SOME ASPECTS OF CARBON MONOXIDE ASPHYXIA

A THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE
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By

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INTRODUCTION

This thesis is the result of two years interest in carbon monoxide asphyxia. It was intended to be somewhat larger but it has been shortened by two occurrences. The first was the publication in the winter of 1938-39 of "Carbon Monoxide Asphyxia" by C.K. Drinker. A large amount of work which had been reviewed for this thesis was there set forth in a way which could be imitated but not improved. The second curtailing factor was the outbreak of war.

My interest in carbon monoxide lay mainly in two fields. Firstly there was the practical aspect of asphyxia of aircraft pilots and secondly the question of aids to present methods of treatment.

I have to thank the Air Ministry for permission to work on these problems and for the loan of certain apparatus.

The work was carried out chiefly at the London County Council North Western Group Laboratory, where, though it is a bacteriological unit, every help was given me by Dr. Robert Cruickshank and his staff.

While the L.C.C and the Air Ministry were very generous in loaning me apparatus and in other ways I must state that any opinions I may voice in this thesis are entirely personal and are not supported by the authority of either body.

The results reported in Sections V and VIII are the results of my own work. This was not directed or supervised in any way. Section VII is a survey of Methylene Blue therapy and endeavours to show how recent events have still further confused an already confused subject. The remainder of the thesis constitutes an endeavour to bind these sections into a coherent whole.

SECTION 1.

APPLIED PHYSIOLOGY

Description of Carbon Monoxide Gas.

Carbon monoxide is a colourless tasteless gas with a faintly acid odour said to resemble garlic. It is commonly said to be odourless. This is not so, but the small concentrations needed to produce symptoms will in nearly all cases pass unnoticed. It is slightly lighter than air but it readily mixes with the atmosphere to form a homogeneous mixture. Also it often shows little tendency to rise or mix if nooks and crannies are available for it to fill. There are many instances in the history of mining and quarrying where this gas has remained in crevices or in the interstices of rubble for days. Thence it has issued in sufficient quantities to cause symptoms or death long after the source of the gas, perhaps a series of blasting explosions or an underground fire has been removed or controlled. Its physical characteristics therefore make it insidious and it will be seen later that its action on the body tends to increase this insidiousness rather than diminish it.

Carbon monoxide is formed by the incomplete combustion of organic matter. While this usually occurs in

confined places, such as mine galleries or holds of ships, yet carbon monoxide is present under many much less obvious conditions. Complete combustion is the exception rather than the rule.

The Carriage and Utilisation of O_2 in the Body.

The poisonous effects of CO are normally due to its interference with the carriage of O_2. In vitro it may also interfere with its utilisation. We will therefore outline the normal workings of these mechanisms before discussing how CO interferes with them.

If O_2 were carried in simple solution roughly a tenth of the O_2 required by the body at rest could be pumped to the tissues by the heart.

250 ccs O_2 are absorbed per minute at rest.

120 litres of blood will carry 250 ccs O_2 in physical solution.

The heart at maximum output can probably only pump 25 litres per minute.

When it is considered that O_2 metabolism may increase tenfold on exercise the importance of haemoglobin may be assessed.

This haemoglobin which has a complex structure composed of a protein globin, and the iron porphyrin haematin, is a passive carrier of O_2. The iron porphyrin $C_{34} H_{30} O_4 N_4 Fe$

has the property of combining with O_2,NO or CO in the ratio of one molecule of gas per atom of Fe. This combination is reversible in a remarkable way which is best demonstrated by a dissociation curve (Fig. No.1) This shows how the haemoglobin under the conditions present in the body becomes highly oxygenated when O_2 is present at its tension in alveolar air, i.e. about 100 mm Hg, and how it gives up this O_2 fully as the O_2 tension drops to that of the tissues. Various figures are given for this. Some tissues apparently can reduce the O_2 tension practically to zero. Meakins and Davies (1920) and Barcroft and Shore (1912) found very low concentrations in venous blood under certain conditions - practically nil by the former and 0 - 9 volumes per cent by the latter observers. J.A. Campbell (1931) on the other hand cites much higher values, namely 50 - 20 mm.Hg for extra-cellular tissue fluid and 40 - 20 mm for the oxygen tension intracellularly. The central steep declivity of the S-curve shows how rapidly the haemoglobin gives up its O_2 when it is most needed.

Hartridge and Roughton (quoted by Roughton 1934) in their classical experiments have shown, using the reversion spectroscope that the acceptance of O_2 by reduced haemoglobin is remarkably rapid. Combination with O_2 while the blood is traversing the capillaries occurs in less than one hundredth of

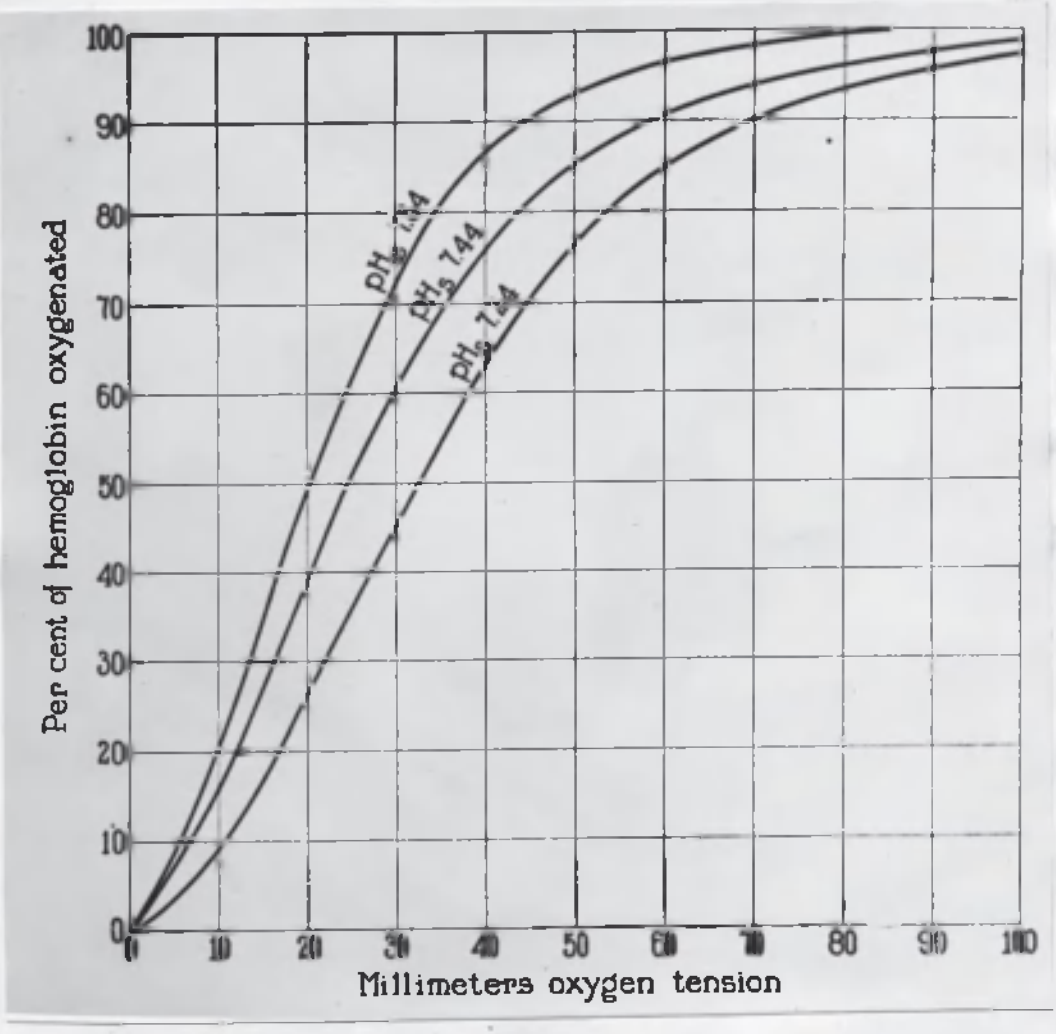

Per cent of hemoglobin oxygenated
100
90
80
70
60
50
40
30
20
10
0
pH 7.44
pH 7.44
pH 7.44
0
10
20
30
40
50
60
70
80
90
100
Millimeters oxygen tension

Fig. I

a second. We can therefore say that the blood is an ideal vehicle for O_2. It absorbs it rapidly and in sufficient quantity, and it gives it up rapidly, varying its speed of dissociation as the need presents itself.

The chief factors which affect this dissociation of oxyhaemoglobin are

1. Temperature. It may be said that the higher the temperature the less do O_2 and haemoglobin combine.

2. Saline concentration. At low O_2 tensions O_2 Hb is more readily dissociated in the presence of salts than in pure solution.

3. H ion concentration. As the pH value rises numerically the O_2 Hb curve shifts to the left.

The inflection in the O_2 dissociation curve of blood is apparently produced and stabilised by the salts present (Barcroft 1928). In the dissociation curve of haemoglobin this inflection is not present at pH 8.3 if the haemoglobin solution is salt free but it is rapidly produced by CO_2 which, to begin with, has a salt effect.

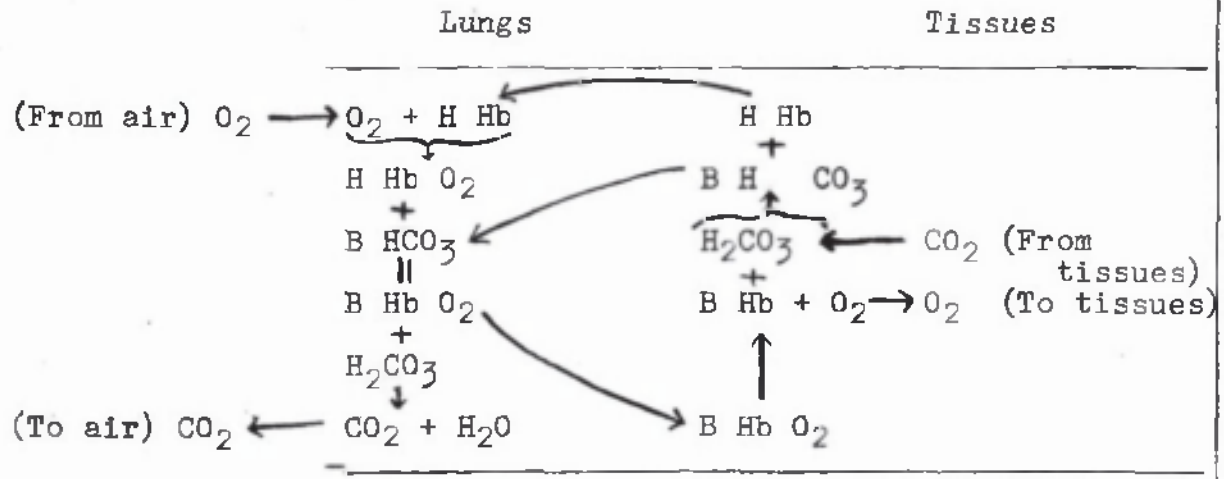
CO_2 has no specific effect. Barcroft has shown that other acids such as lactic may produce similar results.

The chemistry of the union and dissociation of Hb and O_2 is determined by the fact that O_2 Hb is a stronger acid

than reduced Hb. Reduced Hb and O_2 Hb are amphoteric. O_2 Hb has the greater tendency to combine with bases, i.e at a given pH

$$\frac{B\ Hb\ O_2}{H\ Hb\ O_2} > \frac{B\ Hb}{H\ Hb}$$

If this is considered the following scheme by Bodansky (1934) is self explanatory.



The carriage of O_2 up to the point of utilisation may now be considered. O_2 is presented to the blood in the alveolar air at a tension of about 100 mm.Hg. It then passes into the plasma and immediately into the Hb of the erythrocytes. How the O_2 passes the lining membrane of the lungs has given rise to a prolonged controversy. Haldane and Priestley (1935) maintain that while diffusion occurs and is usually sufficient, nevertheless a secretion mechanism exists to deal with

conditions of O_2 want. Barcroft, Krogh and Hartridge have brought forward very considerable evidence to the contrary. Diffusion in their view is the only mechanism present. The oxygen transported by the haemoglobin is then given up in response to what Barcroft calls "the call for oxygen by the tissues". Oxygen is continually being used up and if it is not available autolysis takes place. The oxygen therefore is seen to be travelling from a high tension source through several steps each with a lower tension than the preceding one until it arrives at the tissues which use it.

How the oxygen is utilised or rather how the end products of digestion are oxidised is still a matter of debate. Figure No.2 has been composed to give simply what may be considered as the present usual conception of the main system of oxidation. It can be described as a combination of the Warburg-Keilin oxidation system and Wieland-Thunberg dehydrogenase systems. The cytochrome acts as a hydrogen acceptor having been oxidised through the catalytic action of Warburg's "atmungsferment".

The methods of oxidation are obviously very complicated. A recent development is the discovery of Peters (1938) who has shown that Vitamin B_1 is concerned with substrate oxidation in that pyruvate is not broken down in its absence.

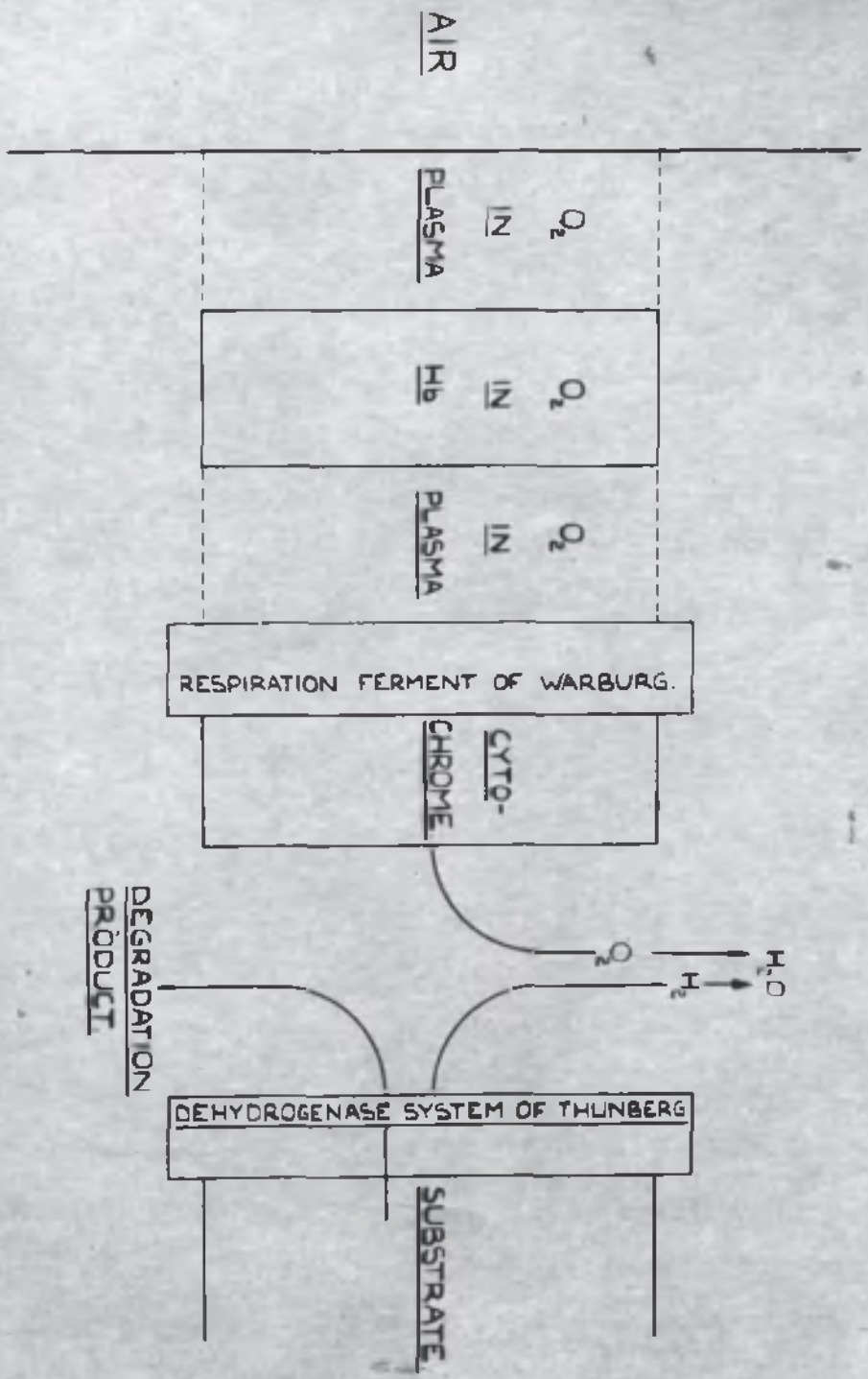

AIR
PLASMA
O_2 IN
Hb
O_2 IN
PLASMA
O_2 IN
RESPIRATION FERMENT OF WARBURG.
CYTO-CHROME
H_2O
H_2
DEGRADATION PRODUCT
DEHYDROGENASE SYSTEM OF THUNBERG
SUBSTRATE

Fig. 2

Effects of CO on O_2 carriage and utilisation.

CO and O_2 combine with the same group in the Hb molecule, each to the exclusion of the other.

Douglas, Haldane and Haldane (1912) say "When a solution containing haemoglobin is saturated with a gas mixture containing O_2 and CO, the relative proportions of haemoglobin which enter into combination with the two gases are proportional to the relative partial pressures of the two gases, allowing for the fact that the affinity of CO for haemoglobin is about 300 times greater than that of O_2"

That is

$$\frac{(\text{Hb CO})}{(\text{Hb } O_2)} = K \frac{\text{P CO}}{\text{P } O_2}$$

Sendroy, Liu and Van Slyke found that K = 210, and lately E.M. Killick has found that K = 240. The last figure is probably most accurate owing to improvements in gasometric technique. The original work of Douglas, Haldane and Haldane was done by the carmine titration method. K is not affected by changes in pH, in CO_2 tension or in electrolyte content of the blood but it is affected strongly by heat and light. Barcroft (1928) found that lowering the temperature of shed human blood from 38 deg to 13 deg increased K by one third. The effect of light is discussed in more detail in Section VIII of this thesis

Light has a strong dissociating effect on CO Hb and relatively little on O_2 Hb.

Under one condition the presence of CO has been found to increase the oxygenation of blood. This is when the blood is exposed to oxygen under low tension. It is due to the S-shaped curve of O_2 dissociation.

Peters and Van Slyke (1931) say of this "It is as though the lust of reduced haemoglobin for oxygen increased with incomplete satisfaction of its appetite. And because of the interchangeable nature of O_2 and CO, the increase can be caused by partial satisfaction with either gas ..... When blood is more than 50 per cent oxygenated, addition of CO has only the oxygen-ejecting effect from the start"

It was early discovered that the symptoms of CO poisoning are not to be estimated by the oxygen carrying ability of the blood. Haldane and Priestley (1935) point out that a patient suffering from anaemia when Hb is reduced to half may be carrying on his usual work but a person with his blood half saturated with CO is practically helpless. This was explained by Douglas, Haldane and Haldane (1912) who discovered that as the blood became saturated with CO so it held more tightly to its remaining oxygen. The S-shape of the oxygen dissociation curve is gradually lost as the CO Hb

figure rises so that the oxygen tension ofthe tissues must fall to a lower level before the blood will part with its oxygen.

There are other iron compounds in the body which will combine readily with CO, the most important of which is the Respiratory Enzyme of Warburg. However, while the formula for the proportions of the respiratory ferment which will combine with CO and O_2 when in contact with the two gases is the same as that for haemoglobin the value of K is very different. Warburg (1925,1930) found that CO inhibited cell respiration but only if exerting a pressure of one atmosphere. It must be evident that the respiratory enzyme plays no part in CO asphyxia in man.

Haldane's classical experiments with cockroaches and mice should be considered in connection with the above facts Haldane showed that CO was, apart from its effect on haemoglobin inert by placing a cockroach, which has no haemoglobin, in an atmosphere of 20 per cent O_2 and 80 per cent CO. The cockroach was still alive and well after two weeks.

Later Haldane added CO to the atmosphere breathed by mice till all O_2 in the haemoglobin was replaced. The mice died but if the O_2 pressure was increased from a fifth of an atmosphere to two atmospheres the mice did not die,as there was

then enough O_2 in the plasma to oxygenate the tissues and there was not enough CO in inhibit utilisation.

Mott (1907) described a case where he found, post mortem, extensive capillary haemorrhage in the brain and he deduced from this that there was an acute fatty change of the capillary walls caused by poisoning by the gas.

This theory has had little support and there is a large body of evidence in support of Haldanes conclusions. Thus Haggard (1922) grew successfully cultures of the neuroblast of the chicken embryo in an atmosphere containing 79 per cent carbon monoxide. Yant and his associates (1934) conducted a very extensive investigation in which they compared the effects of CO asphyxia with simple deprivation of oxygen from the air breathed. The results are too extensive to quote here but it may be said that for all practical purposes the results were the same.

To reiterate, the effect of carbon monoxide when breathed in the concentrations met in every day life, is twofold It reduces the amount of oxygen carried by the blood to the tissues and it makes the blood cling more tightly to the oxygen it does carry. It does not directly affect tissue respiration.

SECTION 11.

SYMPTOMS OF CARBON MONOXIDE ASPHYXIA.

These are divided according to whether they are the result of acute or chronic poisoning, and whether they are immediate or postponed. Of the immediate symptoms it may be said that the victim will either recover or succumb and that treatment in many cases will prevent the latter, but the postponed or after-symptoms are permanent and incurable. They are the results of organic damage which occurred at the time of the poisoning. Prevention is their only cure.

(a) Acute poisoning.

This may again be divided into two types. The first, which is caused by an overwhelming quantity of gas, is called by French authors "l'intoxication massive". The second is what may be called normal acute poisoning. The former is happily far from common and miners, who are probably more often exposed to CO poisoning than any other workmen, are seldom overcome in this way. Cases have been reported by workmen bending over leaking gas mains, inhaling large quantities of gas and immediately dropping dead. Numerous cases have been reported also where the patient having been rendered unconscious by breathing a massive concentration of gas has been resuscitated only to die shortly after. Of

"l'intoxication massive" little can be said regarding its symptomatology. It may be confined to the two states, collapse and death. In the ordinary type of acute poisoning however the multiplicity of symptoms is overwhelming. There is happily a train of symptoms which can be called characteristic. In a report to the American Bureau of Mines, Sayers and Yant (1923) summarised this. Their summary is quoted in full as it gives a clear and definite statement which is the result of vast experience and which can be taken as authoritative.

"The symptoms of carbon monoxide poisoning may be divided into two stages, the first covering the period beginning with normal and ending in syncope, and the second a paralysis of the central nervous system beginning in syncope, extending through coma, and ending in apnea.

Stage 1. Tightness across forehead, dilatation of cutaneous vessels, headache (frontal and basal), throbbing in temples, weariness, weakness, dizziness, nausea and vomiting, loss of strength and muscular control, increased pulse and respiratory rates, collapse. All these are greatly increased and accelerated with exercise on account of the additional need of oxygen in the tissues. Men at rest have often been exposed to carbon monoxide all day without noticing any marked ill

effects, but on walking home or exercising have experienced severe symptoms, even to unconsciousness.

It is seldom that all these symptoms are experienced by the same individual. Also, in some cases the poisoning may proceed to the stage of syncope without the victim feeling any of the subjective symptoms, this frequently occurring if the poisoning has been rapid.

Stage 2. Increased pulse and respiratory rates, fall of blood pressure, loss of muscular control, especially sphincters, loss of reflexes, coma usually with intermittent convulsions, Cheyne-Stokes respirations, slowing of pulse, respiration slow and shallow, cessation of respiration, death".

Two interesting cases of acute poisoning have lately been brought to the present writer's notice, one fatal the other not. The non-fatal case was a medical practitioner who was able to give a very clear picture of his condition. It has the advantage also that he has admitted that he was ignorant of the symptoms of carbon monoxide poisoning except in broadest outline so that while we have the advantage of his professional training in observation, his evidence is quite as unbiased as a layman's. The other case which is taken first shows how difficult the diagnosis of a case of gas poisoning may be.

Case 1. D.B. aged 46 years, a Jewish booking clerk, was brought into Paddington L.C.C. Hospital at 10.30 p.m on 5th August 1938. On admission he was conscious but oblivious to his surroundings. He would not answer questions and mumbled when disturbed. There was no indication that he understood anything said to him, and he appeared to be in a daze. He constantly felt the bedclothes with his fingers. He would take nothing by the mouth. He had incontinence of urine. There were no abnormal physical signs. Reflexes were normal with equal and active pupils. The urine showed a trace of albumen and of sugar. Acetone bodies were present. The specific gravity was 1010.

The history given by his wife was that he was quite normal in every way until the morning of the previous day, when he was found in a room with a gas fire turned on and unlit. On the 8th August he was seen by Sir Charles Wilson and later by Dr. MacDonald Critchley, neither of whom considered that his illness was due to coal gas poisoning, but that it was due to some uncertain neurological condition. On the 8th August also the following pathological examinations were carried out:

(a) Cerebro Spinal fluid:- Clear, under pressure of 120 m.m, W.R. negative, no barbiturates present,

Total protein	20 mgms /100 ccs
Globulin	No excess
Chlorides	740 mgms /100 ccs
Colloidal gold test	Negative
Cells (Lymphocytes	
Cells (Polymorphs	2/c m.m

(b) Blood

Blood sugar	60 mgms /100 ccs
Blood urea	53 mgms /100 ccs

On the 10th August he appeared very dehydrated and rectal salines were instituted. He later lapsed into coma and died at 12.30 p.m on the 11th August. His temperature remained high throughout and rose on one occasion to 104.2 deg F. Spectroscopic examination at no time showed the presence of carboxyhaemoglobin. This was however only carried out by a hand spectroscope.

The post mortem examination was carried out by Sir Bernard Spilsbury who found a bilateral softening of the basal nuclei and gave as his opinion that death was due to carbon monoxide poisoning. The inquest verdict was "Suicide while of unsound mind".

In this case there are seen some interesting points. The gassing occurred on the night of the 4th August. He was removed from the asphyxial atmosphere on the morning of the 5th

August. After removal he showed no sign of recovery and became slowly more and more comatose until his death seven days later. He showed several points of resemblance to a case reported by Pineas (1924). There were firstly the pseudonegativism of the patient, secondly the lethargy responding only to irritation and not to spoken commands, and thirdly the carphologia. This last symptom was perhaps not so marked as in Pineas's case. He refers to them as Wernicke's "hypermetamorphotic" movements. The pseudonegativism in Pineas's case was shown by the drawing away of the hand when his pulse was being taken and so on. In this case it was shown by his muttering when disturbed and his refusal to take anything by the mouth. The pyrexia is very noticeable. It is reported in the "Official History of the War" (1923) that a characteristic early symptom of CO poisoning is a lowering of the body temperature. Later when the patient is recovering there is a rapid rise in temperature with a rapid bounding pulse. This rise of temperature in a recovering case is shown in the next case reported. There was no evidence of any form of infection which might have caused the fever.

A further point to be noticed in this case is that while his blood and cerebro-spinal fluid showed no abnormal constituents his urine contained albumen, sugar and acetone.

Case 2. A medical practitioner in good health aged thirty five years. In this case the poisoning occurred in his car which was later discovered to have a large split in the silencer. This split had probably been present for a few days before the acute poisoning took place as he had noticed a general "heaviness" and loss of appetite with no apparent cause. On the day of the attack he drove his car, a fourteen horse power saloon, on his ordinary rounds in a small town near Hull from 10 a.m until 11.30 a.m. Then he drove to Scarborough the journey taking one and a half hours. He noticed at this time a slight headache and almost complete absence of appetite. He ate four small sandwiches and one bottle of beer. He then went into a cinema at ten minutes to one. Soon a frontal headache developed with a feeling of fulness and distension in the epigastrium with "heartburn". After thirty minutes he had to leave the cinema owing to a definite feeling of "grogginess" and to an extreme desire for fresh air. After driving the car for about a mile he walked down the cliff pathways. When about half way down nausea came on with slight weakness in the legs so he turned back up the slope. After 150 or 200 yards of this climb he began to feel really ill with extreme nausea and desire to vomit. His legs then "crumpled up" and he had to lie there for five or ten minutes. After this he struggled

on a few more yards when a passer-by came to his aid and brought him a drink of water. Immediately this was drunk he vomited very large amounts of fluid and began to feel slightly better. With assistance and rests every twenty or thirty yards he was able to return to his car, which he was able to drive to a hotel in a few minutes. He had at this time full mental control and was able to drive perfectly well, the muscular effort being much less than that required to stand or walk. On arrival at the hotel he passed a large watery motion, then fell asleep for about half an hour. He then drove home with all the windows and the roof open. By this time all the gastric symptoms had passed off but he felt "shivery". Though not dizzy he felt unsteady and disliked moving his head. Reading was impossible. After a light supper he slept fairly well till morning. He got up as usual but found himself constrained to walk slowly. He was able to do his normal work that day but "getting up stairs was a distinct effort". There were in the car his wife, her mother and his small son. Only his wife who was also sitting in front was affected and she only to the extent of headache. At no time during the attack did he lose consciousness, did he have any visual disturbance, or did he feel palpitations.

In this case there are some of the most interesting symptoms of CO intoxication well demonstrated. In the first

place there is the tendency to faint which Haldane and Priestley (1935) stress as being much more prominent in this than in other types of anoxaemia. Also prominent was the loss of power in the legs. Another feature was the shivering fit in the evening. It seems likely that this was due to a rise in temperature which has been mentioned as occurring frequently. Dizziness which is usually described as an almost constant symptom was absent. It will be noted too, that the severe symptoms commenced as he turned up the hill. This is very characteristic. Dr. T also said that when he was lying collapsed on the pavement he felt quite unable to move but his mind was functioning perfectly clearly. His chief anxieties were that he might lose control of his bowels or that he would be mistakenly arrested for drunkenness. This helplessness seems to be the symptom which most impresses itself on the victim. The experiences of Sir Clement Le Neve Foster in the Snaefell mine accident (Glaister & Logan 1914) are classical in this respect. Sir Clement had gone down the pit to assist in rescue work and was overcome by weakness when only a few yards away from the shaft where he could summon assistance. He knew that he had only these few feet to go yet he was completely unable to do so, nevertheless he was able to write a farewell letter to his wife which though

disjointed and reiterative was evidence that his mind was still reasoning soundly. While Dr. T's experiences were not so severe yet there is a marked resemblance. He had never heard of Sir Clement Foster's or any similar experience when he gave this history.

These two cases give an indication of the nature of severe and moderate acute poisoning. The important symptoms have been mentioned but there are many others. Nearly every case reported is able to produce some new variation. Thus Dibelius (1938) considers that the leading symptoms of acute CO poisoning are neurological. Besides the subjective symptoms the most important are nystagmus, pyramidal symptoms, sensory disturbances and a peculiar static ataxia. He contends that the usual belief that neurological symptoms are relatively uncommon is due to inadequate examination. On the face of it this belief is very reasonable as nerve is the first tissue to be affected by anoxia.

(b) Chronic Poisoning.

Henderson (1938) dismisses chronic carbon monoxide poisoning thus "Carbon monoxide is not a cumulative poison. There is therefore, no such condition as the expression "Chronic carbon monoxide poisoning" would imply ..... Repeated exposures ..... may temporarily, but only temporarily, impair health. More often a compensating polcythaemia develops, like

that in acclimatization to altitude".

Despite this broadside there are many who believe that there is such an entity.

If the criteria of Fetzer and Wieland (1934) for chronic CO poisoning are considered it will be seen that few cases of chronic poisoning can remain out of the many so called. These criteria are

1. That at no time should CO be present in such an amount that it would be possible for it to produce demonstrable pathological change after single or repeated action, and

2. That the after effects of acute poisoning are not to be regarded as chronic poisoning.

Chronic CO poisoning has been described by a very large number of observers not all of whom have used the criteria given above. Thus Symanski (1935) describes seven cases in engineers and technicians caused by the waste gases of two crucible furnaces. The general symptoms were headache, nausea and nervous heart troubles. Two suffered from urticaria which later recurred on breathing the exhaust gases from a railway engine. Dassell (1932) reported on seven persons who were exposed to very low concentrations of CO for from eight to nine hours a day for several months. The symptoms were fatigue, headache, difficulty in breathing, indigestion, cardiac pain,

nervous affections etc. All recovered but only after a lengthy period in hospital. Neither of these authors appear to have the same idea of what constitutes chronic poisoning as have Henderson or Fetzer and Wieland.

Beck (1936) conducted an extensive investigation based on the study and analysis of a series of ninety seven cases. "The duration of intermittent exposure ranged from several months to eighteen years. The chief complaints were headache, vertigo, nervousness, neuromuscular pains, digestive disturbances, dyspnoea and palpitation. The most outstanding symptom was headache which occurred in fifty-eight of the cases ..... Next to headache in frequency was the symptom of weakness, which was mentioned in the history of fifty-two patients. This was usually general. However, many of the patients emphasised particularly weakness in the lower extremities. Practically all the patients in the series exhibited functional nervous and mental symptoms. Many were confirmed neurotics. Some were definitely psychotic".

Fetzer and Wieland (1934) carried out animal experiments with inconclusive results but believe that there is a clinical picture, definite though difficult to prove.

(c) Acclimatisation to Carbon monoxide.

Haldane and Lorraine Smith (1896) found that in

isolated experiments on themselves CO had a greater effect than when on a previous occasion it had been breathed more or less continuously over a period. They reasoned from this that they had become acclimatised.

The adaptation of the individual was first intentionally investigated by Nasmith and Graham (1906) who exposed guinea pigs for one hour a day to a CO concentration resulting in a 50 per cent saturation of the blood. They observed no effect on the blood, weight or health. When the animals had their blood left constantly saturated to 25 per cent with CO Hb there was an increase in the erythrocytes so that only 9 per cent of the original O_2 carrying power was lost.

Campbell (1929, 1932, 1933, 1935) carried out a series of experiments on animals. He found that mice which apparently throve in an atmosphere of 0.3 per cent carbon monoxide were infertile (1933). He believes (1932) that hypertrophy of the heart probably follows the increase in viscosity of the blood which is caused by the increase in erythrocytes. It is this increase which is the usual criterion of acclimatisation. He says (1929) "all the pathological evidence, the value of which has previously been underestimated, indicates that circulatory failure was present in some degree even in animals which appeared to be more or less acclimatised.

Killick (1936) after work on human acclimatisation came to some very interesting conclusions. She found that acclimatisation to CO could not be compared to acclimatisation to altitude which, if CO only acts by virtue of anoxaemia should be possible. It was observed that the relationship between the percentage of CO breathed and the saturation in the blood was altered with repeated exposure. This was found not to be an acquired characteristic of the blood, whether of quantity or of quality, but of the body as a whole. The acclimatisation was over a prolonged period. There was no increase in the red cells or any evidence of adaptation whatever.

In further experiments Killick (1937) found that in mice acclimatisation was readily shown. Fertility tests were not carried out. There was no increase in blood volume erythrocyte count and reticulocyte count associated with enlargement of the spleen. She did not observe enlargement of the heart as had Campbell.

This work is particularly important as it casts a certain shadow of doubt on Haldane's assertions that the results of CO inhalation can all be explained by anoxia and that CO is to all intents andpurposes an inert gas.

In a paper read to the Physiological Society on December 16th 1939 Miss Killick described increase in haemoglobin and red cell count in workmen daily exposed to producer gas. The value of K was also observed to be abnormally low in five of the seven cases investigated. Miss Killick suggested that it was perhaps a question of selection; that the workers with a high K would be unable to stand the work and would give in. On the other hand she found that symptoms of poisoning diminished with the length of time engaged in this work.

Miss Killick has since told the present writer that she believes that the difference between these results and those obtained by her in 1936 were due simply to the more frequent exposures of the present series.

SECTION III.

PATHOLOGY OF CARBON MONOXIDE ASPHYXIA.

It would be impossible, even if it were desirable in a thesis, to review the entire literature on the pathology of CO asphyxia. Owing to its medico-legal importance this has always been extremely voluminous.

It has been seen that CO produces its effects by producing an anoxaemia. Its effects are therefore most pronounced in the tissues where most oxygen is needed. These are the central nervous system and the myocardium. Some recent work on the effect of CO on nerve tissue and heart will be mentioned with some which has not found itself into the published symposia on CO asphyxia.

Yant et alia (1934) after extensive investigation into various degrees of CO asphyxia found that even short periods of asphyxia caused pathological changes in the endothelium of the capillaries. There is first dilatation then passage of fluid to the tissues. This results in the erythrocytes packing tight causing perivascular oedema and eventually haemorrhage. Once changes as severe as this have occurred a vicious circle is produced. Thrombosis and

embolism may cause infarcts or merely add to the CO anoxia by diminishing the blood flow to certain parts. It is obvious that this is particularly dangerous in the C.N.S and also that almost any symptom complex may be produced. The classical symmetrical softening of the lenticular nuclei can be replaced by or accompanied by an infinite variety of lesion.

Greving and Geng (1932) report a case characterised by hyperpyrexia, who died 3½ hours after poisoning. There was a symmetrical softening of the pallidum and haemorrhage in other parts of the brain. These haemorrhages were chiefly in the paraventricular nucleus and in the central medullary grey matter of the third ventricle above the corpora mamillaria. It was probably these last which were responsible for the hyperpyrexia. Nichols and Keller (1937) quote Meyer and Strecker who found that, though the globus pallidus is frequently affected to the greater extent, often the white matter is most severely affected. Considering these facts there seems little point in recording, as has been done very largely, the multitudinous variations of nervous symptoms in CO poisoning. Dibelius (1938) for example says that eye symptoms especially nystagmus are the most common. The fact that very many other observers have been interested in the ocular manifestations of CO asphyxia and have only recorded this symptom occasionally

means that either they have not observed this nystagmus which seems unlikely, or that Dibelius has had a series of cases which have happened by chance to be most affected in this particular way. In view of the method by which the symptoms are caused the latter seems most likely. The publication of many and lengthy case histories showing different nervous and psychical symptoms is unnecessary for the proper understanding of CO poisoning. The problem is primarily one of tissue nutrition and of histology. It is possible that case histories added to histological investigation might be of general neurological value in mapping the functions of the various parts of the brain but even this is improbable as the cases which can be examined thus are necessarily fatal ones and lesser effects are masked by greater.

In view of the present day belief that angina pectoris is caused by anoxia of the heart muscle it would seem reasonable to suppose that angina would, at least occasionally, occur as a symptom of CO anoxaemia. This in fact is the case but only in extreme cases of poisoning or where there is an already diseased coronary artery.

Colvin (1927-28) in a severe case of motor car exhaust poisoning found a typical electrocardiagram of intraventricular block. After recovery from the poisoning

the heart showed no abnormality.

Glaister and Logan (1914) record cases of delayed heart failure after gassing.

Stearns, Drinker and Shaughnessy (1938) carried out electrocardiagrams on twenty two cases of CO asphyxia. They concluded that CO might produce no important electrocardiographic changes. The commonest result was an abnormality in the T wave or in the S-T segment. Paroxysmal auricular fibrillation may occur. One case of transitory intraventricular block occurred. No cases of auriculo-ventricular block definitely attributable to CO occurred but one case originally abnormal was aggravated.

Beck and Suter (1938) have made a comprehensive survey of the literature and say "we feel convinced that carbon monoxide has an important etiologic role in the development of myocardial lesions after asphyxiation with carbon monoxide in patients with no history of pre-existing heart disease".

Among the evidence quoted by these authors is that Buchner has found necrotic changes in the heart muscle of rabbits after mild CO intoxication. This is contrary to the majority of experience.

The general impression is that a normal heart is little affected but that an already burdened heart may give way easily.

SECTION IV.

SOURCES OF CARBON MONOXIDE

Carbon monoxide is a very widely distributed gas and it is possible that few people do not have at one time or another a considerable amount of carboxyhaemoglobin in their blood. Thus Hartridge (1920) has stated that the blood of a moderate cigarette smoker may be saturated to six per cent. Gettler and Mattice (1933) found when carrying out investigations in street cleaners that the highest CO-saturation readings were found in the blood of individuals who had smoked on the way to the laboratory. They came to the conclusion that smoking appreciably increases the amount of carboxy-haemoglobin in the blood.

From this we pass to a source possibly little more important in actual fact but one which arouses more interest and controversy. This is the air of towns. The sources of CO in towns are chiefly (a) household and factory fires and (b) motor car exhausts. It would appear that the former produces one part CO to every 12 parts CO_2 (Haldane and Priestley 1935). Haldane states that this would probably give a proportion of one part CO in 10,000 parts of air in a

thick fog, thereby producing in those breathing it a carboxy-haemoglobin percentage of about twelve to sixteen. The air of a city is of course always moving, not only horizontally but also vertically. The air among houses is much warmer than over the surrounding country and considerable up-currents are produced. The climatic conditions which favour high concentrations of CO in the streets of a city are those, therefore, which prevent air movements. Fog is the best example of such weather.

Numerous social and public organisations have at different times endeavoured to prove that city workers, such as traffic policemen or street cleaners, are particularly prone to disease owing to their exposure to CO. A considerable amount of investigation has been carried out in cities throughout the world. Table No.1 gives the major findings of a number of these air analyses. The percentage carboxyhaemoglobin is also shown which would result if the concentration of CO in the atmosphere as shown by the different workers was maintained and breathed until complete equilibrium was reached.

Wilson, Gates, Owen and Dawson (1926) carried out estimations of the CO-haemoglobin percentage in the blood of fourteen Philadelphia traffic policemen after eight hours duty. Using a colorimetric method of estimation they found values

TABLE No.1

AIR ANALYSES OF AIR OF VARIOUS CITIES.

Remarks	Percentage Hb combined with CO - Affinity 210 X	Percentage Hb combined with CO - Affinity 300 X
	%	%
A man standing a few feet from the exhaust of a running car engine may be breathing 4 - 6 parts /10,000. One part common where traffic is heavy	12 - 22	16 - 29
"The only individual who may possibly be exposed to a health hazard from inhaling street air containing automobile exhaust gas is the traffic officer"	10	13
These workers considered that the air of automobile boulevards contains enough CO to be regarded as a danger to those who work (especially energetically) over a period of hours	1 3 6	2 4 8
Suggests danger to inhabitants of centre of city from general products of petrol combustion Similar results	6 4	8 6
Highest value 0.44	1	2
Only one sample over 1 part - Bottle held near exhaust of car Two samples gave 1 part	6	8

X. This assumes complete equilibration.

City	Investigators	Where samples taken.	Parts of CO in 10,000 of air.
New York	Haggard & Greenberg (1923)	Traffic	1 - 2
14 cities in U.S.A.	Bloomfield & Isbell (1928)	Congested traffic	0.8 (average)
Chicago	Connolly, Martinek and Aeberly (1928)	(i) Residential & industrial streets	0.125
		(ii) Traffic & car line streets	0.250
		(iii) Automobile boulevards	0.476
Paris	Florentin (1927)	Streets	Up to 0.5
"	Cambier & Marcy (1928)	Streets	0.1 to 0.4
Dresden	Supfle, Hofmann & May (1933)	Streets	Up to 0.1
London	Hepple (1930)	Traffic blocks	0.5

Remarks	X Percentage Hb combined with CO - Affinity 210	X Percentage Hb combined with CO - Affinity 300
	%	%
A man standing a few feet from the exhaust of a running car engine may be breathing 4 - 6 parts /10,000. One part common where traffic is heavy	12 - 22	16 - 29
"The only individual who may possibly be exposed to a health hazard from inhaling street air containing automobile exhaust gas is the traffic officer"	10	13
These workers considered that the air of automobile boulevards contains enough CO to be regarded as a danger to those who work (especially energetically) over a period of hours	1 3 6	2 4 8
Suggests danger to inhabitants of centre of city from general products of petrol combustion Similar results	6 4	8 6
Highest value 0.44	1	2
Only one sample over 1 part - Bottle held near exhaust of car Two samples gave 1 part	6	8

X. This assumes complete equilibration.

ranging from zero to thirty per cent. (Six were from 20% to 38%). But using the Van Slyke method figures between five per cent, and thirteen per cent, were obtained. Gettler and Mattice (1933) examined twelve New York street cleaners and found CO saturation of from one to seven per cent. Two taxi-drivers were found to show from eight to nineteen per cent saturation.

Carbon monoxide is frequently found in tunnels. In the early days of railways when tunnels were poorly ventilated and all locomotives were propelled by steam, CO poisoning of engine drivers was not uncommon. Haldane in 1897 found in the London Underground Railway tunnels before they were electrified that CO could be present in as high a proportion as six per cent. This is no longer a serious danger in this country but motor vehicle tunnels are still with us. Regan (1930) estimated the CO content of the air in the Blackwall and Rotherhithe tunnels. He found that the average lay between 0.76 in one series and 1.17 parts CO per 10,000 of air in others. On one occasion 11.5 and 8.5 parts CO were observed. When the Hudson River tunnels were being constructed Yandell Henderson advised that they be so constructed that persons passing through the tunnels would be exposed to not more than four parts of CO in 10,000 parts of

air for not longer than forty five minutes. In the Hudson and also the Mersey tunnels ventilation fans are varied automatically according to Hopcalite indicators in the tunnels.

A very frequent and much publicised source of CO poisoning is lighting gas. The cases can be divided into those which are the results of suicidal attempts and those caused by the insidious nature of the gas. The former need no elaboration but it may appear surprising that lighting gas with its extremely unpleasant odour can be called insidious. It may however be insidious in two ways. Firstly one may be overcome by a gradually increasing leak, perhaps when asleep, as one's sense of smell may become fatigued and one's senses may be dulled. Secondly if the leak is below ground the gas may lose its odoriferous constituents as it filters through. Water gas is not now used in this country as an illuminant although it gives an excellent light when used with an incandescent mantle. It contains about 30 per cent of CO and is, therefore, considerably more dangerous than coal gas. The postmortem appearances of a person who has died of coal gas poisoning are those of CO-poisoning and the percentage carboxyhaemoglobin is usually from sixty to eighty per cent.

CO poisoning is frequently met with in ships. Here it is found in coal trimmers owing to the CO formed by the slow oxidation of the coal in the bunkers.

CO has been considered as a "War gas" but it has not been found possible so to use it chiefly owing to the difficulty of maintaining a sufficiently high concentration in the open over a period long enough to have the desired effect. If this could be done it would be a very important weapon as the Service respirator is of course useless against it. Although CO is not a "War gas" yet it can be present in great amount during military operations. It is for example present "in dangerous quantities as a result of bursts of high explosive bombs, in blasting operations, and in burning buildings, if the conditions confine the fumes in a narrow space" (A.R.P. Handbook No.3). It is also present during intensive artillery fire both near the guns and near the exploding projectiles. This has been described by Logan (1939)

It is however in connection with Mines that CO has attracted most attention. The chief gases which contaminate the air of coal mines are (a) Blackdamp (b) Firedamp (c) Afterdamp (d) Whitedamp and (e) Smoke. Of these (c) (d) and (e) may be considered as sources of CO.

Afterdamp, which is the mixture of gases left after an explosion, was estimated by the French Firedamp Commission (cited by Glaister and Logan 1914) to contain 3.9 per cent CO but Haldane and Priestley (1935) give the figure estimated by

Wheeler of 8.6%. This latter result was obtained from the air following a coal dust explosion. This is by far the commonest cause of mine explosions and the residual gas is of course extremely deadly. The amount of CO present is so great that a person breathing it, even if he is not rendered unconscious immediately, is unable to escape since he suffers a sudden onset of faintness and extreme muscular weakness. The mental aberrations especially the stubbornness of anoxaemia are of course added changes. The term "Whitedamp" in this country is used to denote the gaseous products of underground fires. In America it is apparently used as a colloquial term for CO. "Whitedamp" may or may not include "Smoke". From a practical point of view however it hardly matters as they are all products of oxidation whether slow or fast and the poisonous effect is due to CO and the results of breathing them are similar to those caused by "Blackdamp". The entire atmosphere of a coal mine contains at all times a small proportion of CO caused by the slow oxidation of coal and timber.

There are innumerable other sources of carbon monoxide of all degrees of importance but the ones mentioned give a fair indication of the wide distribution and potential danger of the gas.

It is interesting that this gas has provided an

easy death for suicides since classical times. Seneca ended his life with the fumes from a charcoal brazier and, especially in France, this form of room heating until recently has had many victims. The closed garage and the gas oven have however modernised the method if not the result.

SECTION V.

CARBON MONOXIDE IN AIRCRAFT

Sources of Carbon Monoxide in Aircraft Cabins.

1. The sources of CO in aircraft cabins are two in number, the engine exhaust gases and, in the case of military machines, gun exhaust gases.

Peters and Van Slyke (1931) state that as much as 30 per cent of the carbon in the fuel of even a well adjusted petrol engine may be converted into CO. It is thus apparent that an aero engine which has a petrol consumption of approximately 60 gallons per hour must produce considerable quantities of this gas.

There appears to be no doubt that many of the more elderly types of machine contained dangerous concentrations of exhaust gas CO. White (1936) found 20 per cent saturation of the blood with CO in pilot and passenger after flights lasting from four to six hours. He considered this to be dangerous because prolonged exposure to low concentrations would be "likely to produce a cumulative effect". Gowan (1937) describes three cases of acute CO poisoning in aircraft and mentions others. Goett (1937) found that a certain type of

aircraft used as an ambulance had the exceedingly dangerous concentration of seven parts in 10,000 of air. He recommends that one part in 15,000 ofair be the maximum permissible and quotes M.C. Grow ofthe U.S. Air Corps giving a maximum of one part in 20,000 of air. Sayers and Davenport (1936) quote Clousing, who says that the figure of one part in 20,000 was arrived at as a result of many tests and much research. They go on to say "It was known for some time that in military airplanes with short stack radial engines the exhaust gas was breathed by the pilot to some extent. Tests showed that sometimes the pilot breathed as much as 3 parts CO in 10,000 parts air. When it was realised that 3 parts in 10,000 caused dizziness and other discomforts if breathed for 3 to 4 hours, the design of those airplanes was changed. Much of the disagreeableness and air sickness of flight in airplanes of older design andperhaps many of the unexplained accidents were due to CO".

Styns (1937) a medical officer of the Belgian Air Force analysed simultaneously the gases of the cabin and of the exhaust pipe. The machine used was a Fairey Fox. He found

1. At cruising engine revolutions in level flight that the amount of CO in the cabin was on an average 1/1000 of that in the exhaust gases.

2. When taxying exhaust gases only penetrate easily into the cabin when the cabin is open.

3. When gliding or spinning the air of the cabin is less vitiated.

His general conclusions were that the maximum amount found in the cabin during flight was 0.67 parts in 10,000 and he considered that this was safe.

However, all these reports refer to aircraft designed many years ago. In the last year or two the "streamlining" of aircraft has been very greatly improved, and partly as a result of this, and partly owing to more powerful engines, speeds have almost doubled since the papers mentioned above were published. This increase in speed must reduce the proportion of CO in the atmosphere round the machine, and the improved streamlining renders it less likely to swirl in eddies into the cabin.

On the other hand the gases from the breeches of machine guns have only in recent years assumed any importance. This is owing to the fact that until recently machine gunners fired from open gun mountings. Now owing to the increased speeds attained this is impossible, and firing is carried out from rotatable turrets, the breech of the gun being inside. As far as the present writer is aware there is no medical

literature on the subject.

The propellant used for the machine guns is Cordite. The following is a report on its properties received from Dr. Reeve of No.1 Air Armament School R.A.F.

"Cordite is composed of:-

Nitroglycerin,

Nitrocellulose and

Mineral Jelly.

On theoretical grounds, the products of combustion may be estimated to be:-

Carbon dioxide	16.3 per cent by volume
Carbon monoxide	35.1 per cent by volume
Water (as vapour)	34.3 per cent by volume
Nitrogen	14.3 per cent by volume

As a result of practical experiments in which M.D. cordite was exploded in a closed vessel at a pressure similar to that obtaining in the barrel of a gun, the following figures have been obtained:-

Carbon dioxide	14.85 per cent by volume
Carbon monoxide	34.87 per cent by volume
Hydrogen	18.95 per cent by volume
Methane	.29 per cent by volume
Nitrogen	12.89 per cent by volume

Water vapour 18.15 per cent by volume

Of these only carbon monoxide need be considered as a toxic constituent, and, as will be seen from the above figures, it is by no means beyond the bounds of possibility that a dangerous concentration of this gas might be obtained if sustained fire were maintained from a turret which was inadequately ventilated.

A reference can be traced to "dense clouds of reddish-brown fumes" which may be observed when large guns are fired. This seems to indicate the formation of nitric oxide, spontaneously oxidised to nitrogen peroxide on contact with the air. On the other hand, these fumes do not appear to be observed when smaller guns are fired. It is undoubtedly possible that larger proportions of nitric oxide might be formed when large quantities of cordite are exploded, but there is no evidence to indicate that nitric oxide would be present, except as small traces, among the products of combustion of the cordite charges used in small arms ammunition.

Nitrocellulose propellants which might possibly be used in practice, especially in war time, contain smaller proportion of oxygen. Products of combustion of these propellants would therefore contain higher proportions of carbon monoxide and free hydrogen than are yielded by cordites.

With all propellants, very small quantities of solid products are obtained on combustion, but these are probably derived from the cap composition and are relatively unimportant".

The majority of these gases escape from the muzzle of the gun but a considerable amount escapes from the breech during the process of admitting the next round. The machine guns used have a rate of fire ranging from 700 rounds to 1200 rounds per minute.

The concentration of CO which can be considered permissible in aircraft

The question should be divided into three as follows:-

(a) What is the amount permissible on the ground before taking off?

(b) What is the amount permissible at low altitudes only?

(c) What is the amount permissible at high altitudes?

There is always a likelihood of the admission of exhaust gases into a machine on the ground. Assuming that this clears from the cabin when the machine takes off, a calculation might be employed similar to that used by Henderson and his associates (1921-22) when considering concentrations of CO which would be safe in the Holland vehicular tunnels under the Hudson

River. They used Haldane's findings that healthy adults do not complain of symptoms of CO poisoning until the concentration of carboxyhaemoglobin is about 20 per cent. They then conducted experiments which produced the results shown in Fig.3 With these data which were verified in various ways the recommendation was made that the maximum concentration permitted in the tunnel should be 4 parts CO in 10,000 of air. This could be breathed for one hour without effect.

This figure, i.e. 4 parts in 10,000 would appear to be equally applicable to aircraft when running up and taxying. It is seldom that a pilot sits for more than fifteen minutes in the cabin before a take-off, and three quarters of an hour can be taken as an absolute limit.

The second question, namely, how much CO can be permitted at low altitudes is not entirely academic. The common and convenient height for cross country non-operational flying is about 2000 feet. If we take a barometric pressure of 700 m.m Hg as an approximate figure for this height the pressure of Oxygen entering the alveoli will be, allowing 47 m.m Hg for water vapour pressure

$$\frac{20.93 \times (700 - 47)}{100} = 137 \text{ m.m}$$

If there is no increase in the speed of air flow through the lungs the oxygen tension in the alveoli will be reduced by the

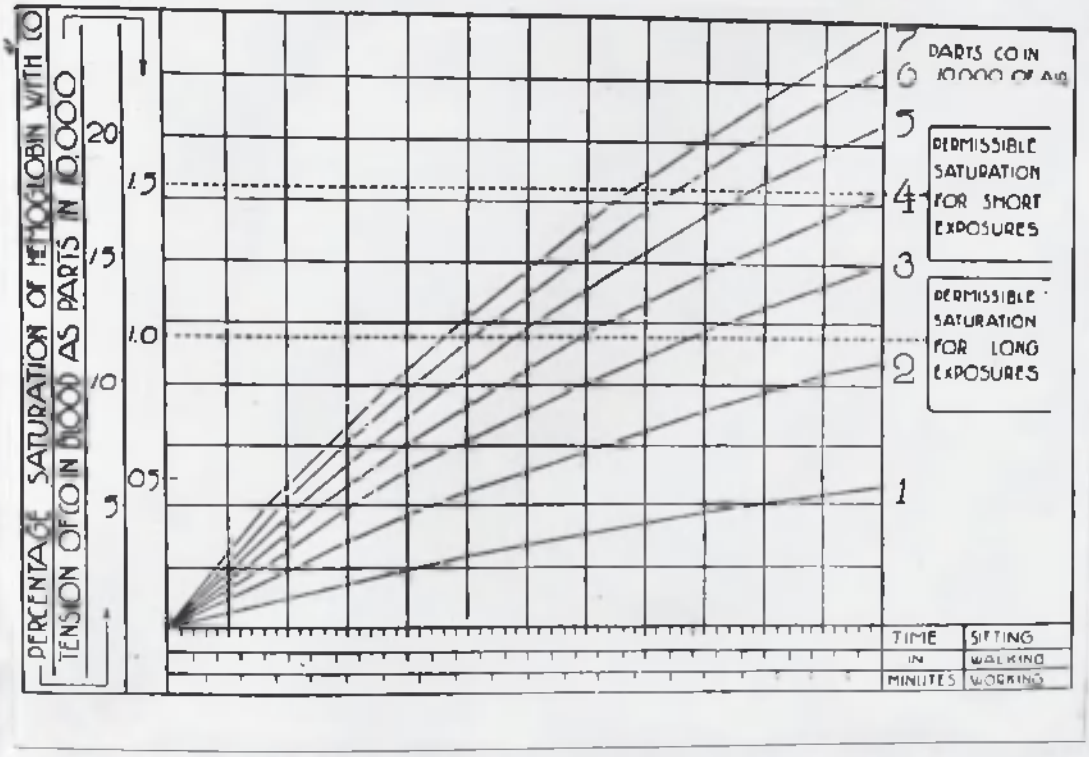

PERCENTAGE SATURATION OF HAEMOGLOBIN WITH CO
TENSION OF CO IN BLOOD AS PARTS IN 10,000
20
15
10
5
2.0
1.5
1.0
0.5
PARTS CO IN
PERMISSIBLE SATURATION FOR SHORT EXPOSURES
PERMISSIBLE SATURATION FOR LONG EXPOSURES
TIME IN MINUTES
SITTING
WALKING
WORKING

Fig. 3

same amount as at sea level, i.e by 49 m.m. The drop in oxygen tension between the alveolar air and the arterial blood has been variously estimated but 5 m.m may be taken as a minimum and 20 m.m a maximum. This will bring the arterial oxygen tension to from 68 to 83 m.m.Hg. If pH is taken as 7.44, reference to Fig.1 will show that the percentage of oxyhaemoglobin in the arterial blood is then 93 per cent to 96 per cent. This could be considered as normal to low normal readings. That is to say at 2000 feet, without hyperpnoea the interaction of CO, O_2 and haemoglobin is likely to be the same as on ground level.

At 660 m.m Hg atmospheric pressure which corresponds to a height of approximately 4,000 feet the haemoglobin is saturated with oxygen from 90 per cent to 95 per cent. At 530 m.m Hg pressure or approximately 10,000 feet the haemoglobin is only 63 per cent to 83 per cent oxygenated, and at 400 m.m pressure or about 18,000 feet the theoretical amount of oxyhaemoglobin would be from 8 per cent to 39 per cent. These figures are of course approximations. They will also vary with the individual, with pH value, with temperature, and so on.

It can therefore be said that at low altitudes the danger to the aviator is similar to the danger to him on the ground with the additional fact that small concentrations of CO might be a precipitating cause of accident owing to a

quickened onset of fatigue.

Long flights, apart from record breaking attempts seldom last for more than six or seven hours. The problems to be considered are therefore : (a) What is the lowest concentration of CO Hb likely to be dangerous to a tired aviator when he is about to land? and (b) What is the maximum amount of CO in the air breathed which will produce this concentration?

Yandell Henderson and his associates (1921-22) give the following table in regard to the probable effects of CO:-

"1. When the time of exposure in hours, times the concentration of carbon monoxide in parts per 10,000 equals 3, there is no perceptible effect.

2. When the result is 6, there is just a perceptible effect.

3. When the result is 9, there will be a headache and nausea.

4. When the result is 15 or more, the conditions are dangerous to life.

5. If the volume of breathing is increased by exercise (even by slow walking and correspondingly more by physical work) the rate of absorption of carbon monoxide is increased proportionately".

Using this rough guide, it would appear that the presence of one part of CO in 10,000 might produce symptoms.

Summing up the available literature on the subject, Drinker (1939) says:-

"For all practical purposes in anticipating carbon monoxide effects, it seems safe to use Henderson's rules of expectancy, particularly where low concentrations of carbon monoxide are encountered. If one sums up the available data on dangerous concentrations of carbon monoxide, a table such as the following is not far wrong.

CONCENTRATION	EFFECT
0.01 per cent, or 1 part in 10,000	No symptoms for 2 hours.
0.04 per cent, or 4 parts in 10,000	No symptoms for 1 hour.
0.06 - 0.07 per cent, or 6 to 7 parts in 10,000	Headache and unpleasant symptoms in 1 hour.
0.10 - 0.12 per cent, or 10 to 12 parts in 10,000	Dangerous for 1 hour.
0.35 per cent, or 35 parts in 10,000	Fatal in less than 1 hour.

In houses, garages, or manufacturing establishments where there is prolonged exposure to carbom monoxide, concentrations above 0.01 per cent (1 part in 10,000 should not be permitted".

For low altitudes it would seem reasonable to say that 1 part CO in 10,000 is safe enough, but entirely different circumstances surround the question when a height of over three or four thousand feet is reached.

It is of course self evident that the figures above for the arterial O_2Hb percentage are theoretical only. Hyperpnoea is brought into play and, for instance, Barcroft (1928) found that his party at Cerro del Pasco which is at

14,200 feet had about 85 per cent of their haemoglobin saturated with oxygen instead of a theoretical maximum possible of 60 per cent. This was after acclimatisation.

There are thus two factors present which are not present at lesser heights, hyperpnoea and the large percentage of unsaturated haemoglobin. Hingston records that in the 1924 Everest expedition one climber had to take from seven to ten breaths for every step forward (Appendix, Barcroft 1928). This hyperpnoea will necessarily bring more CO into contact with the alveolar capillaries assuming that an equal concentration of CO is present in the cabin.

Diringshofen and Hartmann (1935) have published tables showing the calculated effect of CO inhalation superimposed on altitude. They show the effect of concentrations of the gas from 0.25 parts in 10,000 to 3 parts in 10,000 at heights up to 8,000 metres.

Armstrong (1939) working with Heim has reached the conclusion that when the arterial blood oxygen saturation is below 88 per cent it is dangerous to pilot an aircraft. If this figure is taken as a convenient one and Diringshofen and Hartmann's tables accepted, the following facts emerge. In pure air a pilot is safe from anoxic symptoms up to about 12,500 feet. With 0.25 parts CO in 10,000 of air present he

is safe only to 5,000 feet, and with 0.5 parts CO only to 3,300 feet. With one part CO or more present the pilot is not safe at ground level. These figures are of course only true after equilibration.

Heim (1937) shows that breathing one part CO for one hour at 13,465 feet reduces oxyhaemoglobin from 76.9 per cent to 70.6 per cent.

The danger to the pilot of sudden gassing in the air must not be minimised. The hyperpnoea and large proportion of reduced haemoglobin must affect the speed of the reactions between CO, O_2 and Hb. Glaister and Logan (1914) record a case where a fatal gassing occurred with a concentration of 11.5 parts in 10,000. The oxygen in the atmosphere was reduced to 14.49 owing to the presence of Blackdamp and Firedamp, and Dr. J.S. Haldane who was consulted considered that the fatal result was due to "the small percentage of CO being virulent owing to the diminished amount of oxygen present in the air". If in fact this "vacant" haemoglobin will absorb CO very rapidly an interesting phenomenon might occur, namely, that the type of anoxaemic symptoms present in an aviator might suddenly alter from the simple respiratory type to the nervous type characterise by muscular weakness, fainting, and so on. If we consider a specific case, a pilot with 40 per cent of his haemoglobin

unsaturated due to altitude would still be able to fly perfectly well although he would have some respiratory distress. If, however, this 40 per cent unsaturated Hb was converted into CO Hb the result would be extreme muscular weakness with syncope and collapse. This is of course due to the effect of CO in causing a shift to the left of the O_2Hb dissociation curve, or in other words making the haemoglobin cling more strongly to its oxygen. There are unfortunately no data on this subject, and without these data no figure can be set for the safe maximum of CO at high altitudes. The figure of 0.5 parts in 10,000 said to be the maximum permitted in America is probably a reasonable compromise. The German Luftwaffe only tolerate 0.25 parts in 10,000.

Von Diringshofen (1938) says:-

"The reduction in the oxygenation of the blood, and consequently in the oxygen supply to the tissues, must naturally be particularly harmful when the blood is already poor in oxygen, as it is at high altitudes. For example, at 13,000 feet the blood is saturated in the lungs with oxygen to 85 per cent of its capacity, but if 0.02 per cent CO is breathed for one hour saturation falls to 77 per cent and after 4 hours to as low as 70 per cent.

Such additional reduction of the oxygen in blood

through the effects of carbon monoxide may lead to severe altitude sickness even below 4,000 m. (13,000 ft).

It must also be considered that at high altitudes there is insufficient oxygen supply not only to the people in the aeroplane, but also to the motor; in motors without a supercharger, combustion becomes more and more unfavourable with increasing height and the formation of carbon monoxide increases.

The admixture of exhaust gas to the inspired air is particularly harmful for the crew in altitudes of 10,000 ft to 13,000 ft. Above 20,000 ft the respirator should be used as a matter of routine. This makes the subject independent of the outside air and acts therefore as the best protection against exhaust gas intoxication. It is therefore advisable to use the respirator at lower altitudes whenever it is suspected the carbon monoxide is inspired from exhaust gas inadequately discharged.

When the respirator fails at high altitudes the additional effects of CO constitutes a danger to life from 20,000 feet onwards. The "time reserve" (see above) is shortened. The onset of altitude sickness is precipitated; consciousness may be lost within a few minutes and be followed by death even below 23,000 feet.

Exhaust gas in the pilot's seat or in the cabin of an aeroplane used at high altitudes must therefore be at once reported and removed".

It appears that these remarks are theoretical and are not founded on experimental evidence.

All the discussion above is based on the assumption that oxygen masks are not worn nor adiabatic cabins used. In the former case CO must be innocuous, and in the latter it would depend on the pressure maintained. The figures of one part in 10,000 and half a part in 10,000 considered above to be safe at low and high altitudes respectively can of course be exceeded if only breathed for short periods.

The results of an investigation carried out to discover the amount of CO present in modern Service aircraft.

This investigation was carried out with the help of the Air Ministry. Owing to the outbreak of war the names of the aircraft cannot be given.

All the modern types of R.A.F Bomber at present in service were examined and in addition a modern single seater fighter.

Each type will be described separately but the general lines of the investigation are as follows. Each aircraft was tested when on the ground during the warming up


M S A CO INDICATOR

of the engines for the presence of engine exhaust CO. Further tests were made five or ten minutes after the machine left the ground. Then in the case of the Bombers the guns were fired individually and the air tested near the air gunner's head. When all the guns were fired the air near the pilot's head was tested. One aircraft of each type was used to determine if any CO reached the region of the pilot's head when all machine guns were firing at once, Air sampling was also carried out when the machines were on their way home from the Air Firing Range.

Most firing was carried out at 500 feet or less so that the operation of the M.S.A. Indicator would not be affected. It was thought possible that an apparatus depending on oxidation by atmospheric oxygen for its results might not be accurate if it was used under conditions of diminished oxygen pressure. Some of the tests for engine exhaust CO were however carried out at varying heights.

The method of analysis chiefly used in the tests described above was by means of the M.S.A. Indicator. This is an extremely easily used apparatus which uses a catalyst "Hopcalite" composed of various metallic salts mainly manganese dioxide and cupric oxide. This has the power of enabling oxidation of CO to occur at room temperature. The amount of

heat produced is measured by a thermocouple and registered on a galvanometer. Sendroy (1939) reviewing methods of CO estimation shows that this method is sensitive to 0.002 volumes per cent and has a percentage error of + 5%. He says, referring to this method, "The accuracy is amply sufficient however for rapid analytical and control work".

The method of employing Palladium chloride used in the tests on Type X aircraft is not known but its sensitivity is not likely to be better than 0.005 volumes per cent and the range of experimental error may be from 5 to 50%.

The method used by the present writer in one or two aircraft was very simple and possibly as accurate as the $PdCl_2$ method.

This was to take an air sample by blowing air into a bottle with an insufflator until there had been several changes of air, then corking the bottle. In the laboratory a small quantity of blood is introduced and equilibrated by rotating for half an hour. The percentage COHb is then estimated by the Hartridge reversion spectroscope. The amount of CO in the air can then be calculated from the formula

$$\frac{COHb}{O_2Hb} = K \frac{PCO}{PO_2}$$

The experimental error of this method should be about ± 5%.

TABLE 2.

AIRCRAFT TYPE 'A'.

(Twin engined, long distance heavy bomber. Pilot and four crew. Very cramped space incabin. Four machine guns with breeches in cabin. Very efficient ventilating system with entry in leading edge of wings).

Aircraft type and Number.	Height.	Minutes after take off.	Remarks.	Concentration of CO in parts per 10,000.
L.4095	Nil	During warming up.	All hatches and apertures open. Sample from pilot's cockpit.	Nil.
do.	Nil	Taxying and take-off	Pilot's seat with cabin hood open.	1.0
do.	1,000-2,500	3.6	Climbing and normal banking. Pilot's cockpit.	Nil.
do.	3,000-4,000	8	Ditto Observer's cockpit.	Nil.
do.	7,300	23	Level flight Midship cockpit.	Nil.
do.	7,500	27	Wireless Operator's position.	Nil.
do.	8,000	32	Rear gunner's position.	Nil.

Aircraft type and Number,	Height.	Minutes after take off.	Remarks.	Concentration of CO in parts per 10,000.
L.4095	8,000	42-55	All positions tested again.	Nil.
do.	1,000	60	During glide.	Nil.
L.4056	Nil	Nil	During warming up Taxying and take-off. Pilot's hood open. Exhaust smell in cabin.	2.1
do.	Nil-2,200	3	Observer's position Gradual climb. Normal turns. All hoods closed.	1.0
do.	2,300	6	Level flight. Middle of aircraft.	Nil.
do.	2,000	18-34	Samples taken all over machine.	Nil.
L.4048	Nil	Nil	During warming up taxying and take-off.	Nil.
do.	0-1,200	15	Rear gunner's position. Window closed.	Nil.
do.	1,400-2,800	18	Rear gunner's position. Windows open.	Nil.
do.	3,000-5,000	25	Wireless Operator's position. Hood closed.	Nil.

Aircraft type and Number.	Height.	Minutes after take off.	Remarks.	Concentration of CO in parts per 10,000.
L.4048	5,200-6,400	30	Wireless Operator's position. Hood open.	Nil.
do.	6,200	42	Pilot's position. Hood closed.	Nil.
do.	7,400	50	Do. Hood open.	Nil.
do.	8,000	57	All apertures closed.	Nil.
do.	8,000	65	All apertures open.	Nil.
L.4090	Nil	Nil	During warming up.	Nil.
do.	1,400	11	Samples taken in all positions.	Nil.
do.	500	18 onwards	All guns firing 200 rounds each. Navigator's position Pilot's position Wireless Operator's position. Prone gunner's position (Readings were only momentary)	 1.6 1.8 Nil. Nil
do.	1,300	35	About four positions tested.	Nil.
L.4098	Nil	Nil	During warming up of engines.	Nil.

Aircraft type and Number.	Height.	Minutes after take off.	Remarks.	Concentration of CO in parts per 10,000.
L.4098	1,000	13	Four positions as above tested.	Nil.
do.	400	23 onwards	200 rounds fired from each gun. Navigator's position Pilot's position W/Optr. position Prone gunner's position (The gas had completely cleared in 19 minutes)	 1.7 1.2 Nil. 0.4
do.	1,000	42	Four positions again tested.	Nil.
L.407	Zero	Nil	Warming up.	Nil.
do.	500	7	Four positions tested.	Nil.
do.	500	13	Firing front free gun. Acrid smell, cockpit full of smoke. Indicator reading lasted only a few seconds, but smell persisted for several minutes.	0.1
do.	500	25	Firing two rear guns Strong smell noticed.	Nil.

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in parts per 10,000.
L.407	500	35	Firing pilot's fixed gun. Reading taken above pilot's head.	0.6
do.	500	38 onwards	Samples taken throughout aircraft.	Nil.

TABLE 3.

Type 'B'.

(Twin engined, long distance, heavy bomber. Pilot and four crew. Very spacious interior. No bulkheads. Two machine guns in tail, one in nose)

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in parts per 10,000
L.4220	Zero	Nil	During warming up with midway hatch open Ditto with hatch closed	1.5 0.5
do.	500	25	Sample from pilot's position.	Nil
do.	500	35	200 rounds fired from front gun. Reading on indicator evanescent.	0.3
do.	500	45	200 rounds fired from rear guns. Sample taken from near gunner's head.	Nil.
L.4252	Zero	Nil	During warming up, hatch open. Ditto hatch closed	Nil Nil
do.	500	20	Sampling during flight.	Nil
do.	500	35	Front gun firing. after 50 rounds Several short bursts 70 rounds continuous Both readings returned to zero under 8 mins	0.5 Nil 0.8

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in part per 10,000
L.4252	500	45	Rear guns firing. After prolonged burst Retured to zero 1 minute 30 seconds. During further firing reading varied between 0.3 and 0.6 clearing immediately firing ceased.	0.8
do.	500	60	Reading from near pilot's head.	Nil
L.4258	Zero	Nil	Warming up. All sampling in this machine was done near pilot's head.	Nil
do.	500	10	During flight.	Nil
do.	500	35	All guns firing. Strong smell. 800 rounds total.	Nil
do.	500	45	During return flight.	Nil

TABLE 4.

Type 'C'

(Twin engined, long distance heavy bomber. One pilot and four crew. Ample room. Front gunner's and pilot's compartments separated by bulkhead from remainder of aircraft. One machine gun in nose, two in "Dust-bin" in centre and one intail. The gunner in the "Dust-bin" is in an extremely confined space with two machine gun breeches within a foot or two from his head.

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in part per 10,000
K.8965	Zero	-	During warming up. Sample taken at pilot's head.	0.35
do.	1,700	10	All windows closed, sample at pilot's head.	Nil
do.	500	26 onwards	500 rounds fired from front turret. Sample in turret. Reading returned to normal in 45 seconds.	3,5
do.	500	"	Sample from midships "Dust-bin". 2000 rounds fired. Reading evanescent.	0.2
do.	500	"	Sample from tail turret. 600 rounds fired.	Nil
do.	500	60	Sample taken at pilot's head after firing completed.	Nil

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in part per 10,000
K.8974			All readings during this flight were taken at the pilot's position.	
do.	Zero	-	During warming up.	0.5
do.	600	5	During flight.	Nil
do.	500	15	After brief bursts from front gun total 600 rounds fired, all in bursts of about 10. Reading only during actual firing gas cleared immediately.	0.6
do.	500	30	Level flight.	Nil
K.8971	Zero	-	During warming up. Samples taken throughout cabin.	0.2
do.	500	10	During flight. Samples taken throughout cabin.	Nil
do.	300	30	Sampling from front gun turret. 350 rounds fired. Reading persisted for 35 seconds	0.2
do.	300	"	Sampling from middle gun "Dust-bin" 1000 rounds fired. Reading evanescent.	0.7 to 1.3
do.	500	50	During level flight. Sampling throughout aircraft.	Nil

TABLE 5.

Type 'D'

Single engined, medium Bomber. Pilot and two crew. Only rear gunner's gun has breech in fuselage-others in wing. Rear gunner is not in proper turret - merely curved flap to protect from slip stream. No bulkheads in fuselage.

Aircraft Type and number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in part per 10,000.
K.7699	Zero	-	During warming up. Sample from pilot's cockpit.	0.4
do.	500	5	During flight.	Nil
do.	500	30	400 rounds fired from rear gun. No smoke or smell. Cockpit very exposed to slip-stream	Nil
do.	500	45	During level flight.	Nil
K.7832	Zero	-	During warming up.	1.2
do.	500	5	Sample in pilot's cockpit.	0.4
do.	1000	10	Ditto.	Nil
do.	500	40	650 rounds fired. Reading persisted for 10 minutes.	0.3

Aircraft type and number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in parts per 10,000.
K.7832	500	60	During level flight sample from gunner's and from pilot's cockpit.	Nil
K.7702	Zero	-	During warming up Readings in this machine taken in second pilot's seat.	1.5
do.	2500	5	Level flight.	Nil
do.	500	20	500 rounds fired.	Nil
do.	2000	35	Level flight.	Nil

TABLE 6.

Type 'E'

(Twin engined, medium bomber. One pilot and two crew. Only rear gun with breech inside fuselage - in turret with wide slit. No bulkhead in fuselage. Cruising speed 180 m.p.h approx)

Aircraft type and number.	Height.	Minutes after take-off	Remarks.	Concentration of CO in part per 10,000
No.6158	Zero	-	During warming up. Sampling from pilot's and gunners cockpits.	Nil
do.	1500	10	Level flight sampling as above.	Nil
do.	500	25	480 rounds fired. Sampling from near gunner's head. Reading evanescent.	0.3
do.	600	35	Level flight sampling both cockpits.	Nil
do.	Zero	-	During warming up.	0.3
do.	1500	10	During flight.	Nil
do.	200	25	420 rounds fired. Reading evanescent.	0.2
do.	1500	35	Level flight.	Nil

K.7130 In this machine the same procedure was adopted as in the last, except that 540 rounds were fired, and all readings were taken in the pilot's cockpit. At no time either on the ground or in the air did the Indicator show the presence of CO.

TABLE 7.

SINGLE SEATER FIGHTER Type X.

The following are results obtained in these aircraft by Mr. Lang of the Aeroplane and Armament Experimental Establishment, Martlesham Heath, Suffolk.

TESTS OF CO PRESENT IN COCKPIT OF TYPE X.

All tests done on K.9521

Test No.	Air or ground.	Test Conditions.	Wind direction & speed relative to a/cft	Ventilator open or closed.	Hood open or closed
1	Ground	Taxying slowly (5 mph)	Down-wind 25 m.p.h	Closed.	Closed
2	Air	200 ASI at 2000 feet.	-	Closed	Closed.
3	Ground	Taxying	Upwind 35 mph	Closed	Closed
4	Air	270 ASI (full throttle at 2000 feet)	-	Closed	Closed
5	Ground	Taxying slowly	Down-wind	Open	Closed
6	Air	200 mph ASI at 2000 ft	-	Open	Closed
7	Air	260 ASI at 14,000 feet	-	Open	Closed
8	Ground	Taxying slowly	Upwind 25 mph	Open	Closed
9	Ground	Taxying slowly	Wind 20 mph on starboard beam	Open	Closed
10	Ground	Taxying slowly	Wind 20 mph on Port beam	Open	Closed

Time hood closed.	Time to pump up bladder.	%CO by Palladium Chloride method.	%CO by M.S.A. Indicator.	Remarks.
5 mins.	3½ mins	.008	-	Bladders always filled during last period of time hood is closed.
14 mins.	6 mins.	Nil	-	-
3¼ mins.	2¼ mins.	Nil	-	-
7 mins.	5 mins.	Nil	-	-
7 mins.	6 mins.	.01	-	Gentle draught through ventilator felt on hand.
14 mins.	9 mins.	Nil	-	-
16 mins.	14 mins.	Nil	-	Tests 1 - 7 completed on 22.3.39.
6 mins.	5 mins.	Nil	-	-
4¼ mins.	4 mins.	.006	.005 - .007	Ventilator on starboard side. Good agreement between two methods of computation.
5 mins.	4 mins.	Nil	.003	This test 30 minutes after test 9 M.S.A. reading obtained during first minute only. Reading then zero.

Test No.	Air or Ground	Test Conditions	Wind direction & speed relative to a/cft	Ventilator open or closed.	Hood open or closed.
11	Ground	Taxying slowly	Down-wind 20 mph	Open	Closed
12	Ground	Taxying slowly	Upwind 25 mph	Open	Closed
13	Ground	Taxying slowly	Down-wind 20 mph	Closed	Closed
14	Ground	Taxying slowly	Upwind 30 mph	Closed	Closed

Note Ø: The readings obtained with the M.S.A detector have a time lag of 1 minute.

Time hood closed.	Time to pump up bladder.	%CO by Palladium Chloride method.	%CO by M.S.A Indicator.	Remarks.
4¼ mins.	-	-	.018 Ø	Steady at this figure after two minutes.
3 mins.	-	-	0 Ø	Aircraft turned round at end of Test II and taxied straight back - indicator dropped to zero after 1½ mins
4 mins.	-	-	.015 Ø	Reading obtained after 1 minute.
3 mins	-	-	0 Ø	Zero after 1 minute This test consecutive with 13; as for 11 and 12. Tests 8 - 14 completed on 23.3.39.

Table 7a.

Type X.

Carbon Monoxide tests on K.9804
K.9888 and K.9813

A. Taxy down wind with hood and vent closed
Before turning wait for 1 minute and
take reading 'A'.

B. Turn into wind, open hood, wait one minute
take reading 'B'.

C. Maximum on down wind run - reading 'C'.

D. Maximum on upward run - reading 'D'.

	K.9804		K.9888		K.9813	
	1.	2.	1.	2.	1.	2
'A'	.013%	.004%	.007%	.007%	.014%	.000%
'B'	.014%	.005%	.008%	.011%	.006%	.012%
'C'	.015%	.005%	.010%	.007%	.014%	.000%
'D'	.018%	.010%	.012%	.019%	.014%	.014%

TABLE 8.

TRIALS WITH CO DETECTOR APPARATUS.

DOWN AND UPWIND TESTS WITH COUPE OPEN
AND VENT OPEN AND CLOSED

K.9804

	Coupe open. Vent closed
1. Reading after engine started and run for a minute with closed throttle.	.017
2. Reading when finishing taxying down wind.	Increased from .018 - .022
3. Reading at end of taxying down wind after 1 minute halt.	.026
4. Reading on turning up wind.	.035
5. Taxying up wind.	.034
6. Reading at halt half way back.	.015
7. Reading when engine switched off on reaching starting point.	.003
Remarks.	Pilot stated he felt dizzy during the period of maximum intensity (.020-035) Not timed. Wind 6 mph.

K.9804		K.9888		K.9888	
Coupe open.	Vent open.	Coupe open.	Vent closed.	Coupe open.	Vent open
.02		.003		.016	
.029		.023		.015	
-		.013		.015	
.021		.016		.009	
.016		Decreased gradually to .009		.006	
.014		.009		.007	
.014		.009		.005	
Time taken 13 minutes No feeling of dizziness Wind 10 mph		Time taken 16 mins 35 secs. No ill feelings Wind 10 mph		Time taken 21 mins 55 secs. No ill feelings Wind 15 mph.	

TABLE 9.

Further tests were carried out by the present writer using the M.S.A. Indicator on the ground and taking air samples from four machines and estimating the CO present by a method using the Hartridge Reversion Spectroscope. This method is described in the text.

Aircraft type and Number.	Height.	Minutes after take-off.	Remarks.	Concentration of CO in parts per 10,000.
Type X. K.9790	Zero	-	Taxying 15 minutes. This is about the maximum time which the engine in Type X can remain on the ground without boiling	0.3
K.9823	Zero	-	Taxying 9 minutes up wind. Down wind.	0.9 0.5
K.9803	Zero	-	Taxying 15 minutes. Up wind Across wind Down wind	 0.5 0.9 0.4
K.9815	Zero	-	Taxying 12 minutes. Up wind Across wind Down wind	 0.4 1.1 0.6
K.9841	Zero	-	Taxying 12 minutes. Up wind Across wind Down wind	 0.3 1.6 0.9
K.9817	Zero	-	Taxying 10 minutes. Up wind Across wind Down wind	 1.1 0.6 0.6

Aircraft type and Number.	Height.	Minutes. after take-off.	Remarks.	Concentration of CO in parts per 10,000
K.9819	Zero	-	Taxying 8 minutes Up wind Across wind Down wind	 0.6 0.3 1.1
K.9802	Zero	-	Taxying 12 minutes. Up wind Across wind Down wind	 1.0 0.6 0.6
K.9804	7,000 8,000	5	Aerobatics being carried out. Air sample taken in bottle.	Nil
do.	7,000 - 8,000	15	do	Nil
K.9817	3,000	20	As above	Nil
do.	2,000	25	As above	Nil

As a final test two aircraft were sent on a maximum duration flight which in these aircraft is about 2 hours. At the end of the flight five cubic centimetres of blood was taken from the antecubital vein of each pilot. The CO content was estimated using Van Slyke's volumetric apparatus. The result in each case showed that no CO had been absorbed.

4. Conclusions.

The results of the tests are shewn in Tables 2 to 9.

In none of the aircraft tested was there a concentration of CO which could at ground level or moderate altitudes cause any symptoms whatsoever. And despite the possible dangers of alteration of the speed of interaction of CO, O_2 and haemoglobin at high altitudes it is difficult to visualise any effect from the minute amounts of CO found. However, this only holds good in the type of machine tested, namely, one which though well streamlined yet has many apertures for the entrance of air, and in which for this reason the air changes very rapidly. If completely sealed cabins are introduced it would be advisable to have these tested in a similar manner to that adopted in the present series.

If oxygen is used it is difficult to see any eventuality in which CO from guns could assume any importance at any height in any type of machine until heights in excess of 40,000 feet are reached. At this height the alveolar oxygen tension, even when the inspirate is pure oxygen, is only equal to the normal sea level oxygen tension, and it very rapidly diminishes above 40,000 feet. It would appear that engine exhaust CO does not enter the cabin of modern machines in flight.

SECTION VI.

TREATMENT OF CARBON MONOXIDE ASPHYXIA

In practice the methods of treatment of carbon monoxide asphyxia are usually limited to the administration of oxygen and carbon dioxide or oxygen alone, or to artificial respiration, yet on reviewing the literature on the subject one finds about a dozen methods which have been proposed and investigated. These are discussed below but here it may be said that they can be divided into two types which the writer calls "fundamental" and "auxiliary". The former are those in which the object is simple though the method may be complex, namely the exhibition of oxygen to the blood in sufficient amount to displace the carbon monoxide. The latter are designed to aid the process of recovery without invoking the law of mass action.

Briefly, then, the fundamental treatments are:-

1. Removal from the atmosphere containing carbon monoxide.

2. Artificial respiration.

3. Inhalation of pure oxygen.

4. Inhalation of oxygen combined with carbon dioxide.

The first method needs no elaboration. The second is an essential form of treatment and a knowledge of a sound method is necessary in workers in trades such as mining or steel manufacture. The most easily taught and most generally used method is that devised by Schafer. Artificial respiration should be used even if oxygen is available so long as the natural respiratory volume would seem to be in any way diminished. Drinker (1938) gives an exhaustive description of the methods of artificial respiration with an analysis of their various efficiencies. He points out that while mechanical respirators are valuable if available they can never be of real emergency value. They are however a useful second line of defence, especially where CO-asphyxia is complicated by drug poisoning.

Treatment by pure oxygen is comparatively old having been used first by Witter in 1814 but it was not generally employed until the beginning of this century. The results of this treatment have been described by Nicloux (1921) as "resurrection". It had become almost universal when the introduction by Henderson and Haggard in 1920 of treatment by oxygen combined with carbon dioxide began an extensive controversy. This is fully described by Henderson in his "Adventures in Respiration" (1938) and by Sayers and Davenport

(1936) and Campbell and Poulton (1934). In brief it may be said that the chief objections to the $O_2 + CO_2$ therapy were (a) that it was no better in fact that treatment by pure oxygen and (b) that it was theoretically unsound. The former objection is not now generally believed to be true. As for the latter the theories surrounding the control of respiration are by no means crystallised. Thus Gesell (1938) reviewing the situation says:-

"It is therefore with some concern that we note the revival of theories which for some years seemed forgotten. The insistence of a supersensitive response of the respiratory center to the hydrogen-ion concentration of the blood (Haldane and Priestley); the conviction that acidity is not the stimulus to respiration (Nielsen); the combination of these two views - that acidity is the stimulus at the center, but not at the chemoceptors (Comroe and Schmidt); that oxygen lack, independent of acidity effects, is the stimulus at the chemoceptors (Comroe and Schmidt); the control of excitability of the respiratory center by oxygen lack to the normal respiratory stimulant - carbon dioxide (Henderson and Nielsen); the specificity of carbon dioxide as opposed to its effects on acidity (Nielsen) the uncertainty of decision between specificity of carbon dioxide and acidity (Carlson and Johnson) - all taken together,

inspire a new version of Rip Van Winkle, who having worked instead of slept while sleeping, woke twenty years later and found the world unchanged. A commentary on the elusiveness of the mechanisms of respiratory control".

Theoretical considerations apart, oxygen - carbon dioxide treatment is well established and interest now really lies in auxiliary treatments. The more rational of these are:-

1. Caffeine. If this is injected intravenously it may increase the excitability of the respiratory centre. It is useless if injected subcutaneously in collapsed cases.

2. Emetics have been used for centuries. The danger of a septic pneumonia is very great.

3. Strychnine has been found useful on occasion but controlled experiments do not seem to have been done.

4. Blood transfusion. Blood letting was practised in mediaeval days for unconsciousness as indeed it was for most illnesses. It has been superseded, quite recently, by transfusion for CO poisoning. Theoretically this treatment would appear to be sound but by the time the necessary preparations for transfusion are made the patient has, if he is still alive, by the mere act of normal breathing reduced his carboxyhaemoglobin to an innocuous level, and what symptoms there may be are due to the results and not the presence of anoxaemia.

5. The injection of alkali was suggested by Henderson in 1916 believing that acidosis was a result of CO poisoning. This acidosis was later disproved both by Henderson himself and by Haldane.

6. Alpha-lobelin. This drug has a transitory excitant effect on respiration. The work of Norris and Weiss (1937) however has shown it to be exceedingly dangerous. Among other effects it causes a fall in blood pressure of about 50 m.m Hg.

7. Methylene Blue. This is discussed in more detail in Section VII of this thesis.

8. Irradiation. As far as the writer is aware this has only once been used in the treatment of human subjects poisoned by CO. It is discussed in Section VIII.

With the exception of the last, all these "auxiliary" methods involve considerable interference with the patient who is not in a condition to stand this interference. Yandell Henderson (1930) insists that any form of hypodermic injection is dangerous. So also does Drinker (1938) who points out that a further danger of intravenous medication is that when one drug proves useless, others are frequently given.

If the patient is to be disturbed when collapsed then there must be every justification for it. Henderson's treatment (1930) consists of:

1. Immediate artificial respiration in prone position if respiration is stopped.

2. Inhalation of O_2 + 7% CO_2 (Pure oxygen is satisfactory when patients have only inhaled a moderate amount and when breathing is satisfactory.

3..Warmth.

4. Prevention of muscular exercise.

This treatment fully justifies Nicloux's description of it as "resurrection" and therefore a method such as intravenous medication, which, by the mere manner of its administration may be dangerous, must also show dramatic and constant results if it is to be used. On the other hand irradiation can do no harm and if it is even occasionally of benefit or only to a slight degree it might be considered useful.

SECTION VII.

TREATMENT OF CO ASPHYXIA BY INTRAVENOUS METHYLENE BLUE

The treatment of acute intoxication by CO using intravenous methylene blue was first tried by Geiger in 1932. This treatment was suggested to him by M.M. Brooks, and it would appear that it is entirely founded on a misunderstanding.

In one paper (1932a) the latter author discusses the evidence adduced by Barron et alia that methylene blue and other dyes stimulate oxygen consumption by the tissues by promoting oxidation of carbonydrates or their products and that this process, which is catalytic, depends on the reversible reduction and oxidation of the dye. This oxidation-reduction process is independent of tne respiratory engymes for decoloration occurs even when these are destroyed by HCN.

After mentioning these results and the observations of other workers on the effect of methylene blue on tissue oxidation Brooks goes on to say "In view of these observations it was thought desirable to see whether such an effect of methylene blue could be demonstrated on living mammals whose aerobic respiration had been interfered with. Since Warburg has long demonstrated that both CN and CO are specific respiratory poisons, these two gases were used to inhibit

aerobic respiration". In another paper (1932b) she says "Since CO has long been known to resemble CN in its effects on respiration it was thought of interest to see whether methylene blue also favoured recovery in animals subjected to CO".

Also in a private letter dated May 17th 1933 from Dr. Brooks to Dr. Garfield Thomas which has been put at the present writer's disposal Dr. Brooks says "Methylene blue has the ability of transferring oxygen catalytically to the tissues and keeping them aerated until the normal processes again can be resumed".

It is thus obvious that Brooks's suggestion to Geiger was made under the impression that CO, which may be made to act like HCN in vitro, produces effects on the body by interference with the "atmungsferment" of Warburg. This has been mentioned in a previous chapter. Here it may be reaffirmed that carbon monoxide poisoning is caused by interference with the carriage of O_2 and not by interference with its utilisation.

While it might be said that the case for treatment by intravenous methylene blue is thus destroyed before it opens yet several workers have published reports of cases in which this treatment has apparently been successful. If these findings can be sustained it will not of course mean that

Brooks's premises are true but that by some chance it happens that methylene blue acts in a manner beneficent but as yet incomprehensible.

The present writer has therefore surveyed the literature on the subject. The majority of the literature is composed of reviews and surveys and the actual clinical and experimental work is not very extensive. The clinical work will be discussed first.

Geiger (1933 a & b) and Geiger and Gray (1934) have described the results of methylene blue treatment in five cases. A 1% solution of U.S.P (medicinal) methylene blue in 1.8% sodium sulphate was used. Geiger insists that methylene blue is to be used as an adjunct only. He suggests that one should use, in addition to methylene blue, "artificial respiration, oxygen and carbon dioxide, cardio-respiratory stimulants, supportive and eliminative therapy as indicated". It must be considered difficult to isolate the curative effects of methylene blue in such a medley of treatments, and to assume that the credit goes to one form of treatment rather than the others does not appear justifiable unless experimental work shows that type of treatment, when given alone, to be very much superior to each of the others.

Christopherson (1933) Bell (1933) Nass (1933) and

Limousin and Griffiths (1935) have all described cases in which they consider intravenous methylene blue to have been an extremely satisfactory treatment. In all these cases and in Geiger's five cases approximately the same sequence of events occurred. The patient was discovered in an asphyxiated atmosphere; was removed into the fresh air; artificial respiration and oxygen with or without carbon dioxide, were administered; various heart stimulants were given and then methylene blue was injected. In several cases the patients had shewed no signs of recovery until the dye was actually being injected, and during the injection they made rapid progress, being unconscious at the beginning and conscious at the end. There is apparently no doubt in the minds of those reporting the cases that it was in fact the dye which was responsible for the recovery. Geiger and Gray (1934) refuse to theorise over the results and say, "It is also possible that methylene blue may enable intracellular oxidation to proceed in the absence of enough available oxygen in the blood, in carbon monoxide poisoning or when the normal iron oxidation mechanism is interfered with, in cyanide poisoning. We are prepared to state only that the use of the dye has been demonstrated to be beneficial in the treatment of cyanide poisoning, and we believe it shows promise, possibly as a supportive measure, in the treatment of carbon monoxide poisoning also".

There apparently the clinical evidence in support of methylene blue therapy ends. It is not a very strong case as it relies entirely on impressions and not on controlled series of cases.

In the investigation of such a treatment when there is already a good form of treatment in use it is obviously impossible to get controlled results clinically, so its value must be assessed in the laboratory.

Brooks, the originator of the theory that methylene blue is an antagonist for CO poisoning, has produced (1932a, 1932b, 1933a, 1933b, 1934, 1935, 1936) a series of papers in which this treatment is shown under laboratory conditions to be successful. In her first experiments (1932a and b) 40 rats were used, 20 being untreated and 20 treated. The time taken to recover from carbon monoxide poisoning was noted, the criterion being the ability of the animal to run forward. It was found that the untreated rats took about twice as long to recover as the others.

In another communication (1933a) it was shown that rabbits treated with 0.1% methylene blue (1 cc per Kilo body weight) took longer to become unconscious in an atmosphere of carbon monoxide than did those which were untreated. Also it was described how 8% carbon monoxide was administered to rabbits.

The rabbits were then treated by artificial respiration while the others were treated with artificial respiration and methylene blue. Ninety per cent of the latter recovered and only twenty per cent of the former.

Haggard and Greenberg (1933) were probably the first to attack these results. They considered that the antidotal power of methylene blue in cyanide poisoning was due "not primarily in the action of this dye on the tissue ferment, but in an effect of the dye somewhat resembling that of carbon monoxide. Methylene blue converts haemoglobin into methaemoglobin. Cyanide combines with the methaemoglobin. The formation of methaemoglobin and the resulting withdrawal of cyanide from the blood and tissues in the formation of cyanmethaemoglobin thus reduces the concentration of cyanide free to act as a poison on the tissue ferment. In this reaction of cyanide with the methaemoglobin formed under the influence of methylene blue, rather than in any counteraction of the dye on the tissue ferment, is to be found the antidotal effort of methylene blue on cyanide poisoning". But in carbon monoxide poisoning it is the union of the gas with haemoglobin forming a compound incapable of carrying oxygen which causes the poisonous results. Methaemoglobin thus only adds to the evil instead of alleviating it. Haggard and Greenberg consider that the clinical cases reported as showing good results from this treatment were of no value as the cases ha already eliminated a large proportion of the carbon monoxide

before treatment was started. They object to Brooks's experimental work on the grounds that the control animals were not injected with saline solution as a control measure, and explain the more rapid recovery of the treated animals as being due to "countershock" or strong sensory stimulation.

They also describe experiments with rats using the "righting reflex" i.e the ability to return to the normal position after being placed on the back. Also dogs were used and the amount of carbon monoxide in the blood estimated by the Van Slyke apparatus. In those treated with methylene blue marked hyperpnoea occurred and the amount of carbon monoxide in the blood decreased more rapidly than in the controls, "but this was more than counterbalanced by formation of methaemoglobin and other deleterious effects". They found that next day animals which had been treated were ill and weak whereas the controls were perfectly fit.

Bussabarger (1934) also objected to Brooks's criterion of "ability to run forward" and used the "righting reflex". He found that methylene blue did not hasten recovery and indeed appeared to be detrimental rather than beneficial.

Mack and Smith (1934) found no significant action by methylene blue as a prophylactic agent.

Mori and Niiro (1934) could not find that methylene

blue had any effect on the recovery rate, and Bodine and Boell (1937) found that the increased respiration of embryos stimulated by methylene blue was depressed by carbon monoxide just as was the normal respiration.

Estler (1935) found no beneficial effect on CO-poisoned mice or rabbits.

Brooks (1936) taking account of the argument that the only action of methylene blue was to form methaemoglobin carried out analyses on the blood of rabbits as they recovered from carbon monoxide poisoning both treated and untreated. Blood was removed by heart puncture and examined by a spectrophotometric method which gives the proportions of oxyhaemoglobin and carboxyhaemoglobin. Table No.10 shows the progressive change found.

Table No. 10.

Percentage Hb O_2 →		
Time in mins.	Controls.	M.B.
0	26	26
1	43	76
3	54	96
11	63	100
21	82	100

From these results Brooks draws the conclusions that methylene blue changes carboxyhaemoglobin to oxyhaemoglobin in the blood stream. Her original theory is apparently discarded

Nadler, Green and Rosenbaum (1934) observed that methylene blue was beingused intravenously in the treatment of cyanide and gas poisoning althougn practically no definite information regarding its action on the body was available. They therefore carried out experiments on eighteen normal adults and came to the following conclusions.

1. Methylene blue produces methaemoglobin but in small amount; not enough to account for the clinical picture produced.

2. Used intravenously it excites the individual and produces a transitory gastro-intestinal and urinary irritation with restlessness, paraesthesiae, a sense of burning in the mouth and stomach, pain in the chest and strangury. Leakage of the dye round the vein causes a very painful infiltration.

3. Electrocardiographic studies suggest depression of the ventricular musculature.

4. They consider that indiscriminate use of the dye may be unpleasant and dangerous.

It will be seen therefore that the treatment by methylene blue was tried as it was believed to act as a catalyst for tissue oxidation. When it was pointed out that tissue oxidation was unimpaired in carbon monoxide poisoning it was suggested that it changed CO Hb in the blood stream to O_2 Hb.

Also the attackers of the original theory said that it was obviously dangerous in CO-poisoning since methylene blue formed methaemoglobin when injected, and that it was therefore useful in cyanide poisoning, since the methaemoglobin joined with the cyanide to form a stable compound. The supporters then brought forward evidence that while methylene blue in vitro caused O_2 Hb to become methaemoglobin yet in the blood stream the presence of reductants such as glucose prevents this.

This modification of the original idea resulted in the production of a proprietary compound of methylene blue and glucose called "Chromosmon".

Sturm and Wohlfarth (1937) investigated this, injecting chromosmon partly before and partly after the gas inhalation. They treated 44 animals using a similar number of controls. The results were quite irregular and the authors suggest that individual resistance is of great importance and although this makes the results very uncertain they believe that chromosmon injection is of benefit.

They also carried out experiments injecting the controls with a 10% glucose solution. The latter was apparently slightly more effective. The authors, however, taking into consideration the fact that they subjected the more severely poisoned animals with "chromosmon" believed that "The

undoubtedly favourable effect of intravenous injection of chromosmon ..... is not specific".

Despite the present controversial position papers have been published which support, without bringing forward any new evidence, the use of methylene blue. (Erlichman 1936 and Kelly 1933). Kelly mentions that an American firm supplies an emergency kit for use in the treatment of gas casualties consisting of 50 cc of 1% methylene blue solution with syringe, needles, and skin sterilising fluid.

On the other hand work has been published recently which alters the whole outlook on the subject and it is curious that no supporter of the methylene blue treatment seems to have found fresh impetus from it. This is the work on the treatment of methaemoglobinaemia, following medication with sulphonamide using methylene blue.

Williams and Challis (1933) first reported that methylene blue reduced methaemoglobin to haemoglobin. Little attention appears to have been fixed to this discovery until Wendel (1937) pointed out that when an artificial oxidation-reduction system is introduced into the blood stream one cannot guarantee which way the system will act. He says "The accelerating action of methylene blue on conversion of met-haemoglobin is catalytic. Indeed in this reaction the

catalysis is one of reduction. The possibility of using foreign oxidation-reduction systems like methylene blue to catalyze reductions in the body has not been considered heretofore. Methylene blue and similar oxidation reduction systems have been added to isolated tissues or administered to animals by students of biologic oxidation processes, usually with the intent of catalytically increasing oxidation processes. It has been expected, or at least hoped, that the reduced form of the system would react with molecular oxygen, regenerate the oxidised form, and thus complete the oxidation cycle. The possibility that the reduced form of the system might escape autoxidation and accomplish reduction of some constituent appears to have been overlooked.

The reported results are not at variance with the evidence that methylene blue converted Hb to met-Hb and with my explanation of the antagonisms of methylene blue for cyanide in the living animal based on this evidence. A supplementary and to me, unexpected aspect of the question has been revealed".

Hartmann Perley and Barnett (1938), working at Wendel's suggestion, found rapid disappearance of cyanosis caused by methaemoglobin in the injection of methylene blue and they showed spectroscopically that this disappearance was due to a reduction of methaemoglobin.

Campbell and Morgan (1939) also found this to occur.

It will now be seen that the theoretical objections of Haggard and Greenberg and their supporters that the injection of methylene blue is dangerous because of the production of methaemoglobin is ill founded. However, the practical objections of Nadler,Green and Rosenbaum still remain.

Summing up the evidence methylene blue does not seem to be a very satisfactory treatment to say the least. On the other hand, owing to early severe criticism it may not have received all the trial it deserves. But with the safe method of treatment by oxygen and carbon dioxide equally easily available it does not recommend itself. In fact the advice of Yandell Henderson to the New York internes, that, when they saw a case of CO asphyxia they should keep their hypodermic syringes in their pockets seems to be sound.

SECTION VIII.

THE EFFECTS OF LIGHT ON CARBON MONOXIDE ASPHYXIA

Barcroft (1928) after discussing the facts that H - ion concentration and the presence of salts have no effect on the equilibrium between COHb and O_2Hb goes on to say that temperature has an effect, but a trifling one, compared to its effect on the affinity of either gas separately for haemoglobin. Then he says "Whilst the factors which influence the reaction of haemoglobin with oxygen have little influence on the equilibrium of haemoglobin with the oxygen and carbon monoxide simultaneously, there is another factor, namely, light to which the reaction is very sensitive. Light tends to expel the carbon monoxide from haemoglobin to the advantage of the oxygen". This was first shown by Haldane in 1896 and has been confirmed by Hartridge and many others. Hartridge (1912) showed to what extent the saturation of haemoglobin by CO depended on the kind of light incident on the solution. His experiments gave the following results:

Dark	96%	Sunlight	40%	Dark	91%
Sunlight	42%	Electric light	88%	Daylight	80%
Sunlight	35%	Dark	92%	6" Magnesium	64%

He then carried out certain experiments to discover which rays were effective. He considered that it was self

evident that the active rays must correspond to one or more of the absorption bands and he proved this by interposing a solution of O_2 Hb between the solution of COHb and the light. The bands were sufficiently coincident to cause the reaction to take five times as long as before. He then irradiated the solutions with light from the different absorption regions and found that the ultra violet was much more powerful than the light corresponding with the two characteristic bands. He goes on to say "these sources, rich in actinic rays i.e sunlight, magnesium etc. cause a big dissociation, while electric light, lamplight etc. cause very little because of their poorness in their rays".

Hasselbalch (1909) also confirmed this and found that rays around 3100 A.U were the most effective, but he also found that the visible rays had an appreciable effect.

In 1891 Mond and Lenzer produced carbon monoxide by the action of light on iron pentacarbonyl. In 1896 Haldane split COHb with light. Carbon monoxide-pyridine haemochromogen and carbon monoxide-ferro cysteine have also been dissociated with light by Krebs and Kremer respectively. Photo-chemical dissociation is apparently confined to the iron compounds of CO, and Warburg (1925, 1930) used this to prove that his "atmungsferment" was an iron compound. He went on to prove

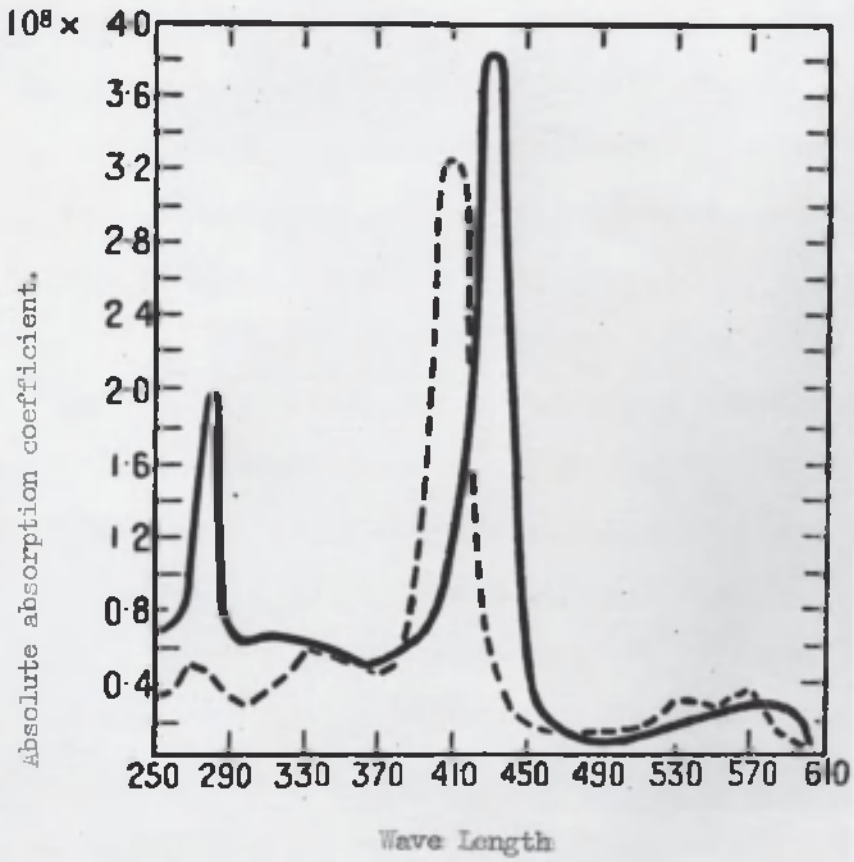


Fig. 4

Absorption spectra of CO compounds.

_____ Compound with "atmungsferment"

----- Compound with haemin.

it to be an iron porphyrin by observing the dissociation by light of different wavelengths of its CO compound. The time required to split this compound must be related to the absolute light absorption by the enzyme. Where the absorption is strong the time required is less and vice versa.

Figure 4 shows Warburg's absolute absorption spectrum curves for CO - Haemin and CO - respiratory ferment compounds. The resemblances pointed out by Warburg are:

1. Minimum absorption around 4,900 A.U.
2. Maximum absorption in blue.
3. Quantitative agreement in maximum.

According to this, therefore, it would appear that COHb, also a CO-iron porphyrin compound, is quickly dissociated by light in the blue-violet end of the visible spectrum.

The Grotthus - Draper Law of photochemical absorption states that photochemical change can only be produced by radiations of wavelengths which are absorbed. Normal blood absorbs all rays up to 4500 A.U with a maximum about 4100 and has two absorption bands one at 5400 and one at 5750 A.U. With reference to the work by Hartridge, mentioned at the beginning of this chapter, there is one point which must be brought out. He says that it must be the ultra-violet which is effective in dissociating COHb because electric light failed to do so. But the electric light bulbs of 1912

produced very little energy in the blue and violet regions of the visible spectrum and, in fact, gave a very yellow light. The reason for this was their low filament temperature. The higher the colour temperature of the emanating body the more energy is emitted in the blue and violet regions and the modern bulb such as is used in the experiments described later in this thesis is quite a powerful source of these rays.

Reflection and penetration of light by the skin.

The radiant energy impinging on any surface must, by the Law of Conservation of Energy, be reflected, absorbed or transmitted. The amount reflected from the human untanned skin has been shown by Luckiesh, Taylor and Holladay (quoted by Luckiesh 1930) to increase with the wavelength. At 4000 A.U. 28% is reflected.

TABLE No. 11.

Percentages of energy of various wavelengths reflected by untanned skin (Luckiesh, Taylor and Holladay).

Wavelength A.U.	% reflected.	Wavelength. A.U.	% reflected.
2400	3	3600	21
2600	3	4000	28
2800	3	4500	35
3000	4	5000	42
3200	11	5500	48
3400	17	6000	54

This does not seem to be of great importance. If a quarter of the light required is reflected the light source can be increased proportionally. On the other hand, the penetration of the light is of great importance. For light to have any effect on the haemoglobin of the body it is obvious that it must penetrate the epidermis which is, of course, non-vascular. The Corium on the other hand is plentifully supplied with blood vessels. "The arteries supplying the skin form a network in the subcutaneous tissue and from this network branches are distributed to the sudoriferous glands, the hair follicles and the fat. Other branches unite in a plexus immediately beneath the corium, and from this plexus fine capillary vessels pass into the papillae". (Gray's anatomy 1926). If light can pass the stratum germinativum of the epidermis it is able to play on a highly vascularised tissue. Russell and Russell (1928) quote Hasselbalch who, using a spectrographic method of estimation found the penetration values set out in Table No.12.

There have been many other observations regarding penetration but the most elaborate and careful study has probably been carried out by Bachem (1929) and Bachem and Reed (1929 and 1931). Their results are shown in Table No.13.

LAYER	mm	200	250	280	300	400	550	750	1000	(1400)	μμ
		100	100	100	100	100	100	100	100	100	APPLIED
CORNEUM	.03	(100)	(81)	(85)	(66)	(20)	(13)	(22)	(29)	(56)	ABSORBED AND REFLECTED
		0	19	15	34	80	87	78	71	44	TRANSMITTED
+MALPIGHII	.05	(0)	(8)	(6)	(18)	(23)	(10)	(13)	(6)	(16)	ABSORBED
		0	11	9	16	57	77	65	65	28	TRANSMITTED
+CORIUM	20	(0)	(11)	(9)	(16)	(56)	(72)	(44)	(48)	(20)	ABSORBED
		0	0	0	0	1	5	21	17	8	TRANSMITTED
+SUBCUTAN.	25	(0)	(0)	(0)	(0)	(1)	(5)	(20)	(17)	(8)	ABSORBED
		0	0	0	0	0	0	1	0	0	TRANSMITTED
		EXTREME ULTRA VIOL.	FAR ULTRA VIOLET		NEAR U. VIOL.	VISIBLE VIOL. GREEN RED		NEAR INFRA RED			FAR INF. RED
GENERAL REMARKS		All absorbed by corneum. No radiation reaching germinativum.	Greatest absorption in stratum corneum. Some radiation reaches corium (papillare). No radiation reaches subcutaneous layers.		Relatively large absorption in stratum malpighii.	Minimum absorption in stratum corneum. Most radiation absorbed in corium. Pronounced radiation reaching subcutaneous layers.		Strongly increasing absorption in upper layers, decreasing in lower layers.			Practically no penetration.

Energy distribution in the layers of the skin. The number 100 designates the applied intensity. The encircled numbers represent percentages absorbed in each layer. The numbers in the narrow zones between layers represent the percentages of the original intensities transmitted through the layer above.

Table No. 13

TABLE No. 12.

Wavelength A.U.	Skin thicknesses.	% transmitted 0.1 mm	0.5 mm	1.0 mm
4359		59	7	0.5
4050		55	5	0.3
3663		49	3	0.08
3342		42	1.3	0.02
3132		30	0.3	0.008
3024		8	-	-
2967		2	-	-
2894		0.01	-	-

It will be observed that there is a rapid rise in penetrative power as the wavelength reaches 4000 A.U. where 57% passes the epidermal layers. The maximum amount of 77% passing to the corium occurs at 5500 A.U. Practically all the light in these wavelengths is absorbed in the corium whereas only half of the light at 7500 A.U. is absorbed there. Light absorption by haemoglobin is greatest at 4000 and between 5000 and 6000 A.U. This is responsible for the immediate almost entire absorption of the rays which are by some curious chance the most penetrative in the avascular layers.

Lucas (1931) found that penetration of different wavelengths from 4040 to 2890 A.U. through 0.08 mm thick epidermis was from 1.5 to 30 times greater than that found by Hasselbalch.

(The wavelengths of different lights are here inserted for easy reference

Short wave ultra violet	1500 - 2200 A.U.
Middle wave ultra violet	2200 - 3000 A.U.
Near wave ultra violet	3000 - 3900 A.U.

(Violet	3900 - 4500
(Indigo	4500 - 4900
(Blue	4900 - 5300
(Green	5300 - 5600
(Yellow	5600 - 6000
(Orange	6000 - 6500
(Red	6500 - 8000

The limits of visible radiation vary with the individual)

It appears, therefore, that if we take Hasselbalch's figure of 3100 A.U. as being the most efficient wavelength for the dissociation of COHb the penetration is so poor that it would be unlikely to produce effects on the haemoglobin of the circulating erythrocytes. On the other hand, violet and indigo light with the very 'near' ultra-violet, penetrates freely to the vascular tissue and according to Warburg's absorption spectrum curves should produce a pronounced photo-chemical effect on the CO - haemoglobin.

Experiments carried out on animals using light treatment.

Macht Blackman and Kelly (1924) considering the phenomenon of the dissociation of COHb by light in vitro attempted to discover if it had any significance when applied to the living animal. They first poisoned rats with CO and compared the recovery rates when the animals were in the dark and in direct sunlight. They found that those exposed to

sunlight recovered more rapidly. Then rats, rabbits and dogs were used and it was found that "animals radiated with ultra-violet rays recovered much more quickly than similar animals poisoned to the same degree, which were left at the same temperature in the dark". They also found that temperature had a similar but slighter effect. A Hanovia Alpine Sun Lamp was used and it appears that when they refer to ultra-violet radiation the authors mean the total light emanation. They make no mention of any form of light filter.

Koza (1930) when considering the fact that ultra-violet radiation increases the dissociation of CO and Hb, raised the question as to whether ultra-violet light decreases the stability of the CO - Hb combination or whether it increases the affinity of Hb for O_2. Sunlight alone cannot dissociate COHb, O_2 must be present. Koza refers to the experiments of Bernhard and Biancani who filled two Petri dishes with CO - saturated blood and exposed one to sunlight and the other to ultra-violet rays. The latter after 30 to 60 minutes showed complete loss of CO while the former showed no change. Koza irradiated CO-saturated rabbits blood for five minutes at a distance of 50 cm. In passing he notes that warmth also accelerates the breaking up of COHb - for every rise in temperature of one degree dissociation is

increased by 0.5%. In five minutes a fifth of the total CO saturation was lost by blood when irradiation was by ultra-violet light. When he used daylight the blood was still 94 per cent saturated after five minutes and using a Siemans "Aureolla" lamp it was 90 per cent saturated.

In his animal experiments Koza used two white rabbits. They were shaved and put in a glass jar containing a small CO content for twenty minutes. One animal was then irradiated by U-V light at a distance of 50 cms. The other animal was left near the other but in the dark. The irradiated rabbit after forty minutes radiation showed a 5 per cent reduction in the CO content of the blood while the one left in the dark showed only a 17 per cent reduction.

He then had the opportunity of studying two nurses who were overcome by gas when sleeping in the same room. They were both unconscious and had stertorous breathing with mucus and vomitus on their lips.

Patient No.1 had 68 per cent while patient No.2 had 70 per cent of her blood saturated with CO. The urine was examined and showed in Case No.1 a pH of 6.2 and in Case No.2 of 6.8. In both cases acetone was present in approximately the same amount.

Both were treated with Lobelin, Caffeine and

inhalations of pure O_2 but No.1 was irradiated with ultra-violet rays front and back for 20 minutes. Patient No.1 showed after 40 minutes only 32 per cent saturation with CO i.e only 50 per cent of previous reading. Patient No.2 after one hour had still CO saturation of 50 per cent i.e 70 per cent of previous reading. The irradiated patient regained consciousness much earlier than the other. Koza's opinion on these experiments may be given as follows:

1. Radiation is an effective treatment for CO poisoning.

2. Optimum radiation is between 3130 A.U and 2800 A.U.

3. O_2 must be present, or COHb will not dissociate even with U-V light.

4. Radiation affects the whole activity of the tissues and alters the water, salt and albumen content of the serum.

5. An important factor is the change in the body produced by radiation leading to a shift of the acid-base balance with consequent changes in the metabolism.

6. "CO enters the body through the lungs and leaves by the same way without having been oxidised or broken up".

7. The only objection to light therapy is the severe erythema caused by the ultra-violet rays.

Engel (1933) criticised both the theoretical bases and the experiments reported by Koza and also his clinical observations.

Nori and Niiro (1934) found that irradiation of CO-poisoned animals was decidedly effective in increasing their speed of recovery.

Estler (1936) at Engel's suggestion carried out experiments on white rabbits taking precautions to meet Engel's criticisms. Pure CO was mixed with a continuous current of air for poisoning the animals. Both the air and the CO were measured. Poisoning was continued until the onset of unconsciousness, the period of inhalation varying from 11 to 71 minutes. Irradiation was by a quartz mercury vapour lamp at 40 cms distance for the first few experiments then at 30 cms. The period of irradiation was 10 minutes. The control was left in an open wire cage immediately alongside the experimental animal, only protected from the rays. The CO content of the blood was determined by the Van Slyke Manometric apparatus. Estler found that this irradiation produced no effect upon the clinical course of the poisoning nor was any shortening of the disintoxication period achieved. He also carried out a series of experiments to test the effect of irradiation during the CO poisoning itself. Here again he found no significant difference between those animals irradiated and controls.

Engel's and Estler's criticisms of the work of

Koza and of Macht Blackman and Kelly which made Estler carry out these experiments were as follows:-

a. It was agreed that light could penetrate the skin and be absorbed by the erythrocytes. But the penetration is small and so only that portion of the total blood flowing at the time through the vessels of the skin is accessible to the rays. Since the dissociation of COHb in vitro by light is reversible when light is removed, it would seem likely that as soon as the blood passed away from the irradiated region the CO would again combine, to the previous degree of saturation.

b. Estler accepts the results of Macht Blackman and Kelly that their animals exposed to light recovered much quicker than those in the dark though he did not confirm it. However, he found the objection that the stimulus of light increases respiration and the elimination of CO. He then finds it difficult to say how far the recovery is due to direct action of light on the COHb.

Bodine and Boell (1937) found that in embryos the CO - inhibition of oxygen consumption was considerably diminished by light. The respiration in light was 75% of normal while in the dark it was only 25% of normal. They used a 450 watt tungsten filament lamp and glass sided water bath.

Discussion.

On reviewing the papers which have just been discussed and outlined, several points strike the unbiased observer.

1. Estler appears to assume that the results of in vitro experiments can be directly applied to the living organism. Surely one cannot believe that everything is known about the biological effects of radiation, and to dismiss the results obtained on animals by Koza and Macht and Blackman and Nori and Niiro because they do not agree with results obtained with shed blood does not seem logical.

2. Estler only irradiated his rabbits for ten minutes. This is a very short time in the somewhat prolonged disintoxication of the blood in CO poisoning.

3. In all the papers it is assumed, because of in vitro findings, that it is the ultra-violet radiation which is or might be effective. No attempt is made to try the longer, more penetrative rays by themselves or, indeed, to isolate the short ultra-violet rays. Mass radiation is used and the ultra-violet rays are given the credit for anything which does/not or does happen.

4. Estler objected to irradiation therapy because he maintained that the CO which is liberated in the skin recombines with

haemoglobin before it can reach the lungs. This argument, however, ignores the fact that the recombination of CO with haemoglobin may take an appreciable time. According to Roughton (1934) the reaction of CO with oxyhaemoglobin may have a half-period of more than 30 seconds when the reactants are in low concentrations. The reaction of CO with reduced haemoglobin is much faster and occupies only a fraction ofa second. Venous blood, however, probably contains very few completely reduced haemoglobin molecules and consists mainly of the intermediate compounds Hb_4O_4, Hb_4O_6 etc. The rate of reaction between these and CO is not known at present but there is no reason to assume that it is necessarily a very fast reaction. Another factor which would tend to slow up the reaction is the diffusion from plasma to corpuscles. CO is liberated by light in the skin capillaries and would then diffuse from the corpuscles into the plasma. In the veins it would tend to diffuse back into the corpuscles butthis process might take some time because the CO diffusion gradients would be very slight. In this connection the Hartridge and Roughton (1927) work is relevant. They found that the reaction between haemoglobin and oxygen takes place much more slowly in whole than in laked blood.

Roughton's work shows that it is possible for CO,

under certain circumstances, which is liberated in the skin to reach the lungs while still in solution in the plasma. Estler's general condemnation is therefore destroyed. It may be that in practice his point of view is borne out but it must be proved or disproved not on paper but in experiment. In addition to this argument why Estler's opinions are untenable the following may be considered.

The results shown by Estler on the one hand and by Macht and Blackman, Koza, and Nori and Niiro on the other are completely contradictory. It follows that one opinion is wrong.

When the recovery from CO poisoning is mentioned it is always assumed that O_2 drives off the CO from the COHb and that the CO goes into solution in the plasma, passes to the lungs and is there expired unchanged. Thus Haldane and Priestley (1935) say "CO is not oxidised or otherwise decomposed in the living body of any animal" and "CO passes in by the lungs and passes out far more rapidly than is generally supposed - by the lungs without there being the smallest loss". In spite of this statement by such an authority one cannot but consider that CO is a step in the oxidation of carbon to CO_2 and that this is a process which is continually going on in the body. A quantitative proof of the accepted theory was sought in the

literature but was not found. On the other hand it was discovered that Hoppe-Seyler some fifty or sixty years ago had believed that CO was oxidised to CO_2 in the blood, and to hasten this he recommended artificial respiration as the treatment for CO intoxication. Those investigating recovery from CO poisoning have entirely confined themselves to estimating the CO present in the blood by gasometric, spectroscopic or similar methods. No records of any experiments could be found where this has been combined with collection and quantitative analysis of the air expired from the lungs.

However Fenn and Cobb (1932a and b) have shown that the presence of CO caused an increase in the respiration of tissue especially heart and skeletal muscle. They then showed by simultaneous determinations of the total gas absorbed and of the O_2 consumed that the increased gas absorption is due to burning of the CO to CO_2. Haldane criticised the results as follows, "It is true that Fenn and Cobb state that CO is oxidised by frogs' muscle. They found that when the muscle, immersed in Ringer's solution, was in contact with an atmosphere of 79 per cent CO and 21 per cent O_2 gas was absorbed more quickly than when air was used. They give no evidence, however, that they allowed for the fact that CO is much more soluble than nitrogen, nor did they apparently take into account

combination of CO with Cytochrome --- Hence their conclusion that CO is oxidised by muscle does not seem to be justified on the evidence".

Fenn and Cobb's experiments were carried out by immersing tissue in Ringer's solution and passing either CO plus O_2 or Nitrogen plus O_2 mixtures over. Samples of the mixtures were taken after this and analysed. In their paper on the "Burning of CO by Heart and Skeletal muscle" there is nothing to show that it is not the difference in solubility between nitrogen and CO which is responsible for the results but in their previous paper on the effect of CO on muscle respiration (1932a) they show that CO increases respiration over a period of three and a half hours samples being taken throughout. During that time respiration in frog sartorius remained about one and a half to three times as rapid as when the muscle was in air. If this phenomenon was due to increased solubility surely absorption would only have occurred at the beginning of the period in CO and when the muscle and Ringer's solution had dissolved all the CO they could it would have ceased and respiration would have been at the same rate as in the nitrogen - O_2 mixture. It is, of course, possible that so little gas in proportion to solution was used that the fluid could not become saturated but it is not clear in the paper if

this was so. Also these authors found that "Washing the minced muscle in water destroys its ability to consume oxygen but this ability is revived by the addition of sodium lactate as substrate". Washing in this way should not affect the difference in solubility of gases.

Schmitt and Scott (1933) have also carried out experiments similar to those of Fenn and Cobb. They found that CO + 21 per cent O_2 produced definite acceleration in O_2 consumption of skeletal muscle, heart muscle, stomach liver and sperm. When O_2 concentration is lower inhibition is produced but this inhibition is removed by irradiation with a lamp rich in rays around 4000 A.U, that is to say, the regions where the respiratory enzyme showed the greatest absorption.

Fenn and Cobb's ideas as to the mechanism of oxidation were as follows "The oxidation of CO to CO_2 is also well known among the bacteria some of which (Carboxydomonas derive their energy from this reaction. More recently it has been shown by Negelein (1931) that CO can be burned to CO_2 by Hemin in $\frac{n}{1}$ NaOH if the O_2 tension is low enough to leave the Fe only partially oxidised. Presumably therefore Warburg's iron-containing respiratory ferment is responsible for the oxidation of CO in tissues".

Other possibilities may be considered such as the

reduction or oxidation of CO in the plasma whether in the actual blood vessels or in the tissue spaces. CO and CO_2 in solution do not readily interact without the presence of some activator. Remembering the opinions of Berzelius that catalysts and enzymes are similar if not the same one must allow the contention that the body including the "milieu interieur" is remarkably well supplied with a diversity of such compounds.

The following are some catalytic reactions involving carbon monoxide.

1. Catalysis of CO to CO_2 and H_2O.

Dakin (1922) in his monograph on oxidation and reduction in the animal body says that CO and O_2 in water will remain un-united but if a catalyst such as platinum black is present the following reaction will occur

1. $CO + H_2O \rightleftharpoons HCOOH$
2. $2HCOOH + O_2 \rightleftharpoons 2H_2O + 2CO_2$

The activated oxygen required for this reaction is obtained by the disintegration of water in the presence of a hydrogen acceptor

$$2H_2O - H \text{ acceptor} - 4H + \text{Activated } O_2$$

The hydrogen recombines with the molecular oxygen to form water.

Substances which can produce this series of

reactions are Palladium Chloride, Iodine pentoxide and concentrated nitric acid.

Enzymes have also been shown to have similar effects. These are the dehydrogenases which as mentioned in a previous chapter activate the hydrogen of the substrate so that it can unite with molecular O_2 either directly or indirectly through an intermediary, to form water. This activation may be caused in the same way as Palladium black causes the reaction shown above, that is, by uniting with hydrogen and then liberating it. If this could be done with water as the substrate the oxygen would, of course, be more active chemically than molecular oxygen. Oxygen is, of course, activated directly in the tissues by the oxidases. That methylene blue may act as a hydrogen acceptor under certain circumstances has been shown with Lactic acid.

1. $CH_3CHOHCOOH \longrightarrow CH_3COCOOH + H_2$
   (Lactic acid) (Pyruvic acid)
2. $H_2 + M.B. \longrightarrow M.B.H_2$ (Leuco methylene blue)
3. $2MBH_2 + O_2 \longrightarrow 2M.B + 2H_2O.$

A dehydrogenase is however needed to activate the H_2 before it can combine with the methylene blue.

In the body oxidised cytochrome takes the part played by methylene blue.

It is suggested that it is possible for the

hydrolysis of CO through Formic acid to CO_2 and water to occur in the body. The oxidation-reduction processes of the tissues are, as described at present, of remarkable variety and complexity and the life of the tissues depends on the activation of oxygen by oxidases and of hydrogen by dehydrogenases. The hydrolysis of CO would appear on the face of it at least as simple a reaction as those involved in the utilisation of carbohydrates, proteins or fats.

2. Catalysis of CO and O_2 by light to CO_2.

Chapman, Chadwick and Ramsbottom (1907) found that ultra-violet light acts as a catalyst for CO and O_2 when in gaseous form and that the presence of moisture does not appreciably interfere.

3. Catalysis of CO by light to HCHO.

Herchefinkel (1909) and Berthelot and Gaudechon (1910) showed that the following reactions proceeded readily

$$CO + H_2 \xrightarrow[\text{light}]{} HCHO \xrightarrow[\text{light}]{} \text{Polymers}$$

It is interesting to correlate this with the theory put forward by Baeyer in 1870 regarding the formation of carbohydrates in the plant. This was that the first step in carbohydrate synthesis was a reduction of CO_2 to CO which is then further reduced to HCHO. This is followed by formation of sugars and polysaccharides. Van Niel (1935)

believes that the primary action of light in plant photo-synthesis is the activation of hydrogen. This is derived from H_2O molecules and is transferred to CO_2 to form formaldehyde. The transfer of activated hydrogen to CO could also result in formation of formaldehyde.

If we summarise these findings and theories it may be said that the conditions favourable to the utilisation of CO in the body after it is liberated from the haemoglobin are:-

1. Presence of activated oxygen or hydrogen.
2. Irradiation.

The former is definitely present in the tissues as it is a sine qua non of tissue metabolism. If this is not available it is possible that ultra violet light may have an activating effect on the hydrogen of the water of the plasma. It might of course be possible to inject some catalyst into the blood-stream but it seems likely that it would have some effects other than those desired.

In brief then it may be said that there is evidence which would make it appear at least possible for combustion of CO to occur in the body. If even this very modified statement can be accepted and if the work of Roughton, which is discussed above, is taken into account the theoretical objection put forward by Estler to irradiation

therapy namely, that the liberated CO after dissociation merely re-unites with the Hb to the same degree as before, is invalid. The original idea of Macht and Blackman that "radiation might possibly influence the toxicity of Carbon monoxide by hastening the dissociation of the Carbon monoxide from the Haemoglobin" could then be considered reasonable.

The present writer with these points in mind and considering that as far as he was able to discover, only five papers had ever been published on this subject considered that further experiments might be of value. These are described below.

Recapitulation.

1. The effect of light on COHb is discussed and it is observed that although ultra-violet light may be more effective in splitting this compound in vitro yet the penetrative power of the visible rays, which have also an appreciable dissociative effect, may make them more effective in vivo.
2. Certain workers have found increased speed of recovery under radiation. One found no appreciable effect.
3. The theoretical objections of Engel and Estler to the work of Macht and Blackman and of Koza are considered and discussed.

EXPERIMENTAL STUDY.

It appeared that the chief objections to results showing benefit to animals irradiated after CO poisoning were

1. That this benefit did not in fact occur.

2. If it did occur it was not due to any effect on CO Hb or O_2Hb in the body but to increased respiration caused by actinic or heat rays.

3. That ultra-violet light is the only light which has any effect on CO Hb and that ultra-violet light is not sufficiently penetrative to reach the circulating blood.

The experiments described below were devised to meet these objections. For them to be met absolutely it would have been necessary to employ some mechanical apparatus capable of producing artificial respiration of a predetermined rate and volume. The present writer did not carry out these experiments in a physiological laboratory and had no such apparatus available. The best he could do, therefore, was to endeavour to eliminate heat and ultra-violet light as far as possible, working on the idea described above that the violet end of the visible spectrum might be effective in aiding O_2 to displace CO in the haemoglobin.

The general lines of the experiments were as follows:-

Twenty white rabbits were used, of both sexes, and of an average weight of 2420 grams. They were shaved as shown

Fig. 5a

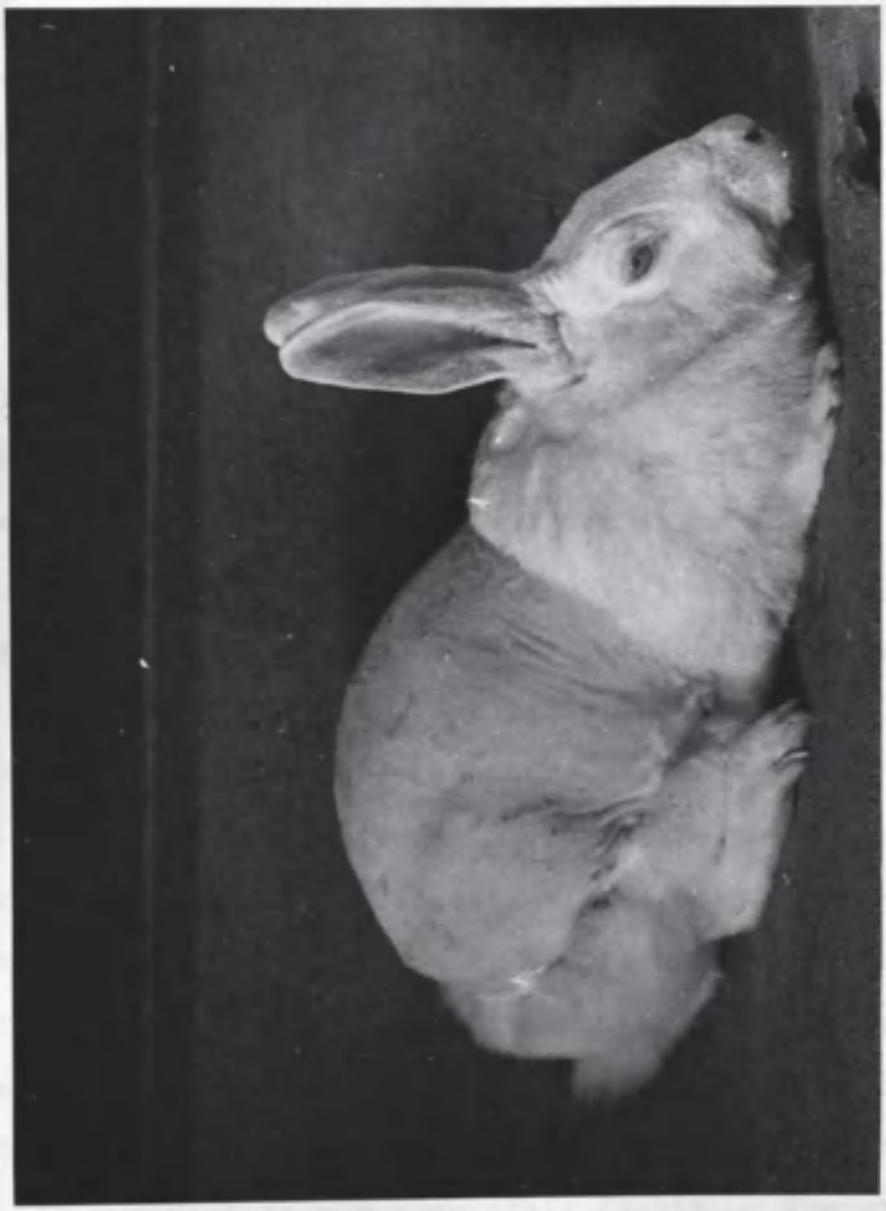


Fig. 5b

in Fig.5. They were asphyxiated in a chamber of approximately 120 litres containing approximately 1% CO until completely flaccid then were removed and a sample of blood taken immediately from the marginal vein of the ear. Then they were put in a cage surrounded by five 500 watt electric lamps. Further blood samples were taken at intervals. The lamps were shielded by water and glass filters. Each animal was asphyxiated four times. On two occasions it was treated as above and on other two in exactly the same way but the current to the electric lamps was not switched on.

The CO was manufactured in the usual way by dropping concentrated sulphuric acid into warm strong formic acid and passing the resultant gases through Soda lime. The CO was collected in rubber bladders.

The chamber used to asphyxiate the animals was a tea chest of 120 litres capacity with a hole large enough to admit a rabbit cut in one side. This hole was covered by a sheet of glass when the animal was in so that it could easily be watched. A bladder containing about one and a half litres of CO was emptied into this box and the rabbit was removed when its musculature was completely flabby. The criterion used was inability to hold up the head even when roused by shaking the box. This stage was usually reached in about

fifteen minutes but variations occurred from four to forty five minutes. It was observed that the smaller animals were more resistant than the larger.

The rabbit was now removed from the box and the observation of the speed of its recovery began. A considerable time was spent before this series of experiments was begun in trying to find the best way to go about this. It was soon discovered that any attempt at estimating the recovery of rabbits or guinea pigs from CO asphyxia by clinical observation was extremely difficult, and indeed useless unless very large numbers of animals were used. Time and expense made this impossible. Therefore, it was decided to endeavour to follow the elimination of CO from the blood. Two forms of analytical apparatus were available, a Van Slyke's Volumetric Blood Gas apparatus and a Hartridge Reversion Spectroscope. The latter was used for the following reasons. The Van Slyke apparatus is admittedly more accurate but two cubic centimetres of blood are needed for each estimation. This meant taking off three cubic centimetres to allow a margin of error, four or five times each experiment. The difficulties in doing this especially after the first one or two experiments on a given animal were too great. It must be remembered that the blood had to be kept air free. Also to make air free solutions, prepare the apparatus and do five analyses took about three

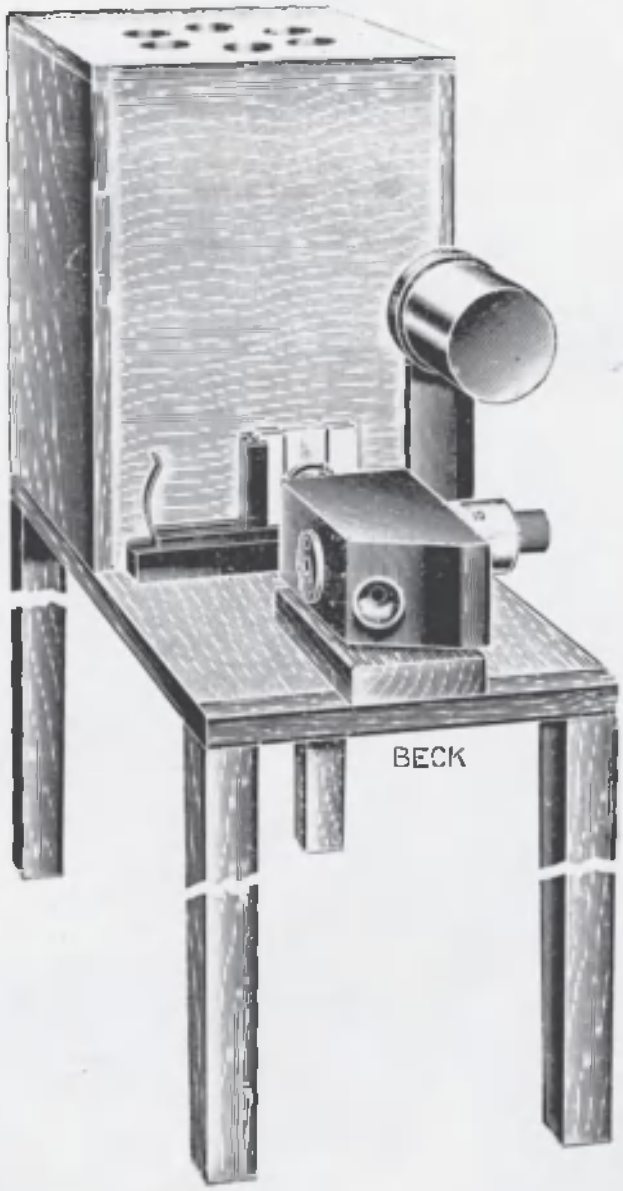


Fig. 6

hours. Using the Hartridge Spectroscope (See Fig.6) however three drops of blood only are needed. The method adopted was to pierce the vein and as the blood welled to the surface collect it in a Pasteur pipette and transfer it immediately to the spectroscope cell which had been previously filled with distilled water. This whole manoeuvre took two or three seconds. Moreover the analysis of the blood taken off could be carried out between each removal of blood from the animal. The saving of time was therefore very considerable. The exposure of blood to the air was minimal.

The method of using the Hartridge Reversion Spectroscope employed was that described by Frederick (1931, 1937). This instrument doubles the movement of the absorption bands towards the blue when O_2Hb is converted into CO Hb, by arranging one spectrum above another in opposing directions i.e. Red to blue and blue to red. By placing the alpha bands which are most convenient, so that they appear to be in line a reading can be taken which will show on a vernier gauge the movement which has taken place. A calibration curve is first produced by each individual who is to use the apparatus. This is done by making solutions of pure CO Hb and O_2Hb diluting them with distilled water, and making optical mixtures. Thus to produce a reading on the spectroscope for 75% CO Hb the

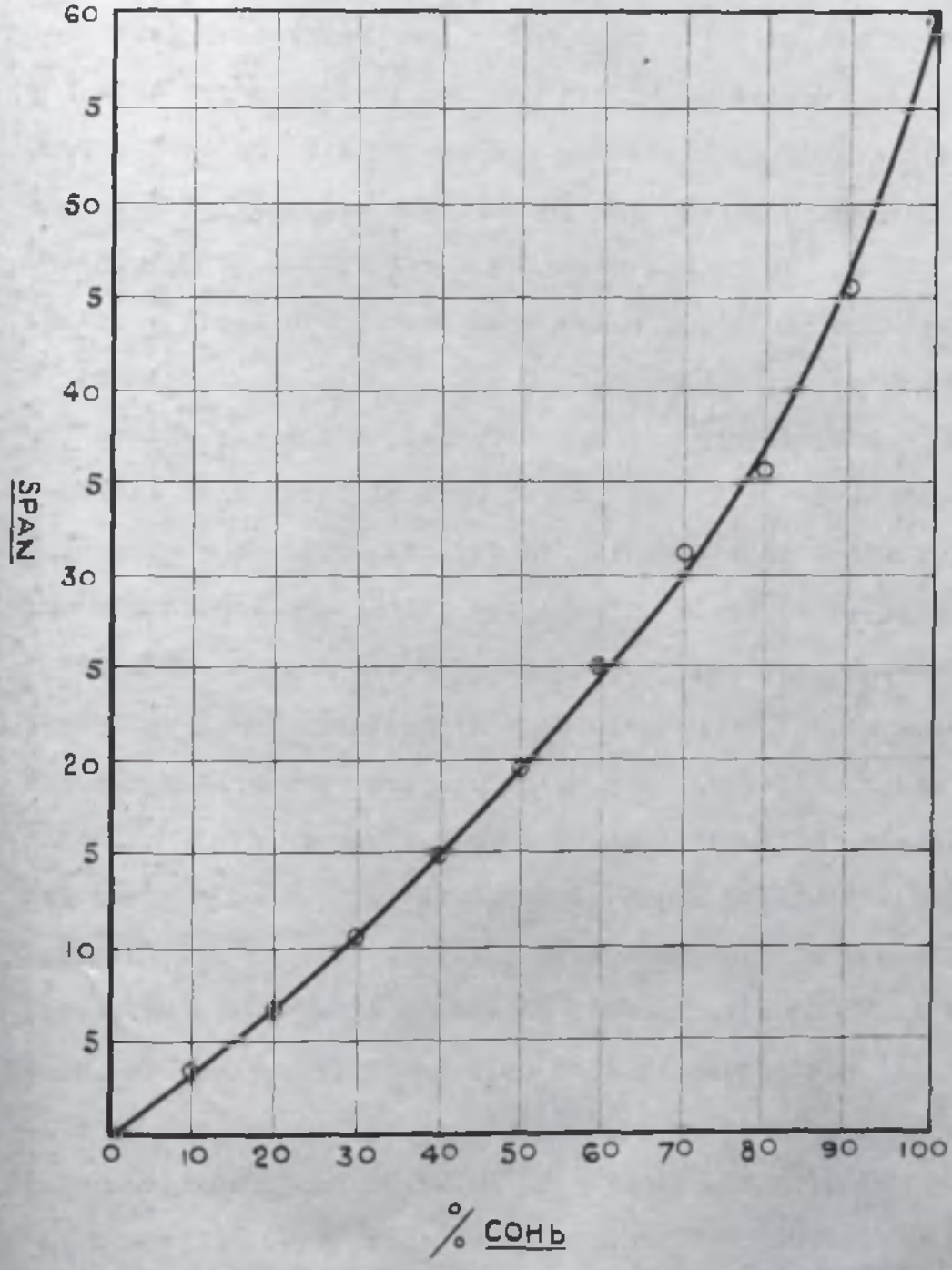


Fig. 7

following is carried out. The O_2Hb solution and the CO Hb solution are made of blood and distilled water in the same proportions until they produce a convenient absorption band. Then two glass cells are filled, the one with 25% O_2Hb and 75% distilled water, the other with 75% CO Hb and 25% distilled water. These are placed one behind the other and an average of ten readings taken. Fig.7 shows the curve produced in this way by the present writer with the instrument used. As readings vary slightly from day to day this curve should be used only for calculating CO Hb percentage from the "span" i.e the difference in reading between the blood to be analysed and a sample of normal blood. The actual readings have not therefore, been inserted in this diagram. The accepted experimental error for this instrument is ± 5% (Sendroy 1938).

The apparatus used to irradiate the animals was extremely simple. It is shown in Fig.8 and in diagrammatic form in Fig.9. It consisted of a wire cage surrounded by five aluminimum reflectors each containing a 500 Watt electric bulb, of the gas filled coiled coil filament type. In front of each lamp was a glass specimen jar containing water. The internal dimensions of this jar were 12 ins x 12 ins x 4 ins and the walls were about three tenths of an inch thick. In addition to this there was placed in front of the lamp a sheet

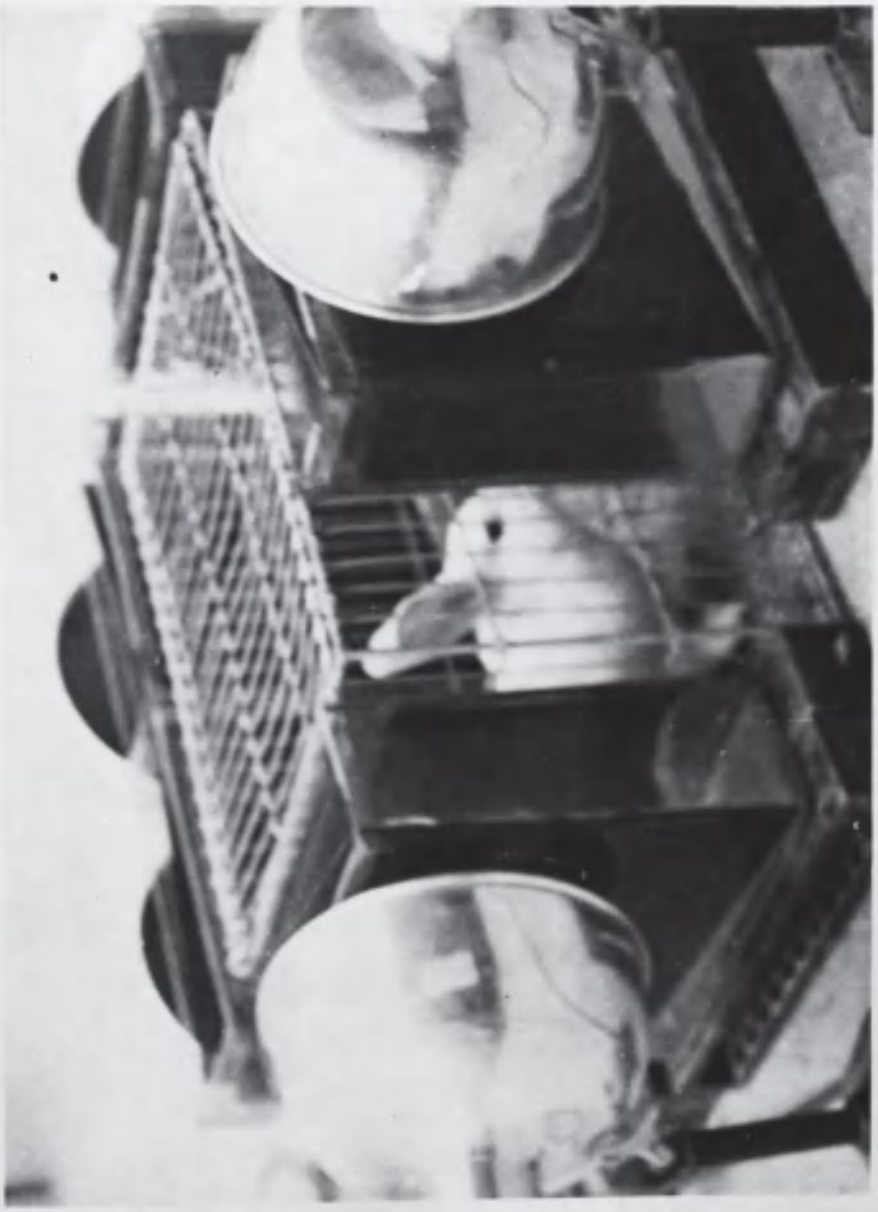


Fig. 8

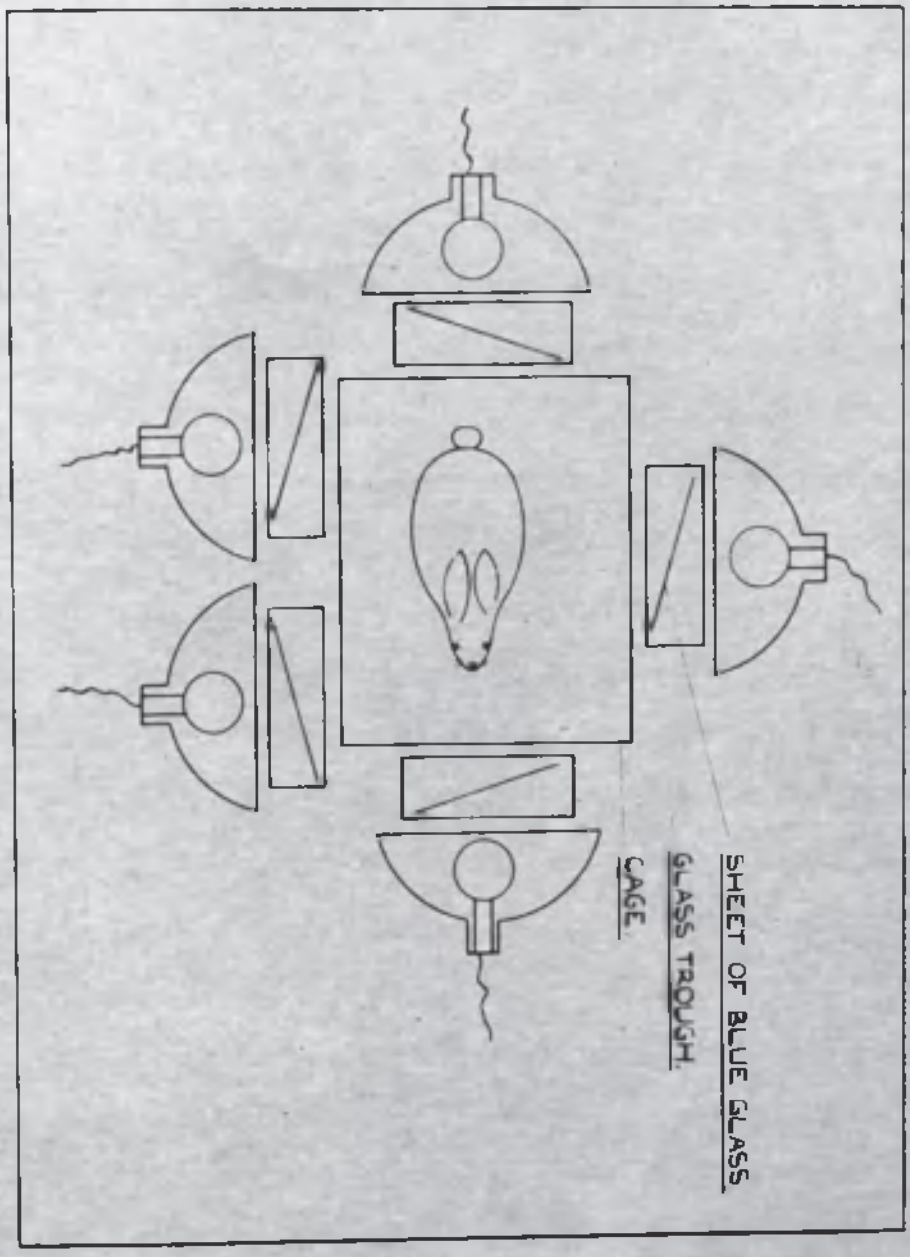


Fig. 9

of cobalt glass one tenth of an inch thick.

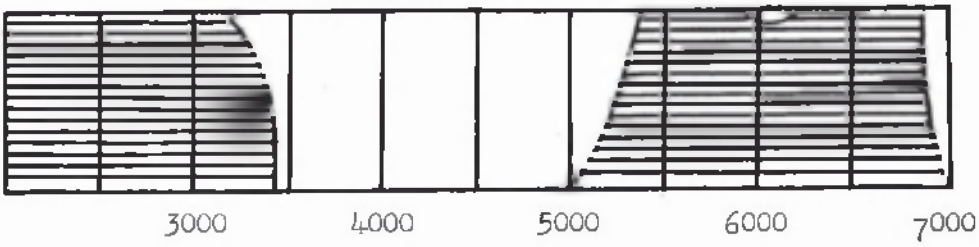
The effect of cobalt glass as a filter is shown in Fig.10. Fig.11 shows the transmission of light through four inches of water from one 100 Watt electric bulb. The combined effect of the cobalt glass and the 6/10ths of an inch thick sides of the glass jars was to make the cut-off for ultra-violet light at least 3250 A.U, if not even nearer the red still. At the other end of the spectrum the cut-off was not so efficient but it was still very good. An ordinary mercury thermometer was not appreciably affected if placed one foot away from the filter on the other side from the lamp.

As was observed above, Hasselbalch found that light of a wavelength of 3100 A.U was the most effective in dissociating CO Hb and other workers have assumed that only these rays are effective. In these experiments these rays are excluded.

Any gross interference of the results by heat was also out of the question.

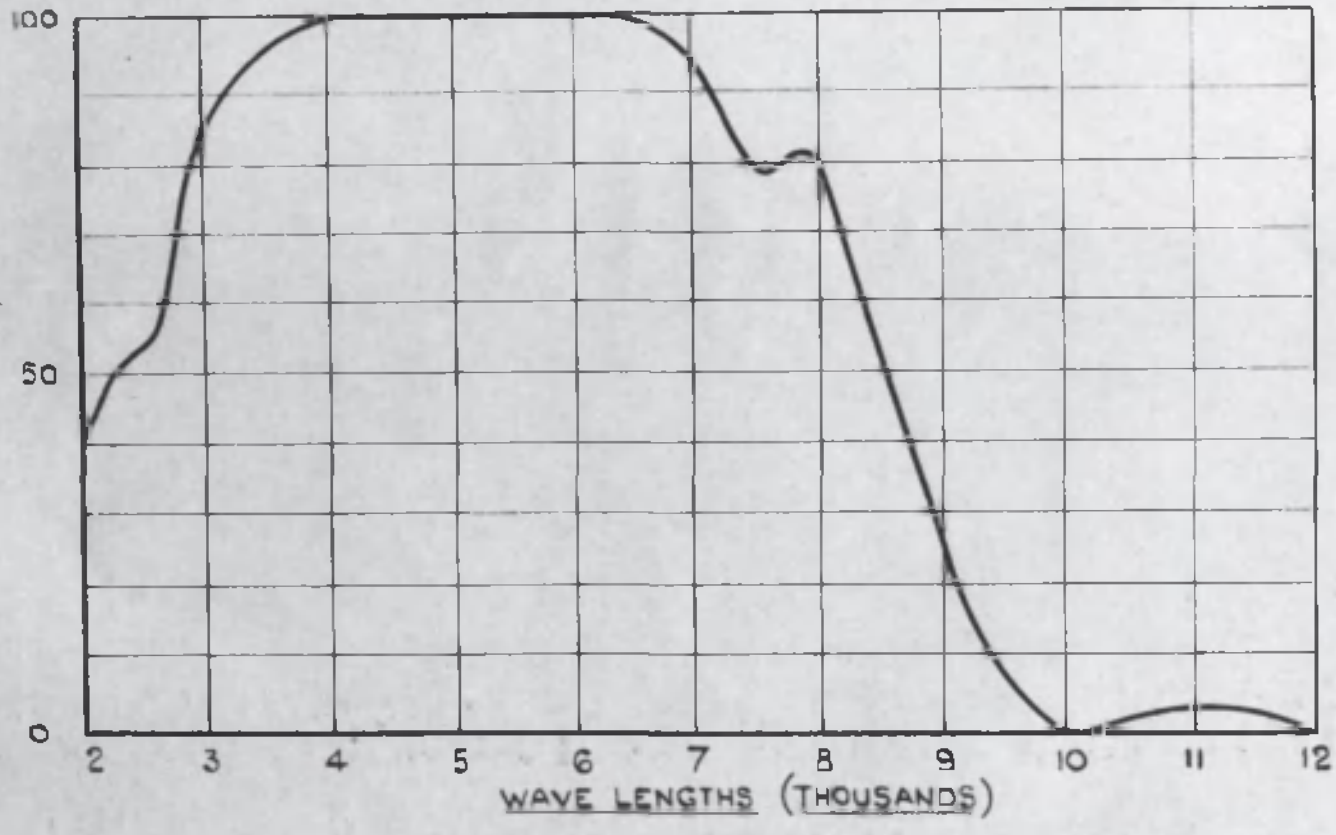
In order to forestall the criticism that acclimatisation might result from carrying out several experiments on the same animal, the rabbits were always allowed ample time to recover before being used again. In a few instances this time was only forty eight hours but

Fig. 10



Cobalt glass as a Light Filter.

(After Wood, 1934)



TRANSMISSION OF LIGHT FROM ONE 100 WATT TUNGSTEN FILAMENT LAMP THROUGH WATER 10 C.M. THICK.

Fig. 11 (After Laurens)

usually it was two weeks. This precaution, together with the limited time at the writer's disposal resulted in over a year being needed to perform the eighty experiments described. This lengthy period with its changes in climatic conditions must be taken into consideration as no difference is noticeable in the results obtained at different times of the year. If heat from the lamps was responsible for any result it would seem likely that this would be more noticeable in the winter than in the summer.

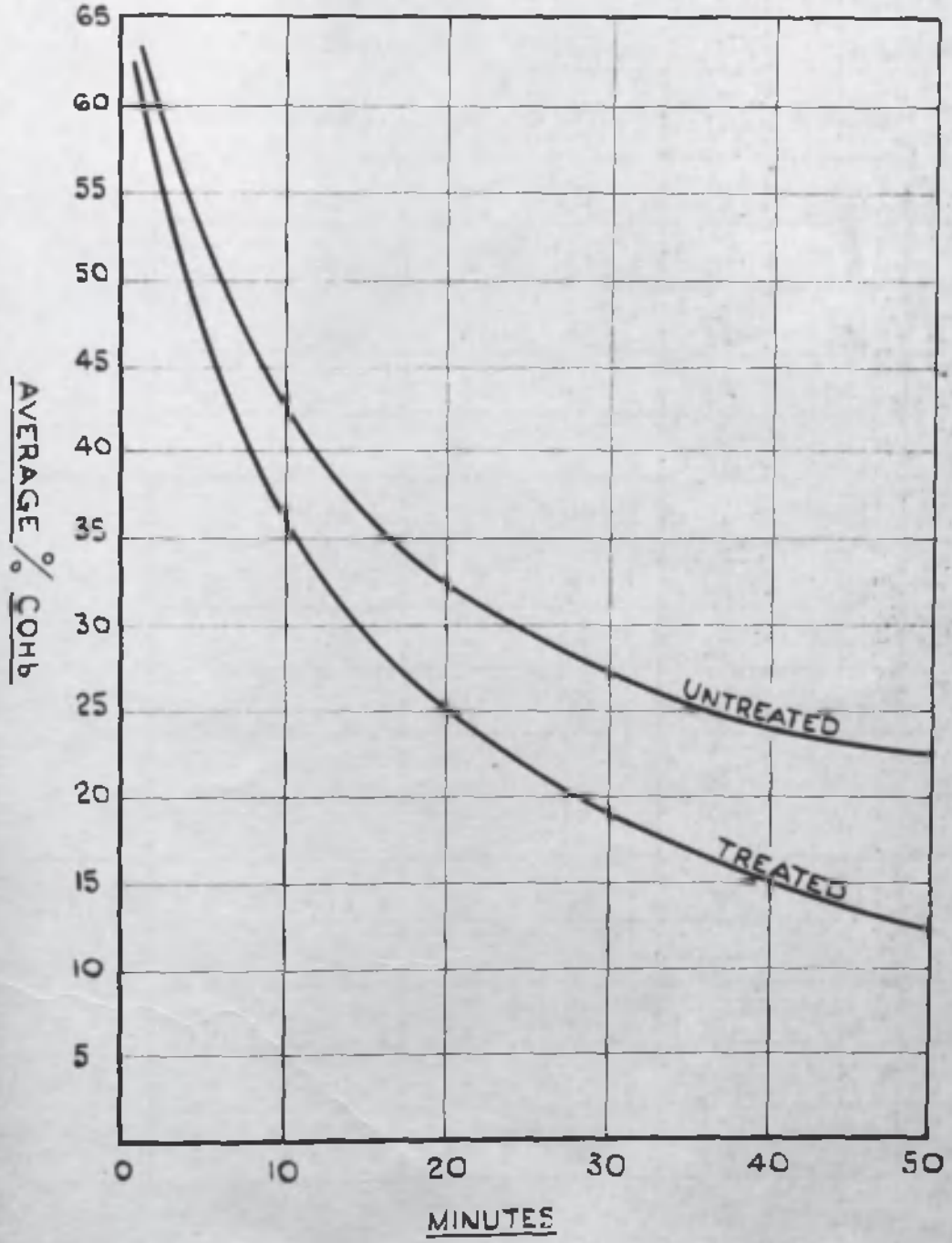
Owing to limitations of time only one rabbit could be asphyxiated each day until the last twenty four experiments. Then two rabbits were done on each day the first being irradiated and the second being used as a control but put into the cage when the lamps were still hot.

The control animal when in the cage was not in complete darkness but in the shade, actually in a basement lit by one small window.

Results.

The results of these experiments are shown in Table 14. They have been set out statistically in Table 15 and shown diagrammatically in Fig.12.

It will be seen that there is a difference between the average treated and untreated animals of 6.9% at from



after removal of animal from gas.

Fig. 12

TABLE 14.

RESULTS OF ANIMAL EXPERIMENTS

Rabbit No.	Untreated				Treated			
	X Time.	% COHB.	X Time.	% COHb.	X Time.	% COHB.	X Time.	% COHb.
I.	2	68	3½	64	2	59½	3	68½
	11	48½	8	51½	20	31	15	38½
	24	36½	14	45	33½	20½	28	26
	38	31	22	41	43	19	42	16
			30	36	57	16½		
II.	1	58½	1	57	1	53½	2	57½
	5	46	11	36	11	37½	11	35
	10½	36½	19	31	21	28	21	26½
	22	29½	36	17½	40	20½	32	16½
	30½	23			48	14	44	15
	40	20						
III.	1	62½	2	59	1	62½	1	62
	14	39	12	47½	11	35	11	29½
	25	32	22	32	21	23½	20	19
	35	25½	33	23½	31½	21	31	6
	46	22½	47	20½	41	15	45	3

X. 'Time' means time in minutes after removal of the animal from the gassing chamber.

Rabbit No.	Untreated				Treated			
	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.
IV.	2	56½	1	57	1½	62½	2	54½
	7	43½	6	43	7	51	12	40
	14	39	12	39	22	30½	20	32
	30	27	20	32½	33½	24	31	29
			30	29	45	18	42	23½
V.	2	57½	2	55½	1	61	1	55½
	10	36	10½	39	11	29½	11	30
	21	32	21½	30½	21	17	21	23½
	31	24	31	26½	31	11½	30½	16
	45	19	45	24	45	6	45	11
VI.	1	58	1	60½	1	61	1	59
	12	43½	10	44	12	35	10	32
	25	32½	21	32	22	25	21	24½
	35	27	31	30½	31	19	30	18½
	46	25½	46	26½	46	14	45	14½
VII.	1	59	1	62	½	59	1	59
	10	35	10½	38½	11	38	10	32
	20	26½	21	29½	21	23½	21	24
	30	21½	30	25	31	15	30	18
	44	15	44	20½	45	11	45	14½

Rabbit No.	Untreated				Treated			
	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.
VIII.	1	57	2	54½	3½	54	2	57
	13	42½	11	39	11	34½	10	33
	23	29½	21	28	21	25	20	25
	36	27½	29	26	32	20½	31	15½
	49	23½	45	20	46	13	45	14
IX.	½	66	½	59	1	57	½	60½
	12	32½	10	38½	11	33	11½	31½
	22	26	20	32	20	22	21½	21½
	30	21	31	27½	30	17½	33	17½
	48	15½	45	25	45	11½	46	11
X.	½	66	1	76½	½	72	2	67½
	10	44	11	39½	10	34½	11	31½
	21	32	21	25	20½	23½	20½	21
	32	27	30½	18	32	14	30½	17
	47	22	45	17	48	11	45	11
XI.	½	67	½	65	½	71½	1	66½
	13	34	13	41	11	34	11	31½
	24	26	21	32	21½	21½	20½	18½
	31	22	31	26½	32	15	30	16
	44	15½	48	25½	45	12½	45½	11½

Rabbit No.	Untreated				Treated			
	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.
XII.	½	60	½	61	½	59	1	56
	12	33	11	41	11	30½	11	31
	23	25	20	39	21	20	21	22
	32	20½	32	28	32	16	32	19
	45	18	46	23½	46	11½	46	15
XIII.	½	71	½	71	½	74	½	72½
	10½	43½	11	42	10½	41	10	39
	21	32	20½	32	20	30	20	29½
	30½	29	30	27½	30	19	30	22
	45½	26	46	24	45	16½	45	17½
XIV.	½	66	½	66	½	61½	½	64½
	11	44½	10½	43½	10½	34½	10	34
	20	32½	20	33	21	24	20	25
	30	28½	31	28	30½	19½	31	19½
	45	27	46	23	46	14	46	15
XV.	½	70	½	68	1	67	½	65
	11	43½	10	44	10½	33½	10½	37½
	20	34½	20	34	20½	25	20	25
	31	29	30½	26½	30½	19½	30	18
	45	26	44½	23	45	14	45½	13

Rabbit No.	Untreated				Treated			
	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.
XVI.	1	67	½	63	½	66	½	63
	11½	44	11	43½	11	33	11	35
	20	32	21	33	20	25	21½	24
	29½	30	30	27½	31½	19	31	19
	46	25½	45	23½	44½	15	45	14½
XVII.	½	63	½	65	½	66½	½	66
	10½	42½	10	44	10½	34	11	36
	20½	32	20	34	20½	21½	20½	26½
	31	28	30½	29½	31	16½	31	16½
	46	22½	45	25	45	12	45½	12
XVIII.	½	66	½	69	1	65½	1	64
	10½	43	11	46	11	37½	11½	40
	21	34	21	35½	20½	26½	21	32
	31	28	32	29½	31	20½	30	26½
	46	23½	46	26	45	18	46	20
XIX.	1	63	1	68	1	64½	½	62½
	13½	42	12	45	12	35	13	36
	22	30	21	36	20	26½	21	26½
	33½	25	32	30½	30	23½	31½	20½
	45½	21½	45	26½	45	16½	46	18

Rabbit No.	Untreated				Treated			
	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.	Time.	% COHb.
XX.	½	63½	½	65½	½	64	1	64
	12½	42½	11½	42½	13½	28	11½	36½
	21½	33	21½	30½	20½	17½	21½	23½
	31	30½	31	28	32	15	33	19½
	46	23½	46	23	46½	9	47½	15

TABLE 15.

STATISTICAL TREATMENT OF RESULTS SHEWN in TABLE 14.

COHb %	After ½ - 2 mins		After 10 - 14 mins	
	Untreated	Treated.	Untreated	Treated.
76-	1			
74-		1		
72-		2		
70-	3	1		
68-	4			
66-	7	6		
64-	3	7		
62-	6	5		
60-	3	4		
58-	5	5		
56-	5	4		
54-	2	2		
52-		1		
50-				
48-			1	
46-			2	
44-			8	
42-			12	
40-			2	3
38-			8	2
36-			3	6
34-			2	11
32-			2	6
30-				6
28-				3
26-				
24-				
22-				
20-				
18-				
16-				
14-				
12-				
10-				
8-				
6-				
4-				
2-				
Total	39	38	40	37
Mean	63.3	62.7	41.2	34.3
σ	5.1	4.9	3.8	3.1
Difference	0.6		6.9	
S.E.	± 1.14		± .79	

After 20-24 mins		After 30-35 mins		After 44-48 mins	
Untreated	Treated.	Untreated	Treated.	Untreated	Treated.
1					
1					
2		1			
5					
15	2				
3	3	3			
4	2	11	1		
3	5	9	1	6	
2	11	4	1	7	
	7	3	2	10	
	5	3	5	4	1
	2	1	12	2	3
	2		9	1	3
			5	3	13
					5
			1		8
					1
			1		1
					1
36	40	35	38	33	36
31.8	24.5	26.7	18.3	22.6	13.4
3.6	3.7	3.4	3.9	3.4	3.3
7.3 ± .84		8.4 ± .86		9.2 ± .81	

10-14 mins, 7.3% at 20-24 mins. 8.4% at 30-35 mins and 9.2% at 44-48 minutes. The similarity at the beginning of the experiments in the average percentage saturation of CO in both groups is gratifying considering the rule of thumb method used in deciding when to remove the animal from the gas. The difference between treated and untreated average is at all points considerably greater than twice the standard error and so can be considered statistically significant.

We can therefore say that the treatment employed was successful in that after 45 minutes the treated animal had fallen from 63 to 13.4 per cent whereas the untreated had only fallen to 22.6 per cent.

If the time taken to recover from 60 per cent to 30 per cent saturation is considered it will be seen from the graph that the treated average is about 13 minutes and that the untreated time is 22 minutes. The treated average is thus 59 per cent of the untreated. Such a result is worthy of consideration.

One point worthy of thought is that there appears to be greater divergence in the treated and untreated results at the beginning of the treatment than later.

Discussion.

The question which now arises is whether this

result which is statistically significant is physiologically significant. What has caused the increased speed of recovery? It would seem reasonable to say that the radiation was responsible in one of the following ways:-

(a) by increasing metabolism, or in other words, by increasing the speed of gaseous exchange in the body

(b) by specific action on the carboxyhaemoglobin.

Engel (1933) made the former possibility his objection to the validity of Koza's work. The present writer was, owing to the limitations under which he worked, unable to measure the respiratory volume of the rabbits used. On the other hand he has reviewed the literature on the subject and there does not appear to be any justification for Engel's objection. Here it may be said that no evidence of increased breathing, whether in speed or in depth was at any time observed when the animals were being irradiated. Also the writer cannot conceive that heat from the lamps could produce the results especially when the flaccid state of the animals is considered. The only heating effect observed was a slight rise in temperature, occasionally up to one degree Fahrenheit, of the air in the room as a whole. Heat did not appear to penetrate the filters. It is possible that some such effect as Hill's nose opening reflex may have occurred but this could not have

any effect if there was no alteration in the respiration. Heliotherapists and clinicians e.g. Russell & Russell (1928) are accustomed to say that irradiation especially when resulting in erythema produces deeper and slower respiration. This has not been borne out in controlled experiments in men or animals.

Hill and Campbell (1922) carried out experiments on children both at Alton in England and Montana in Switzerland and came to the conclusion that any increase in metabolism was due to the open air and not to the sun. Also Fries (1925, 1927) and Fries and Topper (1927) showed that the improvement in the general condition of children receiving ultra-violet treatment was not due to a rise in the basal metabolic rate because the same children showed no difference when being irradiated and when not.

Early work by Von Platen (1875) and Speck (1880) is reviewed by Laurens (1933). Von Platen believed that light increased O_2 consumption and CO_2 output by its effect on the retina. Speck concluded that this was not the case but that pulmonary ventilation is less in the dark than in the light. Crofts and Laurens found that any sudden change of illumination produced a very transitory increase in a frogs respiratory movement.

Harris (1926) found that various parts of the spectrum had different effects. Rays from 4360 A.U to 2910 A.U produced rapid and considerable increase in the gaseous metabolism and in the movements of the isolated stomach of the frog. However, he found that this stimulation was completely annulled by the presence of visible radiation.

Campbell (1926) using mice, rats and healthy men was unable to find this increase due to ultra-violet light. He found no increase in metabolism when the quartz mercury vapour lamp was used either giving the ultra-violet alone, the visible or the total emanation.

Eichelberger (1926) irradiated nine women and two men for 5-50 minutes with a carbon lamp at 6 to 7 feet and found no appreciable effect or metabolism.

Mason and Mason (1927) review the literature and observe that Harris's findings concerning the neutralising power of visible radiation on the increase in metabolism caused by the ultra-violet is borne out by work by Henri and Henri on the slowing of protoplasmic movements in unicelluiar organisms and by Hill in infusoria. They found that the basal metabolism was lowered in certain individuals after irradiation.

Crofts (1928 a and b) and Hardy (1928) carried out a series of experiments on canaries rabbits and human subjects.

Crofts found that irradiation of canaries by quartz mercury vapour lamps produced a sudden drop in oxygen consumption and produced no effect whatever on the human subjects. Hardy carried on this work using rabbits. Quartz mercury vapour lamps were used and irradiation of the shaved side of one animal and of the ears of another for 20 minutes each at a distance of 18 ins had no effects. Not only was there no increase in metabolism during and after one dose but there was none after successive doses.

Faced with this evidence the present writer cannot believe that the 500 Watt bulbs shielded as they were by 4 ins of water and over half an inch of glass could produce any alteration in the gaseous metabolism. Laurens (1933) says "Practically all of the work that has been done from the experimental and clinical point of view indicates that the benefits of irradiation are not accompanied by any influence on basal metabolism. A man by a few small muscular contractions per minute can change his metabolism much more markedly than by several hours of irradiation".

As for the possible effect of heat in experiments Wright (1936) says "Exposure to heat of brief duration has little effect on metabolism as compensation is effected mainly by increasing heat loss; if the exposure is prolonged a gradual

fall in the metabolic rate takes place".

It is submitted that Engel's objections to Koza's work is not borne out by experimental evidence. It is further submitted that the method of irradiation described in this thesis is even less likely to produce changes in respiration than when the naked arc is used.

If this is accepted another cause must be found. The cobalt glass filters used permitted the free passage of rays between 3500 A.U and 5000 A.U. But blood absorbs all rays up to 4500 A.U namely, two thirds of the total ultra-violet and visible rays transmitted, and penetration has been shown by Bachem & Reed (See Table 13) to be very free at these wavelengths down to the first vascular layer of the skin, when of course they are entirely absorbed. The light in the neighbourhood of 4000 A.U will cause a dissociation of CO Hb ~~in forming O_2~~ if O_2 is present. What then happens to the CO in solution in plasma? The present writer believes that in the rabbit, with its high rate of metabolism and the small time necessary for the blood to pass from the skin to the lungs, the gas will in great part remain in solution and be breathed out by the lungs. He believes that this is a reasonable explanation of the results obtained. While the possibility of combustion of CO in the body was used as an argument earlier

in this thesis it was used frankly as an argument and it is felt that the answer will be found in the study of the kinetics of haemoglobin. Nevertheless the question of oxidation of CO in the body should not be entirely shelved. The writer believes that there has been an over simplification of thought in connection with CO. This has been due to the dominating position of Haldane's work and opinions. There are, however, details which can not be fitted to these opinions, such as Miss Killick's work on acclimatisation and in addition somecase histories show little resemblance to simple anoxaemia.

Conclusions.

It is believed that it has been demonstrated in this experiment that irradiation by visible light, chiefly from the violet end of the visible spectrum, has a beneficent effect on the speed of recovery of rabbits suffering from carbon monoxide asphyxia.

It is also believed that the improvement is sufficient to justify trial on human subjects. The light source would of course be as intense as possible but could be filtered and so erythema or the effects of heat could be avoided.

Further it is submitted that light treatment in men should not be condemned on theoretical grounds. The

complexity of the interaction between CO, O_2 and haemoglobin in the circulating corpuscles is such that practical experimental results must be more convincing than any theoretical objections to their validity.

It may be said that the present system of treatment of CO asphyxia by oxygen and carbon dioxide combined with artificial respiration is so good as to need no aid. Deaths still occur from CO poisoning when this treatment is used. Irradiation may help a little to rid the blood of the gas. If it does not do so, it can do no harm. This is markedly different from the majority of other auxiliary treatments suggested.

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