms at 55 min., and recovered in 2 hours.

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Charts 18, 19 and 20 illustrate the effects of still higher concentrations of HCN—about 1 in 40—on animals similarly protected by $Na_2S_2O_3$ and, if they are compared with Charts 4–8, some degree of protection is evident even here.

These results appear to be in parallel with those of many authors who have demonstrated the protection afforded by $Na_2S_2O_3$ against the effects of HCN administered intravenously. (Amongst others: Buzzo and Carratala, 1933; and Turner and Hulpieu, 1933.)

IV. Note on the effects of liquid hydrocyanic acid on the skin

On account of the statement by the International Labour Office (1930, **1**, 995) that experiments by Lehman on chemists prove that severe symptoms may occur through dipping the fingers into a solution of HCN, a simple experiment to investigate the possible danger from spilling or splashing the liquid upon the skin was carried out.

A $4\frac{1}{4}$ lb. rabbit was selected and amounts of liquid HCN (about 80 per cent. pure) up to 1 c.c. were dropped on to the clipped skin from a pipette, and allowed to evaporate in the open air on a winter day. No symptoms developed.

Ten c.c. of the liquid was then splashed upon the skin. The rabbit developed convulsions in 30 sec. and collapsed within a minute, but had completely recovered in 4 hours.

As far as it is permissible to argue from the results on a single rabbit to a hypothetical case in man, this experiment suggests that an 11-stone man could spill 29 c.c. of pure HCN on his bare skin with impunity, and would still have a chance of recovery if he so spilled 290 c.c.—again of the pure compound—without taking any precautionary measures other than allowing free evaporation in the open air.

It is suggested that free facility for evaporation is the important factor, and that, in conditions such as those of Lehman's experiments, this factor would be absent. Again, in the case of clothed skin, danger might well occur from hindrance to evaporation.

No study has been made of the effects of dilute solutions of HCN on the skin. The solution of HCN vapour, from an atmospheric concentration, into sweat on the body surface might amount to the same thing, and constitute a greater risk than the strength of the vapour concentration in the atmosphere would suggest.

V. Post-mortem appearances in acute hydrocyanic acid poisoning

Referring to accounts of two fatal cases of acute poisoning in man, Hamilton (1925) mentions a blue-green coloration of the liver and of the cerebral grey matter, and colour changes in other tissues, and Rambousek (1913) and Henderson and Haggard (1927) refer to the bright red colour of the blood due to O_2 not being extracted from it by the tissues.

A careful autopsy was made of every animal used in the experiments described in this report, and in no case could either of these features be elicited.

In most cases the blood in the inferior vena cava was rather darker than normal, and this tended to occur with an engorged right side of the heart—exactly the picture which would be expected in an animal dying with symptoms of oxygen deficiency, as many did in this series.

It was suggested that a blue-green coloration might occur as a post-mortem change. In order to test this, four goats were killed by HCN inhalation (a concentration in the order of 1 in 2500), and autopsies were carried out at intervals up to 72 hours after death. Although the weather was mild and decomposition fairly rapid, no degree of any abnormal coloration could be detected in the brain, the liver, or in any other organ.

The smell of HCN was naturally strong in all animals dying from experiments or freshly killed, but in most cases it was not possible to trace this smell to any definite organ.

The number of autopsies conducted on animals in the whole series comprised in these experiments was: goats 4, guinea-pigs 11, rabbits 56, and it cannot be claimed that any single appearance, or combination of appearances, was found which could be described as characteristic of poisoning by HCN.

Apart from the transient smell, and the history of the casualty, it is not considered that a diagnosis of "Poisoning by a Cyanogen compound" could have been made in any animal of this series from post-mortem appearances alone.

VI. Conclusions

1. Even in a small apparatus, a concentration of HCN cannot be expected to maintain its initial, or calculated, level without frequent additions of fresh liquid acid. This tendency to a fall in concentration is increased by the presence of moisture, or by using clean apparatus which has not yet absorbed its quota of HCN, and probably by other factors.

2. An atmosphere saturated with HCN is readily absorbed by a skin surface amounting to $\frac{1}{60}$ of the body area in the guinea-pig, and will produce death if the exposure be prolonged.

3. Atmospheres containing HCN, in different concentrations, readily pass through the skin of the rabbit, which, with its respiratory system protected or excluded, can just tolerate a concentration which averages 1 in 210 for 90 min.

4. Sodium thiosulphate afforded a definite but limited degree of protection against the effects of skin absorption of HCN, in that it approximately doubled the time of exposure without symptoms, except in high concentrations.

5. Owing to the great volatility of HCN, the danger resulting from spilling the liquid on the bare skin appears to be slight as long as there is complete freedom for evaporation.

6. In the absence of the odour of the drug, acute poisoning with HCN does not appear to produce any post-mortem appearances, either macroscopic or microscopic, which are characteristic, or from which a diagnosis could reasonably be made.

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