INDUSTRIAL PHOSGENE POISONING

A Study of Acute Pulmonary Oedema

by

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INTRODUCTION.

As might be expected, exposure to noxious vapours and fumes is not an uncommon occurrence in the chemical industry. Indeed, throughout industry as a whole, accidents due to the inhalation of toxic gases must be assuming increasing importance, for most industrial processes at some stage employ noxious liquids or gases that form a potential source of danger to those coming into contact with them. Some of these substances are dangerous on account of the remote systemic effects that they may produce, as for example, benzene and its derivatives in the production of toxic or aplastic anaemia, trichlorethylene and other solvents for their effects as general anaesthetics and liver poisons, carbon monoxide under its various guises producing carboxyhaemaglobin and so interfering with the transport of oxygen by the blood, or hydrocyanic acid gas that interferes with the use of oxygen by the tissues. Other toxic vapours are dangerous mainly on account of their local effects, as for example, bromine, hydrofluoric acid and dichlor-ethylsulphide, all of which affect the skin and eyes. Another considerable group of toxic vapours are the lung irritants, whose main danger lies in the damage that they do in the respiratory tract, quite apart from any other harmful effects that they may have. In this group are included simple substances like ammonia, chlorine, phosgene and sulphur dioxide, as well as more complex materials such as chloropicrin and chlorsulphonic acid.

Although this latter group of compounds is referred to generally as the lung irritants, not all members act in the same

way. Ammonia, for example, causes intense necrosis and sloughing of the tissues; chlorine tends to cause suffocation or primary asphyxia, while phosgene is renowned for its delayed action and its readiness to produce pulmonary oedema. Indeed, it seems to be quite clear that these so-called lung irritant gases must exert their effects in many different ways, and it is probably on this account that so little is at present known of the intimate pathology of the injuries associated with any particular one of them.

One of the most interesting of these lung irritants, and one that has been known for a very long time, is phosgene, a simple compound notorious for its capacity to produce fatalities from oedema of the lungs if it is inhaled in any considerable quantity. Indeed, it is mainly because of its widespread use as a chemical warfare agent in the conflict of 1914-1918 that phosgene is so generally known, though industrially it has many applications. Yet in spite of its very extensive use in war and the great number of casualties deliberately induced with this substance, very little is known for certain, even now, of how phosgene acts upon the body. Moreover, many misapprehensions have for long existed among medical writers even about the nature and properties of phosgene, many of them describing it as an unstable compound and most, if not all, describe its almost instantaneous and complete hydrolysis on coming into contact with water. Neither of these statements is however, unreservedly true, yet it is on the second of these assumptions that the current concept of the pathology of phosgene gassing has been built up, for it is generally believed that hydrolysis takes place in the lungs with liberation of carbon dioxide and hydrochloric acid,

and that the latter substance acts upon the alveolar tissues to cause lung oedema. It is hoped to show in this present thesis that such an hypothesis is quite untenable and an attempt will be made to find an alternative explanation. It is most remarkable, however, that such an hypothesis should have been held for so long and still be so generally accepted, when of all the lung irritants, phosgene has been studied more than most.

The scope of this thesis is very limited. It has not been possible for the writer to investigate the biochemical implications of phosgene poisoning, though much requires to be done in this field. Clinical observation of affected persons has made it appear, however, that there are certain very constant features which seem to have considerable significance in assessing the severity or prognosis of a particular case and in providing a means of controlling or judging the response to oxygen therapy; they have also led to further review of the supposed manner in which phosgene gas produces its effects upon the body. Simple observations of the pulse, respiration and body temperature, and above all, the serial recording of the blood pressure have led to the belief that herein lies a method of assessing severity, prognosis and response to treatment with considerable degree of accuracy. The recording of serial blood pressure readings moreover led to the recognition of constant changes that take place in cases of differing degrees of severity - changes that were not explainable on current theories of the pathology of phosgene poisoning. This has necessitated some further enquiry into the nature and production of pulmonary oedema in general, and more particularly, into that form of lung oedema found in association with certain forms of

heart disease and variously described as acute pulmonary oedema, cardiac asthma or nocturnal paroxysmal dyspnoea. Indeed, one of the most striking features of phosgene poisoning is its remarkable clinical similarity to acute pulmonary oedema as above defined. Because of this similarity the two conditions have, to some extent, been considered side by side in this thesis, in the hope that an understanding of the one might lead to some further knowledge of the other.

Much of the literature of phosgene gassing has been based on the experience with this substance during the Great War, and in the military casualties reported there was often considerable doubt as to whether or not other substances had been inhaled at the same time. The series of cases on which the present work is based are, however, indubitable cases of pure phosgene poisoning. They were all personally investigated by the writer, when for a period of close on five years, he was Medical Officer to a group of factories engaged upon the manufacture of general heavy chemicals and chemical warfare agents for the purposes of the recent war. Most of the casualties occurred in the latter part of 1941 and early 1942 when the phosgene programme was at its height, and no really serious incidents were encountered subsequently. As a result of this, the reported series of cases gave sufficient opportunity to learn something of the effects of phosgene gassing, and enough material for speculation and the elaboration of theories on its mode of action. The lack of subsequent cases, however, prohibited the carrying out of somewhat more detailed and elaborate investigation that had been planned and provided for.

Owing to the strategic disposition of the factories in out of

the way and relatively unimportant places, hospital facilities were not at all good. In the small town where the present series of cases occurred, there was only a cottage hospital with no facilities for pathological investigation, hardly any trained nursing personnel, and a very scant and precarious supply of oxygen. It was therefore essential that the factory should be self-reliant for the treatment of its gassing casualties. To this end a compact but reasonably well equipped Medical Department was established, with a staff of qualified and experienced nurses covering the whole of the 24 hours, and an unlimited supply of oxygen. This arrangement proved entirely satisfactory and the only disadvantage was that the small amount of accommodation precluded the keeping of patients under prolonged supervision for the whole of their later treatment. Therefore, as soon as the patient no longer required special care or nursing supervision he was sent home under the charge of his own doctor, or in one instance, transferred to hospital some thirty miles away.

Such, then is the background of the present report.

CHAPTER I

GENERAL CONSIDERATIONS.

PROPERTIES OF PHOSGENE.

Phosgene or carbonyl chloride, $COCl_2$, is a colourless suffocating gas with a disagreeable smell that has been likened to musty hay. The comparison, however, is not a very apt one, for the odour depends entirely upon the purity of the compound and the concentration in which it is met.

Although it exists in the gaseous form at ordinary temperatures, carbonyl chloride readily condenses to a colourless mobile liquid which boils at 8.2°C. The vapour is three and a half times as heavy as air, while the liquid has a specific gravity of 1.432 at 0°C. At a temperature of -118°C phosgene assumes the solid form as a snowy white crystalline mass.

Phosgene is a stable compound at ordinary temperatures and in absence of moisture. At somewhat elevated temperatures it tends to revert to carbon monoxide and chlorine, the reaction being a simple splitting of the molecule, thus -

$$COCl_2 \longrightarrow CO + Cl_2$$

Even at 101°C the dissociation is only 0.45% and at 400°C 21.26%; not until a temperature of 800°C has been reached is the breakdown complete.

In contact with water, or still more effectively, hot water or steam, the disintegration of the molecule takes place by hydrolysis according to the equation

$$COCl_2 + H_2O = 2HCl + CO_2$$

The reaction is not a very rapid one, particularly if the water is in the vapour phase. Thus Sartori (1) quotes an experiment in which 1 c.c. of phosgene gas was placed in a 500 c.c. flask of atmospheric air fully saturated with moisture. The odour of phosgene was still present after 15 days. Hydrolysis is, of course, much more rapid with great excess of water in the liquid phase. It is far from being instantaneous, however, as is commonly believed, for phosgene can actually be bubbled slowly through water with very little loss from hydrolysis.

Owing to the mobility of its chlorine atoms, phosgene is a very reactive substance and readily takes part in chemical combination.

Although the solubility of phosgene in water can not be determined with any degree of accuracy on account of the complicating hydrolysis, it is readily soluble in organic liquids such as toluene, benzene and carbon tetrachloride (2), as well as in fats and oils (1). From such solutions it can readily be removed by passing a current of air. Use is made of this fact to market phosgene in the form of a 30% solution in toluene, where only small quantities are required. More generally it is distributed in iron cylinders.

HISTORICAL.

Phosgene was first discovered in 1812 by Davy, who made it by exposing to sunlight a mixture of equal volumes of carbon monoxide and chlorine, and from this reaction the resulting compound was given the name Phosgene, which means "the product of light".

Though previously used to a limited extent in industry, phosgene did not come into prominence until the war of 1914-1918 when it became one of the principal asphyxiating or lung irritant gases used by all belligerents, either alone or more usually mixed with chlorine or mustard gas. Indeed it is probably as a chemical warfare agent that the substance is generally best known.

Recently, however, a new interest has been added, for it has been shown that phosgene is evolved by the thermal decomposition of chlorinated hydrocarbons in the presence of a limited supply of air or oxygen (3). In their monograph on Industrial Solvents, Lehman and Flury (4), speaking of the chlorinated hydrocarbons write as follows:-

> "Through oxidation the hydrogen can be replaced by oxygen so that in the methane series chlorine derivatives of carbonic acid, (that is, of chlor-formic acid) especially the highly poisonous phosgene, can be formed....." (p.72)

Important among these chlorinated hydrocarbons is carbon tetrachloride, speaking of which Lehman and Flury later say (p.145):-

> "Further dangers exist when carbon tetrachloride is used as a fire extinguisher. In this case poisoning can be caused by the products of decomposition - hydrochloric acid and phosgene".

Now, carbon tetrachloride is the fluid most extensively used in chemical fire extinguishers, and in the suitable conditions mentioned above, the fumes evolved during the use of these appliances

may contain phosgene which has been held to be responsible, at least in part, for the toxic effects such fumes are known to exert upon persons exposed to them (5). Yant and his co-workers (6) found that the concentration of phosgene which resulted from spraying a fire with carbon tetrachloride varied from 4 - 92 p.p.m. (parts per million), while the spraying of red hot steel produced a concentration of 119 p.p.m. However, it is mainly during the use of the gas in industrial processes that cases of phosgene poisoning occur, in normal circumstances.

MANUFACTURE OF PHOSGENE.

The methods by which phosgene can be prepared are numerous. Since Davy first made it in the laboratory by the action of solar rays, various methods have been devised for its production on a large scale. Schuttzenberger, in 1868, made it by the action of carbon tetrachloride on carbon monoxide at a high temperature. It has also been prepared by reacting anthimony pentachloride with carbon monoxide, under suitable conditions; the reaction takes place in accordance with the equation -

$$CO + SbCl_5 = COCl_2 + SbCl_3$$

This method was used on a commercial scale in the war of 1914-1918. In several countries, during that war, phosgene was made, for a time at least, by a method that was simpler and quicker, though more expensive and less efficient as regards output, than any of the above. Fuming sulphuric acid containing 60-80% of free sulphur trioxide was heated in iron boilers fitted with cooling coils down which carbon tetrachloride was caused to flow. The reaction took place as follows -

$$CCl_4 + 2SO_3 = COCl_2 + S_2O_5Cl_2 \text{ (pyrosulphuryl chloride).}$$

Until a few years ago phosgene was made by direct synthesis from carbon monoxide and chlorine in the presence of dry animal charcoal. This method has been greatly improved and made more efficient of recent years by substituting vegetable for animal charcoal. The method nowadays is to manufacture producer gas by blowing air over red hot coke. This producer gas is the source of carbon monoxide. Mixed with chlorine it is passed over beechwood charcoal which becomes hot owing to the exothermic nature of the

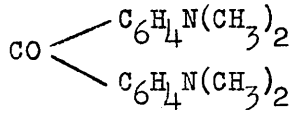
reaction that is slow at first, but which speeds up with the gradual heating of the catalyst. The mixture of gases, mainly phosgene and atmospheric nitrogen, is passed through cooling towers impregnated with cocoanut charcoal on which the phosgene is adsorbed. The phosgene is subsequently removed from the charcoal by heating.

USES OF PHOSGENE.

On account of its capacity to dissociate, phosgene is used in the chemical industry for transforming into chlorides certain mineral oxides, such as those of thorium and cerium. It can also be used to form the chlorides of many metals. Hydrochloric acid is usually employed for this purpose, but by using phosgene the formation of water during the reaction is avoided, and this, in certain instances, is of very great advantage.

The greatest quantity of phosgene is undoubtedly used, however, in the dyestuffs industry. Among such uses are the following -

(a) With dimethylaniline phosgene produces tetramethyl diamine benzophenone, a substance known as Michler's ketone, of which the formula is -

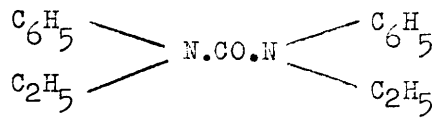


This ketone is used in the manufacture of dyes such as crystal violet, ethyl violet and Victoria blue.

(b) By passing phosgene and sulphur dioxide gas over heated wood charcoal thionyl chloride, $SOCl_2$, is formed. Thionyl chloride is also used in the manufacture of dyestuffs.

Other examples of the commercial application of phosgene include

(c) The reaction of monoethylaniline and phosgene produces symmetrical diethyl-diphenyl urea -



This substance is also known as ethyl centralite or carbamite, and is used as a stabilizer and plasticiser, e.g. in the manufacture of cordite.

(d) Ethyl chloroformate, $Cl.COO.C_2H_5$, is formed by the reaction of one molecule of phosgene with <u>one</u> molecule of alcohol. this compound is a lachrymatory gas and is used as a warning agent for leakage of hydrocyanic acid gas from storage cylinders. It is also an intermediate in the manufacture of other products. (For examples see below).

(e) Diethyl carbonate, $(C_2H_5)_2CO_3$, is formed by the reaction of one molecule of phosgene with <u>two</u> molecules of alcohol. Ethyl carbonate is a neutral solvent.

Apart from the manufacture of various dyes used in bacteriology and histology, phosgene is employed in the making of other materials of medical interest. These include -

(f) Salol or phenyl salicylate, $C_6H_4\begin{matrix}OH\\ \diagdown\\ COO.C_6H_5\end{matrix}$, is prepared from sodium phenate and sodium salicylate in the presence of phosgene as a condensing agent.

(g) Urethane or ethyl carbamate, $CO\begin{matrix}NH_2\\ \diagdown\\ OC_2H_5\end{matrix}$ is made by reacting ethyl chloroformate (see (d) above) with ammonia.

The British Pharmaceutical Codex also describes the preparation of such substances as guaiacol carbonate, creosote carbonate and quinine ethyl carbonate by means of reactions involving the use of phosgene (7). The same gas has also been employed in the manufacture of diethylbarbituric acid, or barbitone, and its homologues; of hedonal; and of codein, by reacting methyl chloroformate with morphine (8). It

is also used in the preparation of acetyl chloride which may in turn be reacted with salicylic acid to produce aspirin (9). Urea is also manufactured on a commercial scale by reacting phosgene with ammonia (10), while Suramin (Germanin), as described in the British Pharmacopoea (11), also involves the use of phosgene.

TOXICOLOGY.

Before presenting a series of cases of phosgene gassing, as will be done in the next section, it is necessary to consider briefly the general toxicology of the substance.

Phosgene is a lung irritant and a primary asphyxiant. Its action is, therefore, similar to that of chlorine, but according to Prentiss (12) the toxicity is ten times that of chlorine. Poisoning by phosgene is always more or less acute. There is at present no evidence to suggest that prolonged or repeated exposure to minute concentrations has any cumulative effect.

As a respiratory irritant phosgene has not nearly such a severe and immediate effect as that due to a similar quantity of chlorine. The latter substance is much the more irritating, while the former is by far the more dangerous. Because phosgene is so much less irritating it is possible to remain for some time in an atmosphere containing dangerous concentrations of it. On the other hand, a very small concentration of chlorine produces such immediate and painful irritation that it is not possible to remain in it for any length of time; a person finding himself in an atmosphere contaminated with chlorine would be immediately aware of its presence and remove himself forthwith from the irritation. Even an impaired sense of smell could not prevent him from recognising at once the presence of chlorine vapour. In the case of phosgene, however, an individual with a poor or absent sense of smell might remain for some time in a dangerous concentration of the vapour before the irritation of his respiratory passages developed sufficiently for

him to become aware of its presence. Moreover, the smallest concentrations of phosgene diminish and distort the sensations of smell and taste (13). The best known example of this is the peculiar flat metallic taste experienced by the individual when he attempts to smoke tobacco after having been exposed to phosgene. Indeed, this so called "tobacco phenomenon" which is very typical of phosgene is well recognised by those who habitually come into contact with the gas, and it has been used extensively as a rough test for the presence of the vapour, both by workers in the chemical industry and by soldiers in the field.

In the matter of effective concentrations of phosgene gas in the atmosphere, there appears to be general agreement among the several writers, as will be seen from the following tables. The various authorities use different units, and so for purposes of comparison they are recorded here in the equivalent mgms./litre, as well as in the original form quoted from the author concerned. British figures, taken from a report by the Department of Scientific and Industrial Research (14), are as follows:-

mgms. of phosgene per litre of air	vol. of phosgene per vol. of air	Effect
0.7	1 in 6,000	Very severe lung injury in all cases in 2 minutes with 50% deaths.
0.14	1 in 30,000	Very dangerous in 2 minutes with risk of serious lung injury.
0.02	1 in 200,000	Probably fatal in 30 mins.
0.008	1 in 500,000	Dangerous to life if prolonged.
0.004	1 in 1,000,000	Maximum permissible for prolonged exposure.

American figures according to Henderson and Haggard (15) are as follows:-

mgms. of phosgene per litre of air	parts phosgene per million of air	Effect
0.024	5.6	Least concentration detectable by odour.
0.017	4	Least concentration causing immediate irritation of eyes.
0.0125	3.1	Least concentration causing immediate irritation of throat.
0.02	4.8	Least concentration required to cause coughing.
0.004	1	Maximum permissible for prolonged exposure.
0.1	25	Dangerous even for short periods.
greater than 0.1	greater than 25	Rapidly fatal.

RECORDED CASES.

During the War of 1914-1918 a large number of cases of phosgene gassing among soldiers were reported. From the clinical point of view, most of these reports are unsatisfactory because of the obvious difficulty of getting such cases in their early stages under medical observation in anything like reasonable surroundings, or with adequate facilities for proper clinical investigation and recording. Furthermore, according to the Medical History of the War (16), it was never certain that a patient had been exposed only to phosgene, for this gas was usually used with chlorine as a diluent or mixed with mustard gas, tear gas, or toxic smokes.

In the official publication of the International Labour Office (17) it is mentioned that the pathology of phosgene poisoning in industry had been studied by Bréaudat as early as 1892, by Trummel in 1896 and Schumberg in 1898, though references are not given and it has not been possible to trace these reports. Mention is also made of twelve non-fatal and two fatal cases of industrial poisoning reported by various authors between the years 1906 and 1917. Two fatal cases of gassing of chemists, when a storage cylinder of liquid phosgene burst over them and drenched their clothing, were briefly recorded by Delepine in 1923 (18). A unique opportunity of observing cases of phosgene gassing occurred at Hamburg on 20th May 1928, when an explosion occurred in a depot containing about eleven tons of commercial carbonyl chloride. In all, about 300 persons were affected and there were ten fatalities. Hegler (19) reports on 195 of these patients seen at the Hospital of St.George, in Hamburg. Of these cases 17 were serious (including 7 fatalities), and 15 severely affected, the remainder being comparatively trivial. More recent cases of similar industrial poisoning have been reported by Jones (20), Shaw (21) and Steel (22).

CHAPTER II

CLINICAL SECTION

PRESENTATION OF CASES.

The clinical reports presented in this section are derived from personal observation of 13 cases of phosgene poisoning. None of them was fatal. All were known for certain to be affected by phosgene and nothing else. The series is described in two groups - those mildly affected and those severely gassed.

Only six mildly affected cases will be described and they are very typical of this group. Mild and trivial cases were seen in considerable numbers, but there were no special features that made any of the others more worthy of inclusion in this report than the six chosen for illustrative description, and they are sufficient to exemplify the symptomatology of the group.

Seven serious cases are also described. These were noticed to fall readily into two sub-groups - casualties who reported for treatment immediately after exposure, and those who delayed for some time before doing so. As will later be apparent, this delay caused in general a greater severity of symptoms and a greater tendency to complications.

The division of the series into two groups, designated respectively as "mild" and "severe", was made on purely clinical grounds. It is not possible to define accurately the two types, though it later became apparent that the blood pressure curves were were quite characteristic for each group. This, however, was not the original basis on which they were classified. The following brief general description of each of the two types gives some idea of the main differences between them.

Mild Cases.

In general, the mild cases had but a short exposure to phosgene vapour, and to low concentrations of it. In a few instances, however, exposure was sharp and short, for the patient was quickly aware that the atmosphere had become contaminated with phosgene. He therefore, removed himself forthwith from the danger and reported at once for treatment. All the mildly affected patients recovered quickly with rest, warmth, and oxygen therapy. None of them developed clinical signs of pulmonary oedema, and no case gave any cause for alarm in respect of its clinical course, or at any stage raised doubts about its eventual recovery. In the course of time, however, it became apparent that certain constantly recurring signs were typical of the group - namely, a hot flushed skin but no sign of cyanosis, a normal body temperature and pulse rate (though sometimes the pulse was noted to be slow), and little or no deviation in serial blood-pressure recordings. Where any significant change in blood pressure was noted, it was always towards a slight and transient fall. Abnormally raised blood-pressures do not occur among mildly affected cases.

Severe Cases.

The severely affected cases all developed pulmonary oedema, though in varying degrees. All were obviously very sick patients, and in some instances it did at first appear that the case would end fatally. Exposure to phosgene vapour had, in this group, been either very heavy or very prolonged. There had been actual contamination with liquid phosgene in some instances. All severely gassed persons exhibited a mixture of pallor and cyanosis. In most instances the body temperature became elevated a short while after exposure, even though no septic or infective respiratory complications

appeared. Some of these severely affected cases did, however, develop complicating lung conditions, varying from a mild acute bronchitis to a bronchopneumonia. As a rule, the pulse was rapid and in all instances serial blood-pressure recordings showed considerable elevations of pressure above the level normal for the individual concerned.

Moreover, in this group two separate classes are apparent - three cases who received treatment immediately after exposure, and four, who for one reason or another, delayed in reporting for treatment until ten or twelve hours had elapsed. The distinction is an important one, for the symptoms of those who delayed in seeking treatment were comparatively more severe, respiratory infections ensued, and absence from work was more prolonged.

Having thus briefly outlined the main features of the two types of case encountered, it remains to describe the total series of thirteen casualties in greater detail, and this will be done under the following headings:-

A. Six mildly affected cases.

B. Seven severely affected cases

(a) three of whom reported at once for treatment,

(b) four of whom delayed before seeking treatment.

MILDLY AFFECTED CASES.

Case M.1. C.B., Male, aged 36, process labourer in filling plant.

History The patient reported at 4.30 one morning, complaining of cough and tightness of the chest. He had been working since 10 p.m. on the previous night at the filling cabinet. His job was to screw down the plug of the cooled container that had been filled with liquid phosgene. No respirator was worn at this job as the

-filling cabinet was so designed and ventilated as to render the use of a gas mask unnecessary. During the course of the shift this man had also removed from the storage section of the plant seven containers found to be leaking. He wore a gas mask for this work and stated that he believed the mask to be efficient. At his pre-employment examination the blood-pressure was noted to be 132/90.

Clinical Report. The patient complained principally of coughing and tightness of the chest, but also of some irritation of the throat and smarting of the eyes. The cough was unproductive. There was slight frontal headache but no nausea or vomiting. The eyes were not injected nor were any physical signs of abnormality detected in the chest. Skin slightly flushed, Temp.97, pulse 80, resp.18, B.P. 140/90 on first reporting.

The patient was put to bed with hot water bottles and was given hot drinks. A simple linctus was prescribed to allay the irritating cough. Pure oxygen was administered continuously by means of a B.L.B. mask during the first four hours and intermittently thereafter. During this time no further symptoms developed and twelve hours after his accident he was fit to go home. He returned to work on the following day completely recovered.

Serial recordings of blood-pressure, pulse rate, temperature and respiratory rate, and a record of the sequence of oxygen administration, for this and the other mildly affected cases will be found in Table 1.

Case M.2. H.C., Male, aged 50, process labourer in filling plant.

History. The patient was exposed to fumes from a leaking phosgene container. The leakage was not a very bad one, and indeed was only discovered when the patient began to complain of dryness

of the throat with a sensation of tightness and pain in the chest. The maximum duration of exposure in this case was about 4 hours, which illustrates well the insidiously irritating properties of the gas. As soon as he was aware of what had happened the patient reported for treatment. At his pre-employment examination the blood-pressure was noted to be 100/66.

Clinical Report. On first coming for treatment the patient complained of a dry tickling cough and of pain in the chest, mainly in the mid line. He also stated that his chest felt tight. There was slight headache but no nausea or vomiting.

On examination the skin was noted to be flushed on face and body and the patient looked excited. There was no real dyspnoea, but some wheezing was present. Physical examination of the chest revealed a few rhonchi anteriorly and posteriorly. No signs of pulmonary oedema were evident, nor did they subsequently develop. Temp.97.8, pulse 80, resp.24, B.P. 100/75.

The patient was put to bed with hot water bottles, a simple linctus was prescribed and oxygen therapy was instituted by means of a B.L.B. mask.

With this treatment the sensation of tightness in the chest quickly subsided and an hour later the patient had dozed off to sleep, and slept fitfully for about one hour. At the end of six hours he was obviously very much better and the rhonchi were very few indeed. The pulse rate by this time had dropped to 56 and respirations to 16 per minute, the blood pressure being 100/60. The patient still complained of headache. He was now able to take a light meal of tea and toast. After nine hours, his general condition being still good, oxygen therapy was stopped and an hour later the patient was sent home

by car.

He remained away from work on the following day on account of headache and feeling tired, but returned to duty the following morning. Before starting work he was again examined. The chest was clear and no abnormality of any kind could be detected. Progress record in Table 1.

Case M.3. M.K., Male, aged 34. Process chargehand.

History. While working at the filling cabinet a leak developed in one of the valves on the phosgene pipe line and the patient inhaled phosgene fumes while trying to bring the escape under control. He reported at once for treatment. The blood pressure noted at his pre-employment examination was 126/78.

Clinical Report. The patient complained that his eyes were smarting, of tightness in the chest and that he felt nauseated, though he never actually became sick. Headache was only slight.

On examination there was some reddening of the conjunctivae with watering of the eyes and the skin was generally rather flushed. He had slight cough which he ascribed to irritation of the throat, but the fauces appeared normal. No physical signs were detectable in the chest. Temp.98.4, Pulse 70, Resp.20, B.P.130/90. He was put to bed and oxygen therapy was instituted in the usual way.

After four hours the patient insisted that he was very much better, apart from headache, and he wanted to return to work at once. As he could not be persuaded to remain in bed any longer nor to continue with oxygen inhalations, he was sent home by car. The following day was his normal day off duty and he reported for work as usual the day after, saying that he felt completely well. On examination no abnormality could be detected. Progress report in table 1.

Case M.4. C.H., Female, aged 50. Stencil painter.

This woman had been directed into industry under a wartime conscription order. She suffered from chronic bronchitis and was subsequently discovered to be a chronic alcoholic. Since a job had to be found for her she was employed on stencil-painting batch numbers on phosgene containers. She had been drinking before coming to work on the day of her accident, but there is no doubt that by a rare mishap, she was actually exposed to phosgene fumes.

History. Four hours after the commencement of her shift the patient reported to the medical department in a very breathless state, saying that she had been affected by phosgene. It was confirmed by the foreman that she had been exposed to fumes from a container that had suddenly sprung a leak but that exposure, though sudden and sharp, had been comparatively slight. The patient was put to bed and routine treatment instituted. Blood pressure at pre-employment examination 140/90.

Clinical Report. The nurse reported that when the patient first arrived she looked grey and frightened and complained of pain in the left side of the chest. Her breath smelled strongly of alcohol, but nurse did not consider her to be intoxicated. The patient vomited a little dark fluid shortly after admission. Temp. 97, Pulse 74, Resp.28, B.P. 144/90. She was examined by me one hour after admission. Her subsequent history is as follows:-

1 Hour. When first seen the patient had improved somewhat for her skin was now slightly flushed, though she was still rather breathless. Cough was slight and there was very little sputum. It was noted that she smelled strongly of alcohol but she answered questions coherently and one could not say that she was drunk. The pupils were

normal in size, equal and reacted normally to light. On examination the chest was rather emphysematous and coarse rhonchi were audible throughout. No moist sounds were heard. Temp. 97.6, Pulse 80, Resp. 26, B.P. 120/75. Oxygen therapy was ordered to be continued throughout the night.

2 Hours. Nurse's report: Breathing rather more easy and no further sickness. Temp. 97, Pulse 80, Resp.26, B.P.110/60.

4 Hours. Nurse's report: Has slept fitfully at intervals. Cough still troublesome and expectoration continues, though slight. Recordings as in table I.

7 Hours. By this time (i.e. the following morning the patient had greatly improved and the tightness in her chest, though still present, was causing less complaint. She was still coughing at intervals with expectoration of a little mucus. Oxygen therapy had been continued without interruption all night. On examination of the chest no impairment of the percussion note was detectable and apart from a few scattered rhonchi, no abnormalities were found.

10 Hours. The patient was by now moving freely about the bed and appeared to be quite comfortable. Oxygen therapy had been intermittent during the past three hours without producing undue distress. It was now finally stopped.

12 Hours. For the past hour the patient had been asleep and was now much refreshed. She had no complaints but was insistent that she should go home.

14 Hours. Apart from a few rhonchi, no abnormal signs were present in the chest and arrangements were made for the patient to be sent home. Temp. 97.8, Pulse 70, Resp.20, B.P.140/90.

9th Day. The patient, after being discharged home did not return to work. She was visited in her home by one of the nurses who found her up and about but full of vague complaints and demanding compensation for her injury. She was not receiving any form of treatment from her panel doctor and indeed had not reported to him. However, on the ninth day after her accident she reappeared at the medical department, obviously having been drinking, and said that she felt bad, that her chest had been permanently damaged, that she was quite unable to work again and that she would have to be paid compensation.

Examination revealed no abnormality apart from an occasional rhonchus in both lungs. The blood pressure was normal. She refused to resume work.

Of the subsaquent history nothing is known. The woman never returned to work as she had been forced into employment in the first place, and she had dreams of a large sum in compensation for the alleged permanent damage to her chest. She was eventually released from her obligations under the industrial conscription orders and was never seen or heard of again.

Case M.5. R.H., Female, aged 41. Stencil painter.

History. After having been at work for two hours the patient complained of smarting of the throat and eyes and of tightness in the chest. A search was made and it was discovered that she had been working near a leaking phosgene container.

Clinical Report. The patient reported to the medical department for treatment as soon as she discovered that she had been exposed to phosgene fumes. Her complaint was of smarting eyes, pain in the throat, cough and tightness of the chest. Temp. 97.6, Pulse 60, Resp.24, B.P. 100/65. Treatment was begun in the usual way. She was seen by

me one hour after admission.

1 Hour. The patient was generally flushed and was perspiring slightly. She complained mostly of a dry unproductive cough and to a lesser degree, of headache and tightness in the chest, although she volunteered the information that the chest symptoms had improved very considerably since beginning oxygen therapy. Her eyes appeared to be perfectly normal and she no longer complained that they were paining her. Examination of the chest revealed nothing abnormal apart from an occasional coarse rhonchus.

4 Hours. Cough still present and patient bringing up a little tenaceous mucus. Chest examination as before.

8 Hours. Condition very satisfactory. Oxygen therapy had been interrupted for an hour without any ill effects.

10 Hours. Patient stated that she felt quite well again. Colour normal, skin cool and no sweating. Attacks of coughing were by this time few and far between and very little mucus was being brought up. On examination the chest was found to be clear and oxygen therapy was stopped. Temp.98.2, Pulse 60, Resp.16., B.P. 100/60. On account of the lateness of the hour, the patient was detained overnight, though she required no further treatment.

20 Hours. The patient had slept soundly all night, and now made no complaints beyond slight headache for which Veganin (aspirin, phenacetin and codein compound) was prescribed. There was no abnormality detectable in the chest and the patient was sent home by car. Temp. 98, Pulse 84, Resp.24, B.P. 110/60.

On the following morning the patient resumed work.

Case M.6. C.L., Male, aged 37. Process labourer.

History. The patient had been working at the filling cabinet for six hours when he began to feel sick and dizzy. He had not smelled any escape of phosgene or noticed any mechanical defect in the filling machine. A very small leak on the feed pipe was subsequently found but the exact duration of the man's exposure remained uncertain.

Clinical Report. On arriving at the medical department the patient complained of nausea, dizziness and weakness of the legs with a feeling of tightness in the chest. He was very flushed and was sweating profusely. An irritating unproductive cough was noted and retching took place occasionally though he did not actually vomit. Treatment was begun in the usual way. Temp. 97, Pulse 72, Resp.22, B.P.105/65.

1 Hour. The general condition of the patient was still as described above. He stated that he could taste phosgene even now. He still suffered from headache but had not been dizzy since lying down. No abnormality was found on examination of the chest. Temp.98, Pulse 72, Resp.22, B.P. 100/70.

2 Hours. The response to oxygen therapy and rest had been very satisfactory during the previous hour. The skin by now was less flushed and felt cooler and sweating had apparently stopped. The patient was most anxious to go home but with difficulty was persuaded to stay.

4 Hours. The general condition remained satisfactory and there was but little cough or expectoration. The chest was still clear on examination. Oxygen therapy was stopped.

6 Hours. During the previous two hours the patient had remained well without inhalation of oxygen. The skin colour was normal and the chest clear. As the patient insisted on going home

he was sent off by car. Temp.97, Pulse 78, Resp.22, B.P.120/80.

On the morning of the second day the patient reported back for work, stating that he had not done so on the previous day because he felt tired and shaky. Physical examination revealed no abnormality and the patient was allowed to return to his job.

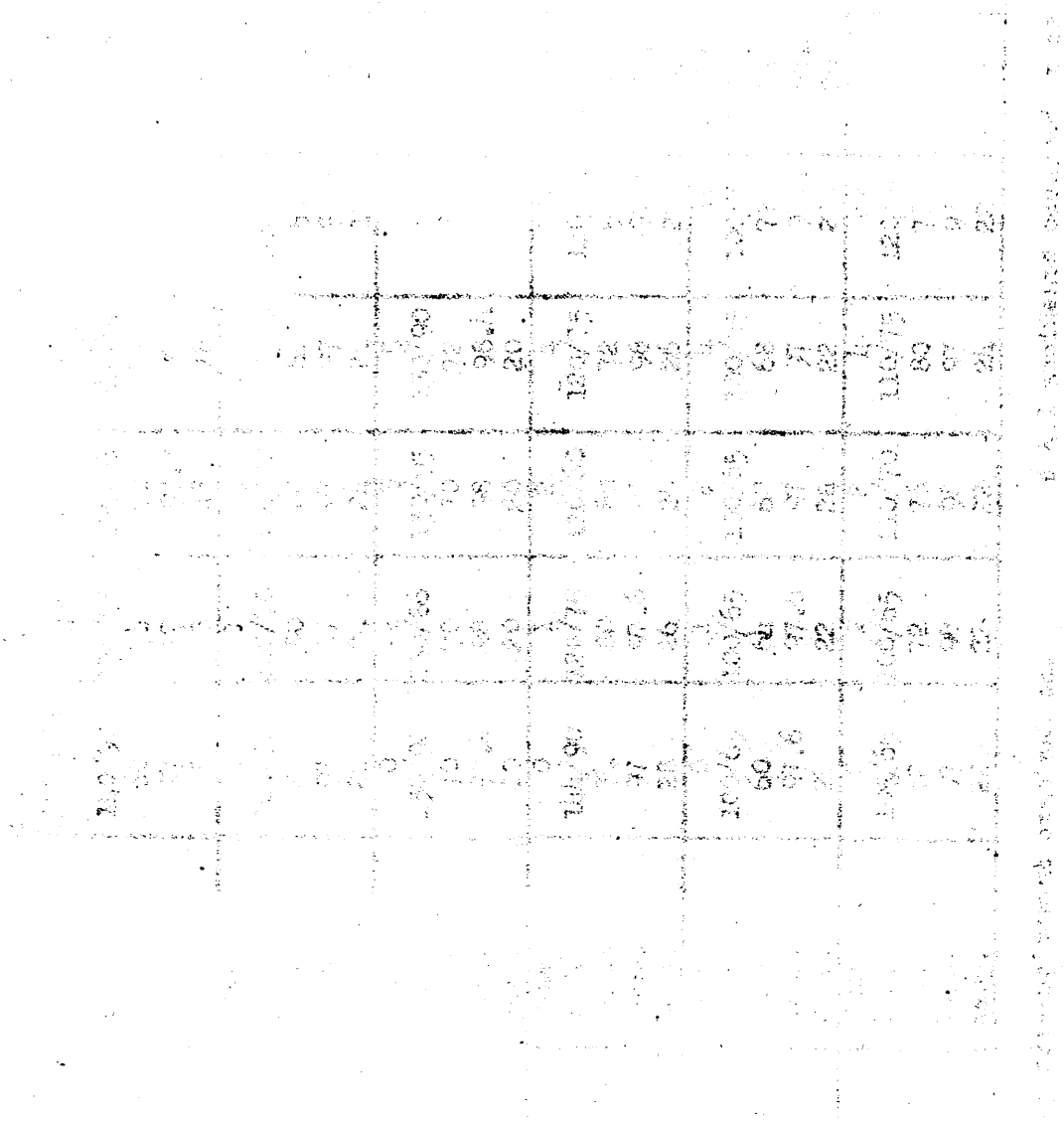


TABLE I. MILDLY AFFECTED CASES.

Case No.	Normal¤ Blood Pressure		First ϕ Reporting for Treatment	Hours Subsequent after Zero Hour						
M.1.	130/90	Time	0	2	4	5ǂ	7ǂ	10x	12	
		B.P.	140/90	138/98	136/96	140/90	140/90	140/90	140/90	
		Pulse	60	74	72	72		80	90	
C.B.		Temp.	97	97	97.2	97		97.2	97.4	
		Resp.	18	18	18	18		20	20	
M.2.	100/66	Time	0	1	3	4	6ǂ	9x	10	
		B.P.	100/70	100/70	100/70	100/70	100/60	100/65	100/65	
		Pulse	80	80	80	84	56	58	76	
H.C.		Temp.	97	97	97	97	98.2	98.2	98.2	
		Resp.	24	24	24	24	16	16	22	
M.3.	126/78	Time	0	2	3	5				
		B.P.	130/90	130/86	130/95	130/90				
		Pulse	70	70	70	72				
M.K.		Temp.	98.4	98	98	98.4				
		Resp.	20	20	20	20				
M.4.	140/90	Time	0	1	2	4	7ǂ	10ǂ	12x	14
		B.P.	144/90	120/75	110/60	120/75	140/76	140/90	140/90	140/90
		Pulse	74	80	80	72	50	50	68	70
C.H.		Temp.	97	97.6	97	98	97.6	97.8	97.2	97.8
		Resp.	28	26	26	26	26	16	20	20
M.5.	110/65	Time	0	1	2	4	6ǂ	8ǂ	10x	20
		B.P.	100/65	100/65	100/65	100/65	100/70	100/70	100/60	110/60
		Pulse	60	64	68	68	72	64	60	84
R.H.		Temp.	97.6	97.6	97	97	97.4	98.4	98.2	98
		Resp.	24	22	24	22	22	20	16	24
M.6.	120/90	Time	0	1	2	4	6x			
		B.P.	105/65	100/65	110/70	110/75	120/80			
		Pulse	72	72	76	80	78			
C.L.		Temp.	97	98	98	97	97			
		Resp.	22	22	22	24	22			

ǂ Indicates oxygen reduced or administered intermittently
x Indicates oxygen therapy finally stopped.

¤ Recorded at pre-employment examination.

ϕ All accidents occurred at zero hours.

COMMENTARY ON MILDLY AFFECTED CASES.

It is desired to draw attention to the following main features of this group of patients:-

1. Mildly affected cases, as will be seen from Table I, show little deviation of the blood pressure from normal. When blood pressure changes do take place these changes are in the nature of a slight fall. Such a fall is evidenced by cases 1, 4, 5 and 6, and varies between 10 m.m. and 30 m.m. of mercury.
2. It will also be noticed in Table I. that in some instances (cases 2, 4 and 5) there is a marked slowing of the pulse to 50-60 beats per minute. This drop in pulse rate occurred with marked improvement of the patient's condition; in fact, it will be seen that slowing of the pulse usually occurred about the time when the patient's condition warranted a reduction in the amount of oxygen being administered. (It will be shown later in the thesis that this effect is directly due to oxygen therapy and not to phosgene gassing; moreover, the phenomenon has previously been described in the literature.)
3. No patient among the mildly affected cases developed even a mild pyrexia.
4. No complications in the way of respiratory infections, ensued among the mildly affected cases, and none of them developed pulmonary oedema.

Seven more seriously affected cases will now be described under two headings - three who reported for treatment immediately after exposure and four who delayed for several hours before doing so. It will be seen at a later stage that this division is not quite an

arbitrary one, for generally speaking, delay in receiving treatment is not without significance in the subsequent course of the illness.

Case S.1. W.H.A., Male, aged 45, Process labourer.

Since this patient showed in a marked degree all the outstanding features of a really severe, but uncomplicated, case of phosgene poisoning, his case history will be presented in considerable detail.

Exposure. While discharging a leaking container the patient was drenched from head to foot with liquid phosgene. The hair and clothing were soaked by the liquid which escaped under pressure.

History. This accident resulted from the imperfect technique adopted by the patient in disposing of a leaking phosgene container. Normally when such a container is discovered it is placed in a refrigerator and cooled to a temperature of less than 8°C. At this temperature, phosgene will remain in the liquid state even at atmospheric pressure, and so the container may be safely opened. Above this temperature, the phosgene vapourises rapidly at atmospheric pressure, building up a tremendous internal pressure that may cause a severe explosion. After cooling, the phosgene cylinder should be taken to a special cabinet for opening. This cabinet consists essentially of a cupboard with a glass top and doors at either side, the front and back being solid, apart from a small front hatch capable of admitting a hand. It is ventilated by an exhaust current of air, so that the fumes gradually evolved in the cupboard are drawn off to an alkaline neutralising bath. Opening of the particular type of container in question is performed by unscrewing a threaded plug from the base of the inverted cylinder. The standard procedure adopted

for this job is to place the inverted cylinder, previously cooled in a refrigerator, close to an opened door of the cabinet. The second door on the opposite side of the cabinet is kept closed. The operator, wearing a gas-mask, unscrews the plug so far and then slides the cylinder, which is sitting on a runner, into the cabinet and closes the door. By reaching through the small front hatch removal of the plug is completed under direct vision through the glass top of the cupboard. The hatch is then closed and the phosgene can be drawn off to a storage tank, or if the container is a small one, the contents may be allowed gradually to boil off and the vapour is drawn away to the neutralising bath.

In this instance, the operator W.H.A., correctly placed the container in the refrigerator to be cooled. He did not make certain, however, that the refrigerator was working. It had, in fact, been switched off so that the cylinder was not cooled to the requisite low temperature. The next stage of the job was correctly performed by W.H.A. beginning to unscrew the plug with the container properly positioned outside the cabinet. He did not, however, wear his respirator. After a few turns the plug shot out with great force because of the high internal pressure, and narrowly missing the operator, struck the roof and landed 20 or more feet away. The patient was drenched in liquid phosgene, some of which probably entered his right eye.

His overalls were quickly removed by his workmates, wearing respirators; he was then wrapped in blankets and transported by stretcher to the medical department on the factory site. Here he was completely undressed and put to bed.

Symptoms and Clinical Course.

By the time the patient had been brought to the medical station, the phosgene had, for the most part, evaporated from his hair, but as it still smelled heavily of the vapour, the head was at once washed with soap and warm water.

On admission, the patient was pale and cold and shivering and complained of tightness in the chest and pain in the right eye. He was in a state of great fear and agitation, realising as he did, that he had been very heavily exposed to a highly dangerous substance. He was put to bed with a radiant heat cradle and oxygen therapy was instituted, using a E.L.B. mask. The temperature on admission was 96.4, Pulse 70, resp. 36 and B.P. 150/90.

Three quarters of an hour after admission he was first seen by me. By this time the temperature had risen to 98.2°F. and the respiratory rate had dropped to 22 per minute, the pulse being regular at 72 beats per minute. Blood-pressure 135/90. The patient complained of a slight dry cough but no pain or tightness in the chest, though his right eye was causing him some discomfort in spite of having been irrigated with warm bicarbonate solution. The eye was very infected. His colour was good, there being neither cyanosis nor pallor. No abnormal physical signs were found in the chest, and respiratory movements were regular and seemingly effortless.

Oxygen therapy was continued without interruption and a short while later, after a warm drink, the patient slept comfortably for two hours.

5 Hours. When seen again five hours after the accident, the patient's temperature had risen to 99.2°F. and the blood-pressure to 210/110, though the pulse and respiration rates were still

only 80 and 24 per minute respectively. Cough was still present but unproductive and the patient complained of pain and tightness in the chest, and of frontal headache. The skin was pale and clammy, but there was no cyanosis. The eye was rather more inflamed and liquid paraffin drops were instilled. On examination of the chest a few harsh rhonchi were noted anteriorly and posteriorly, but no other abnormality was found.

7 Hours. Seven hours after exposure the patient was still fairly comfortable and had been receiving continuous inhalations of oxygen all the while. He complained, however, of nausea and headache and his cough was now more productive, a little mucus being brought up. Rhonchi were still present throughout the chest, and some moist rales were audible at both bases. Breathing was easy, but the patient still complained of tightness in the chest.

10 Hours. Though he had been treated continuously with inhalations of oxygen from the onset, the patient after about ten hours had become a little cyanosed on the lips, the lobes of the ears and under his finger nails, the rest of the body being of a greyish colour. He had vomited once, the vomitus consisting of some tea that he had drunk. His right eye by now was very inflamed and watery, and the pupil was smaller than on the left. Guttae hyoscine hydrobromide ½% were instilled and a little liquid paraffin.

13 Hours. The breathing by now was laboured, being shallow and rapid and the blue cyanosis of the tips of the ears and nose and of the lips and fingers had become more marked, the remainder of the integument being a pale grey. The skin felt very cold and sweating was profuse. The temperature, taken in the axilla did not register on the clinical thermometer, while the pulse rate had risen to 100

beats per minute and was of poor volume and thready. The blood pressure was 240/110. Respirations were now at the rate of 30 per minute and vomiting had occurred a further three times. Cough had become more marked and persistent and a great deal of thin mucoid fluid was being expectorated.

Examination of the chest at this stage revealed a grossly impaired percussion note throughout, with diminished fremitus and resonance. Bubbling rales were audible throughout both lungs. Oxygen therapy was meanwhile continuing.

By this time also the conjunctiva of the right eye had become intensely hyperaemic, swollen and oedematous, and was protruding from between the lids, completely obscuring the orb itself. The vessels were greatly congested and the larger ones were readily visible against the dark red background of general hyperaemia. The lids themselves were tense and shiny, being very swollen with oedema. A pale straw-coloured sticky fluid dripped from the eye in copious quantities and was soaking the pillow on which the patient was tossing restlessly. The patient was, of course, kept well propped up as breathing was easier in that position.

Mentally the patient was clear and well aware of the things going on around him, but he was restless and agitated indeed. Morphia, grain 1/6, was given hypodermically with some effect in that it quietened the patient a little.

14 Hours. Expectoration was now copious and continuous and a thin, frothy, blood stained fluid flowed constantly from between the patient's lips.

The entire skin was intensely pale with a superadded cyanotic

tint giving a generalised steely grey appearance, although on the lips, ears, fingers and toes the cyanosis assumed a definite purple colour. The patient was bathed in sweat and was struggling for breath. Considerable difficulty was experienced at this stage with the B.L.B. mask on account of the patient's restlessness. This necessitated the holding of the mask in position by hand so that oxygen was being administered rather after the fashion of an anaesthetic from a Boyle's machine.

The pulse was still rapid at 100 beats per minute and very thready. No cardiac enlargement was clinically detectable and there were no signs of congestion or engorgement of the great veins in the neck. Neither liver nor spleen was palpable. The heart sounds were normal. No cutaneous or sub-cutaneous oedema was seen. The lung was not examined beyond auscultation anteriorly, which revealed an abundance of bubbling sounds. Neither was the blood pressure recorded.

Blood withdrawn for a cell count showed the red blood cells to be 6,720,000 per cub.m.m., the haemoglobin being $\bar{e}$.140% (Haldane).

15 Hours. The patient was now a little quieter but was still expectorating copious amounts of blood stained fluid, and fluid still dripped from the eye.

16 Hours. Respirations were still shallow and occurred at the rate of 32 per minute. Pulse rate 100. B.P.160/130. Expectoration still abundant and blood stained, and vomiting had occurred again.

18 Hours. The respiratory rate had now risen to 40 per minute and the breathing was very shallow. The pulse was very thready, and running at 118 per minute. B.P. 170/130.

19 Hours. The patient by now had grown very quiet and appeared to be exhausted, the pulse being difficult to palpate. One cubic centimetre of Coramine (25% solution Nikethamide B.P.) was given subcutaneously. Oxygen therapy had meanwhile been continued without interruption.

20 Hours. After the injection of Coramine the pulse rate rose to 130 per minute and was full and bounding. Respiration still very shallow at a rate of 40 per minute. The general condition had improved considerably but the patient was still expectorating freely, though less copiously, and the fluid was less blood stained. The eye condition remained as previously described, save that very much less fluid was now flowing from it.

21 Hours. Breathing had now become less difficult and the respiratory rate had fallen to 32. The skin appeared to be less bloodless and grey. Cyanosis was however, still present on mouth, ears and fingers. Perspiration was at this time very free. The patient complained of great thirst but was drinking well of unrestricted glucose-saline flavoured with lemon juice.

22 Hours. During the past hour the patient had dozed fitfully. He was still perspiring but the expectoration had become much less. B.P. 180/32.

28 Hours. The patient had slept off and on during the last six hours. His general condition had greatly improved and the cyanosis had considerably lessened. Examination of the chest revealed an impaired percussion note and moist sounds were still audible throughout.

30 Hours. The pulse had now become rather weaker though the patient appeared to be more comfortable. Expectoration of mucoid fluid continued and the sputum was now only occasionally streaked with

blood. The eye condition was much improved and the swelling had receded considerably. Coramine, 1 c.c. was again administered hypodermically with good effect. The patient complained of feeling hungry and partook of switched egg in milk. This he was able to retain without difficulty.

32 Hours. Having had two hours unbroken sleep the patient awoke much refreshed. Coarse rales were still audible throughout the chest and the percussion note was still impaired. Air entry seemed, however, to be considerably improved. Temperature 97, Pulse 100. Respiration rate 26 per minute and breathing was now much less shallow. B.P. 140/110.

36 Hours. Clinically the patient was very much improved. He was still expectorating freely and breathing was much more easy. The percussion note was still impaired at both bases but the air entry was very markedly improved. Cyanosis had greatly diminished and by now the general colouration of the skin was practically normal. Some congestion and inflammation was still present in the right eye but there was comparatively little discharge.

Oxygen therapy had been interrupted for about 20 minutes but was restarted as the patient was not so comfortable without it. Temp.97.6, Pulse 96, Resp.28, B.P.140/115.

44 Hours. The patient had apparently slept well during the night and was much refreshed by it. There was by now very little expectoration and no blood staining; expectoration was now more difficult and the sputum had to be definitely coughed up. The patient complained that his throat was sore from coughing. No abnormality was found, however, beyond some reddening of the fauces and simple linctus was prescribed as necessary.

Examination of the chest still showed slight impairment of percussion note towards the bases posteriorly. Some fine rales were still audible in these regions and coarse rhonchi were heard throughout the lungs. Oxygen therapy had been intermittent during the night. Temperature 98, Pulse 86, Resp.24.

50 Hours. The patient could now take light meals of custard or switched egg, tea and toast. His colour was quite normal. Expectoration still thick and mucoid and was being brought up with difficulty. Chest condition remained unchanged. Oxygen was by now being administered only at intervals, especially after bouts of coughing which left the patient very breathless. Temp.97.6, Pulse 80, Resp.24, B.P.138/112.

68 Hours. The patient by this time was saying that he felt perfectly fit. There was still some cough, but expectoration was now relatively easy. The cough was still occurring in infrequent bouts which left him rather breathless. After these attacks he liked to have an inhalation of oxygen, but otherwise did not require it. For practical purposes oxygen therapy had by now ceased. Temp.97.8, Pulse 82, Resp.22, B.P.132/110.

80 Hours. By the time that eighty hours had elapsed after the initial exposure the patient was very comfortable, and beyond a slight and scantily productive cough, had no complaints. His colour was again perfectly normal and he was breathing easily. There was now no impairment of note on percussing the chest. Some moist rales were, however, still present at both bases and rhonchi remained scattered throughout both lungs. The eye was very much improved, and most of the oedema had gone, though the conjunctiva was still badly infected. Argyrol 10% (silver vitellinate) was instilled. The

patient stated that he felt comfortably tired and felt like settling for the night. Temp.98.2. Pulse 83. Resp.22.

92 Hours Throughout the night the patient had slept soundly, and no oxygen had been administered during the previous twelve hours. On examination of the chest only a few scattered rhonchi were audible and the moist sounds had disappeared from the bases of the lungs. There was still slight cough but little expectoration. The eye remained rather bloodshot but had otherwise healed and the patient stated that it was scarcely painful. He had taken a light breakfast and enjoyed it, and stated that he was anxious to get home that day, if possible. Temp.97.4; pulse 70; resp.20.

100 Hours The patient remained comfortable all day and was still very keen to go home. Examination of the lungs revealed no abnormality beyond a few scattered rhonchi. The heart was normal and the blood pressure had resumed its usual level, being now 136/90. Temp.98.2; pulse 70; resp.20.

The patient was sent home in the factory ambulance to be under the care of his own doctor. Twelve days after his accident the patient reported to the factory Medical Department to ask if he would be allowed to resume work. He had been under the care of his own doctor for the past five days and had been given a bottle of medicine for bronchitis. No cough was now present and the patient looked very fit. No abnormalities were found on clinical examination. In view of the strenuous illness that he had so recently been through, arrangements were made for the patient to spend a fortnight at a convalescent home.

On the twentysixth day after his accident the patient returned to work looking very fit and refreshed by his holiday. The chest was perfectly clear and the blood pressure was 130/90, and the patient was therefore allowed to return to his former job.

Case S.2. D.McA., Male, aged 23. Process labourer.

Exposure The exact duration of exposure in this case is not certain, though it is probable that it extended over a period of rather more than three hours. Towards the end of the night shift the patient became aware of the fact that he had been exposed to phosgene fumes escaping from under the door of the filling cabinet which contained a leaking gas cylinder. It was verified that the escape had been quite a considerable one.

History The patient, a keen intelligent man, had worked all night in the phosgene plant and had spent the last 3 to 4 hours near the filling cabinet from which phosgene fumes had been escaping. Immediately he became aware of his exposure he reported to the medical department.

Symptoms and Clinical Course On first reporting the patient complained that he felt faint, and weak in the legs, of a feeling of suffocation, and of tightness in the chest. He was put to bed and kept warm by means of an electric cradle. Oxygen therapy was instituted and he was given hot drinks and simple linctus for the dry cough of which he complained. Temp subnormal; pulse 128; resp. 24. B.P. 178/118.

1 Hour When first seen one hour later the patient was rather pale and there was no sign of cyanosis. Neither was he perspiring. The pulse was rather rapid and full, but regular. An unproductive cough was

present and he was complaining of pain behind the sternum, and also of the fact that his throat felt dry and irritated. There was no headache but he stated that he could "taste phosgene." Clinical examination revealed no abnormality apart from a few coarse rhonchi on both sides of the chest. Temp.97; pulse 124; resp.22. B.P. 164/118.

3 Hours The cough by now was much more troublesome and had become somewhat productive, a little tough mucus being expectorated. The expectoration was not bloodstained. The patient complained of frontal headache and nausea but had been unable to vomit.

Examination of the chest showed no sign of consolidation in the lungs. A few crepitations were audible at the bases and rhonchi were scattered throughout. Breathing was a little laboured with a considerable expiratory wheeze. Oxygen therapy was continuing without interruption. Temp.99; pulse 102; resp.24. B.P.150/110.

5 Hours The patient was now definitely cyanosed on the lips, ears and digits which were of a purple colour. The remainder of the skin was a leaden grey colour, due to a mixture of pallor and cyanosis. Sweating had become very profuse. The patient was rather agitated and restless and was bringing up considerable quantities of thin fluid with occasional flecks of blood. Breathing was difficult and had become more shallow. Some impairment of the percussion note was found at the bases of both lungs and on auscultation coarse bubbling rales were heard throughout the chest, but were more marked and profuse at the bases. There was no enlargement of the heart detectable, and no signs of venous congestion or engorgement, or of subcutaneous oedema. Examination of

the blood showed Red blood cells 6,260,000 per cub.m.m. Haemoglobin, 120% (Haldane). Temp.98.8; pulse 100; resp.28. B.P. 180/120.

6 Hours The general condition remained much about the same. Cyanosis was still very marked in the ears, lips and fingers, and the general skin colour was still grey. Moist sounds were audible throughout the chest and the lungs were obviously very wet. Expectoration had been copious during the past hour, and was still streaked with blood. The patient vomited once and was sweating profusely. Temp.98.6; pulse 96; resp.30; B.P.176/120.

8 Hours By now the patient's condition appeared to be improving and the amount of expectoration to be diminishing, though it was still quite abundant. The general skin colour was still grey with the purple cyanosis of the extremities as previously described. Oxygen therapy had been continued without interruption.

Temp.98; pulse 90; resp.28; B.P. 160/118.

10 Hours After the lapse of ten hours from the time he first began treatment the patient began to say that he felt very much better and that his breathing had become easier. In actual fact there seemed to be little or no dyspnoea. His colour was much better and the cyanosis of the extremities was very much less. He had no headache now and no pain, apart from throat irritation due to coughing. On examination of the chest the percussion note and air entry were diminished at both bases and moist sounds were still generally audible, though again mainly at the bases. A few rhonchi were heard in the upper part of the chest anteriorly.

Temp.98; pulse 92; resp.22; B.P. 146/110.

12 Hours During the previous two hours the patient had slept comfortably and continuously. His colour was now practically normal. The pulse was regular and of good volume, the rate being 86 beats per minute. The skin felt rather cool and clammy but breathing was easy and regular at 22 respirations per minute. Oxygen therapy was still continuing.

15 Hours When seen again three hours later the patient stated that he felt very comfortable and ready to settle down for the night. His colour had remained very good indeed, and he was now expectorating freely a thin mucoid material. He also stated that his chest felt quite easy and the feeling of tightness had gone, there being no pain of any kind, apart from the slight throat irritation that accompanied bouts of coughing. Examination of the chest revealed no detectable impairment of percussion note, but moist sounds were still audible at both bases and a few rhonchi were scattered throughout both lungs. Instructions were given that oxygen inhalation might now be reduced as much as possible during the course of the night.

Temp.98; pulse 86; resp.20; B.P.146/120.

24 Hours The patient slept well all night and oxygen had been administered only after bouts of coughing. He had had no oxygen at all during the past three hours and his colour was quite normal. There was no difficulty in breathing and expectoration only occurred after paroxysms of coughing. Some fine crepitations were audible at both bases and an occasional rhonchus could be heard in the upper parts of the thorax. The patient was now most anxious to get home.

Temp.97.2; pulse 84; resp.18; B.P.128/96.

32 Hours The condition had remained entirely satisfactory and cough was only slight. The chest was clear apart from a few rhonchi. In order to demonstrate his fitness to go home the patient was moving himself very vigorously about the bed.

Temp.97.4; pulse 74; resp.18; B.P.150/116.

The patient was sent home by car and his own doctor was informed.

On the fifth day after the accident the patient reported back for work and as he had his own doctor's permission to do so he was allowed to return to light duties. On examination the chest was perfectly clear and no cough was present. B.P.130/90.

Case S.3. P.P., Male, aged 27, Process labourer.

This case is included as an example of short and heavy exposure, though not overwhelming as occurred in case S.1. Treatment was begun very promptly indeed, and frank oedema of the lungs did not develop.

Exposure and History While unscrewing the plug of a supposedly empty container, liquid phosgene spurted out and soaked the upper part of his clothing. It did not, however, reach his hair. The contaminated garments were instantly removed by the man himself, who was then wrapped in a blanket and transported to the factory medical department by ambulance.

Clinical Course On admission the patient was rather pale and frightened and was coughing a good deal without actually bringing up any sputum. He complained that his chest felt tight and sore and that he was very dizzy. The foul taste of phosgene was also one of his complaints

and he had frontal headache. Temp.98.4; pulse 78; resp.20. B.P.170/110. He was at once put to bed and oxygen therapy was instituted, some simple linctus being given to allay throat irritation and cough.

When examined shortly afterwards it was noted that he was still rather pale but there was no evidence of accompanying cyanosis. Breathing was easy and there were no physical signs in the chest beyond a few harsh rhonchi easily dispelled by coughing.

Temp.98.6; pulse 72; resp.22; B.P. 152/100.

3 Hours By the time that three hours had elapsed after exposure the patient was expectorating thick mucus freely, but was neither breathless nor cyanosed. The skin was perhaps a little flushed and there was no sweating. Apart from diffuse coarse rhonchi no abnormal physical signs were detectable in the chest.

Temp.98.8; pulse 80; resp.22; B.P.140/96.

4½ hours The patient's colour was now rather paler but there was no evidence of cyanosis. He was still expectorating freely, but the thin mucoid sputum contained no visible blood. Examination of the chest revealed an abundance of moist medium rales at both bases, but the percussion note was not impaired nor could other clinical signs of consolidation be detected. Numerous coarse rhonchi were still audible over most of the chest. There was no dyspnoea.

Temp.99.0; pulse 80; resp.24; B.P.160/100.

6 Hours The general condition remained much the same and the patient made no complaints. Oxygen therapy continued without interruption.

Temp.99.4; pulse 88; Resp.22; B.P.150/84.

8 Hours Expectoration had by now considerably lessened and was still free from blood staining. The skin colour was normal and the patient was sweating profusely. In the chest no evidence of consolidation was noted and the basal rales were very much diminished in number. The patient had no complaints.

Temp.97.4; pulse 70; resp.20; B.P.140/84.

10 Hours The patient stated that he felt quite comfortable but tired and that he thought he would settle down for the night. Cough was still present but occurred in less frequent bouts, and the sputum was much less and somewhat thicker. Apart from a few crepitations at both bases, and some scattered rhonchi, examination of the chest was negative. Instructions were given that oxygen therapy should be reduced and if possible discontinued during the night.

Temp.97.6; pulse 70; resp.20; B.P.140/80.

23 Hours The patient was moving freely about the bed, protesting that he felt quite well and wanted to go home. He had had no oxygen during the past 6 or 7 hours. A slight cough was still present and it was but scantily productive. Examination of the chest revealed only an odd crepitation at the bases and a few scattered rhonchi. The patient was allowed to go home by car.

Temp.98.0; pulse 74; resp.20; B.P.140/84.

Two days later the patient reported back to work completely recovered and was allowed to return to his former job.

Case S.4, F.B., Male, aged 48, Process labourer.

This case demonstrates well the false sense of security engendered by

the so-called "latent period," for the patient went home after known exposure to phosgene and did not seek treatment until 15 hours later. He became very ill and had to be admitted to hospital, having developed a broncho-pneumonia.

Exposure The patient was exposed to the fumes from a badly leaking container beside which he had been working for 7 hours of the night shift. It is not known for how long the container had been leaking during this period.

History Towards the end of his shift the patient began to feel a dryness in his throat, slight headache and excessive tiredness. On searching he discovered a leaking phosgene container and this he removed. He then went for a short walk outside the building and remained on the factory site for another hour until the end of the shift. He did not report to the medical department for treatment but went off home, where he felt unable to eat his supper and went straight to bed. That same evening, 15 hours after he had become aware of exposure to phosgene vapour, he came to the factory medical department for advice and treatment rather than go to his own doctor.

Clinical Course

15 Hours On first reporting for treatment the patient complained of severe headache, a feeling of tightness and oppression in the chest, of giddiness and of weakness in the legs. He looked ashen grey, and there were beads of sweat on his forehead. Cough was severe and there was much expectoration of mucus which was not, however, streaked with blood. He was at once put to bed with the electric cradle and warm

drinks and oxygen therapy was instituted.

Temp.98.2; pulse 100; resp.28; B.P.150/105.

16 Hours On examination an hour after admission the patient was very grey, and haggard in appearance, with deep cyanosis of hands, lips, nose, ears and feet. His temperature had risen to 99.2° and breathing was very laboured but shallow. Expectoration was abundant. Examination of the chest gave an impaired percussion note over the lower parts of both lungs and on auscultation the whole chest was bubbling with coarse moist rales. The patient was sweating profusely. He complained only of headache, nausea and breathlessness and had vomited a little dark fluid shortly after admission. The blood pressure was as previously stated.

18 Hours The temperature had by now risen to 101.2° and the pulse was bounding at a rate of 112 per minute, the respiratory rate being 26. Breathing was difficult and the patient looked very ill indeed. His condition was otherwise unchanged and he relied entirely upon the oxygen he was receiving from the B.L.B. mask, for he became intensely blue when it was shut off for a few moments. The blood pressure was now 140/110. Instructions were given for oxygen therapy to continue throughout the night.

26 Hours The patient had slept fitfully for intervals during the night and breathing was now less laboured at a rate of 24 respirations per minute. There was little expectoration by this time and the sputum had become rusty in colour. The temperature had risen to 100.2° with a thready pulse of 120 beats per minute. Cyanosis was still present round the lips and ears, and the alae nasi were moving during respiration.

On examination of the chest there was a dull percussion note elicited over the base of the left lung and considerable impairment over the right. Air entry was very poor over both these regions and definite tubular breathing could be heard on the left side. Coarse rales were audible throughout most of both lungs. The blood pressure was now 170/124.

It was considered that although still suffering from the effects of phosgene gassing the patient was mainly affected by a pneumonic condition rather than a pure pulmonary oedema. Since prolonged treatment in bed was likely to be necessary it was decided to arrange for the patient's admission to hospital in the city, some miles away.

Two grammes of sulphapyridine (4 tablets M.& B.693) were administered, oxygen therapy continuing.

32 Hours The temperature had now dropped to 99.4, the pulse remaining at 120 and the respiratory rate at 28. The clinical condition was otherwise unchanged, save for a slight drop in blood pressure which was now 160/130. One gramme of sulphapyradine was given orally and the patient left by ambulance for hospital, oxygen therapy to continue en route.

The patient was treated in hospital for broncho-pneumonia and remained there for 19 days after which he was sent for two weeks to a convalescent home. The next fortnight he spent under the care of his panel doctor in his own home, returning to his normal work, completely recovered, 6 weeks and 5 days after his accident.

Case S.5. H.McA., Male, aged 48. Process labourer.

This case also demonstrates the delayed action of phosgene and the tendency to a more prolonged invalidity when early treatment is not obtained. It is also of interest that this case was complicated by the presence of chronic emphysema.

Exposure The actual exposure in this instance was difficult to assess. Judging from the course of the subsequent illness, exposure could not have been very severe. All that could be ascertained was that the patient had been in contact with leaking phosgene cylinders during the course of the day previous to his coming under medical observation.

History Although well aware that he had been exposed to and affected by phosgene fumes, the patient went home at the end of his working shift rather than report to the medical department, since he was unwilling to run the risk of being detained for observation and treatment. Some nine or ten hours later he summoned his own doctor on account of developing chest symptoms, mainly dyspnoea, with pain and constriction in the thorax, and cough. The doctor diagnosed "gas poisoning" and asked that the patient be taken over by the factory medical organisation. Accordingly the patient was brought by ambulance and admitted to the sick berth.

Clinical Course It was reported that on admission the patient was very breathless and had considerable expiratory dyspnoea. He was grey in colour and slightly cyanosed and looked as if he had been exerting himself unduly. He complained of pain and tightness in the chest, headache, and a foul taste of phosgene being constantly in his mouth. The patient was put to bed with warmth; oxygen therapy was begun,

and simple linctus was given to allay coughing. Temp.97.4; pulse 84; resp.24; B.P.260/86. As nearly as could be estimated, the patient came under our care about 12 hours after exposure had ceased.

14 Hours Two hours after admission the patient was seen by me for the first time. Propped high up in bed he was obviously having considerable difficulty with his breathing - particularly expiration. His skin colour was grey, with cyanosis of lips, ears and fingers. Cough was frequent and harsh and he was expectorating considerable amounts of the mucoid sputum. There were no signs of venous congestion or generalised oedema and no abnormality was detected in the heart. The chest, however, was markedly barrel shaped, and the patient was using all his accessory muscles of respiration. He stated that he was troubled a great deal by winter coughs, but that his chest was "not too bad at this time of year (August)". A loud expiratory wheeze was audible at some distance from the patient. Percussion revealed, at any rate, no gross impairment, though anything less than this would have been difficult to detect on account of the emphysema present. Moist sounds were abundant and audible throughout the chest, particularly at the base, with some dry rhonchi anteriorly in the upper regions on both sides. Temp.97.8; pulse 84; resp.26; B.P.260/96. The administration of oxygen was continued without interruption.

16 Hours The patient's condition was unchanged apart from the fact that he was sweating profusely while the temperature had risen a little to 99° F. and the blood pressure was now 166/100.

20 Hours By this time the breathing had become much less difficult and the patient was more comfortable. He was still coughing a good

deal, however, and expectorating freely. The grey colour of the skin had now nearly gone and cyanosis was only slight. Numerous rales were still present throughout the chest and coarse rhonchi were audible, though the lungs did seem rather less wet than when last examined. The patient stated that he felt very tired as he had not slept during the previous night and looked forward to doing so now. Instructions were given for oxygen therapy to be continued during the night.

Temp.98; pulse 78; resp.22; B.P.146/86.

28 Hours The patient was reported as having passed a very good night and slept for long intervals. Cough was now much less troublesome, occurring only in occasional spasms, and expectoration was very much reduced.

Temp.97.6; pulse 70; resp.20; B.P.148/90.

30 Hours On examination the patient was seen to be of normal good colour and there was no trace of cyanosis. Breathing was easy and of more normal depth. Cough was still present but was accompanied by little expectoration, and what sputum was brought up appeared to come away with little effort. A slight expiratory wheeze was audible whenever a deep breath was taken.

Inspection and percussion of the chest revealed no other signs than those of chronic emphysema, while auscultation showed the presence of numerous and diffuse harsh rhonchi and some fine basilar crepitations. Oxygen therapy was stopped in view of the improved general condition and the noticeable drop in the pulse rate, instructions being given for its continuance again if the patient should require it.

Temp.97; pulse 60; resp.20; B.P.150/108.

36 Hours The patient's colour was still normal and there was no trace of cyanosis, although he had had no oxygen during the last six hours. He stated that he felt fine and would like to go home, as he was breathing normally again. There were, indeed, no signs of respiratory embarrassment. Auscultation of the lungs revealed the usual scattered rhonchi, and an odd crepitation could be heard at the bases. Permission was however given for the patient to be sent home to remain there under the care of his own doctor.

Temp.97.2; pulse 74; resp.20; B.P.136/96.

Twelve days after exposure the patient resumed work, having meanwhile been under the care of his own doctor with an attack of acute bronchitis. He had, however, recovered completely and was able to return to his normal duties.

Case S.6, A.T., Male, aged 39, Process labourer.

This case too demonstrates the "latent period" that follows phosgene gassing, and probably because of the time that elapsed before receiving treatment this patient also developed a complicating bronchitis.

Exposure The patient was exposed to a fairly heavy concentration of phosgene vapour from a defective valve on the pipe line of the filling apparatus. The duration of exposure may have been as long as four hours.

History Ten hours before coming for treatment, the patient had first become aware of having been exposed to phosgene. He had been engaged in

filling phosgene containers and had also, for a time, been disposing of leaking cylinders. For the latter job he had worn a respirator, a normal practice in the particular work, and he believed the gas mask to be efficient. No respirator was worn at his next job on the filling machine, nor was it normal practice to do so, as the filling cabinet was so designed and ventilated as to render this inconvenience unnecessary. Smarting of the eyes and irritation of the throat after working at this job drew the patient's attention to the fact that he had been exposed to phosgene vapour, and search revealed that one of the valves on the pipe line was leaking badly. The leak must have existed for some time, probably getting worse all the while. The duration of the patient's exposure was probably as long as four hours.

Lulled into a false sense of security by the fact that the smarting of his eyes had considerably lessened after a short while, the patient did not report to the medical department but instead went home at the end of his shift.

Ten hours later he returned to the medical department in a very distressed condition to obtain advice and treatment.

Clinical Course On arrival the patient was reported as being in very poor condition, extremely grey and cyanotic, with rapid shallow breathing and considerable pain in the chest. He was coughing a great deal and bringing up copious quantities of thin watery fluid, occasionally tinged with blood. The usual treatment with rest, warmth and oxygen was begun at once. Temp. 100; pulse 150; resp. 30; B.P. 260/220.

11 Hours When first examined, probably about 11 hours after exposure had ceased, the patient's general appearance and condition were as described above, the temperature, pulse rate, respiratory rate and blood pressure being unchanged. The degree of cyanosis was severe and breathing was very laboured, being rapid and shallow. Sweating was profuse and the patient complained of retro-sternal pain and headache. He had vomited once.

There were no signs of venous congestion or general oedema, and no cardiac abnormality could be detected apart from the very rapid rate of the heart's beating. Percussion over the lungs showed a marked impairment on both sides, particularly at the bases. On auscultation coarse bubbling rales were audible throughout the entire chest.

Veganin (aspirin, phenacetin and codein compound) was prescribed for headache and one fluid drachm of linctus diamorphinae B.P.C. on account of the very disturbing cough. Oxygen therapy continued without interruption.

12 Hours The general condition of the patient remained very much the same except that the respiratory rate had become slow and irregular, being rather gasping in type but not true Cheyne-Stokes breathing. The entire skin was intensely grey , due to a faint generalised purple cyanosis mingled with pallor, and a deeper blue cyanosis of hands and feet, lips, ears and nose. Sweating was very profuse and lay in great beads on his rather cool skin.

Temp.99.2; pulse 122; resp. 12. B.P. 260/200.

Note: In no other case has this slow gasping respiration been noted.

At this time the patient's lungs were very water-logged and anoxia was

severe; there was a dusky cyanosis. Yet the fact remains that the patient had had one fluid drachm of linctus diamorphinae B.P.C., which contains 1/18 grain of heroin. While such a dose does not usually have any very marked effect on respiration, and especially when given orally, it may be that the drug, in conjunction with the anoxia and serious irritation of the respiratory centre (as will be discussed later) did in fact contribute to the production of a slow gasping type of respiration. Heroin was not employed in this type of case on subsequent occasions, and it is therefore not possible to give further information on the point.

13 Hours The patient's condition had now somewhat improved. He looked less grey and haggard, but cyanosis was still present in the extremities. He was expectorating freely, and sputum was not now blood-stained. The headache had gone and the patient stated that he felt much more comfortable. He was still sweating slightly, but breathing more easily than on admission; the respiratory rate had returned to 28 per minute, and the respirations were regular and shallow. Moist sounds were still audible throughout the chest, though the lungs did not seem quite so wet. The patient now felt prepared to settle for the night. Temp.99; pulse 94; resp.28; B.P. 160/100.

17 Hours The night nurse reported that the patient had been sleeping at intervals and seemed to be very comfortable. He was very thirsty and had been drinking well and expectorating freely, no further blood having appeared in the sputum, which had considerably lessened in amount. Respirations were still regular, but much less rapid. Sweating had been profuse and the patient felt better after tepid spongeing. Oxygen therapy continuing. Temp.97.8; pulse 92; resp.22; B.P.140/80.

24 Hours The following morning the patient was very much more composed, was of good normal colour and all cyanosis had gone. He had respired oxygen all night, though this had been stopped for a short time while he had a light breakfast of egg switched in milk with toast. Oxygen had then been restarted, but at a greatly reduced rate of flow.

Breathing was now easy and regular, cough very slight and mucus was being expectorated in small quantities only after bouts of coughing. The patient was moving freely about the bed.

No impairment of note was demonstrable on percussing the chest. Air entry was good and only an odd crepitation was audible at the bases with some rhonchi to be heard at all parts of the chest. Instructions given for oxygen therapy to be stopped gradually. Temp.97.2; pulse 80, resp.20; B.P.150/98.

32 Hours For the previous six hours the patient had had no inhalation of oxygen and the cessation of this treatment had been without the slightest ill effect.

Examination revealed no abnormality in the chest apart from occasional harsh rhonchi which persisted.

As the patient was most anxious to get home again, he was sent by car, and his own doctor was informed.

Temp. 97.6; pulse 78; resp. 20; B.P. 142/80.

On the third day after exposure the patient returned to the factory, asking to be allowed to resume work. He had actually come in spite of his own doctor having certified that he was suffering from bronchitis. This was confirmed by clinical examination and the patient was sent home

again with instructions not to return until his doctor had given him permission to do so.

On the twelfth day after exposure the patient presented himself again. He had recovered completely, and was therefore allowed to return to his normal employment.

Case S.7. J.K., Male, aged 36. Process labourer.

In this case, exposure had not been unduly heavy and the case was not a very severe one. Yet, the "latent period" is well marked, there being a delay of ten hours before treatment began. It is probable that with early treatment the symptoms would have been less severe and the complicating bronchitis might have been avoided.

Exposure After being at work for two hours, the patient experienced sore throat, cough and smarting of the eyes, with slight frontal headache. Upon searching, he found a leaking phosgene container close to where he had been working. Exposure was of two hours' duration and to vapour only.

History Having found the leaking vessel which his early symptoms caused him to seek, the patient disposed of it, went out for a short while into the open air and then had a cup of tea in the canteen. He returned to his job, worked for another four hours and then went home. Early in the evening, about ten hours after exposure had ceased, the patient returned to the factory to seek medical advice and treatment because his symptoms had become more severe. He was admitted to the sick bay and oxygen therapy was begun.

Clinical Course

10 hours On arrival the patient complained of cough, tightness in the chest, and headache, with a foul taste of phosgene in his mouth. He also stated that his throat felt dry.

In appearance he was rather pale with slight cyanosis of the extremities and was obviously having some difficulty with breathing. The fauces were rather injected, a condition probably worsened by the cough from which the patient suffered. Expectoration was, however, not great in amount.

On examination there was definite diminution of air entry into the lungs, though actual impairment to percussion could not be detected. Moist sounds were audible throughout the chest, although they were by far more numerous at the bases of the lungs. Some sonorous rhonchi were audible in the upper areas of both lungs.

Temp.99; pulse 110; resp.26; B.P. 160/100.

12 Hours Coughing was now much more easy and had become more productive, a good deal of thin fluid being brought up. There was no blood staining of the sputum.

In the lungs, some impairment of percussion note was elicited at the left bases, while auscultation showed that the moist sounds had become more abundant, especially in the upper parts of the lungs. Breathing was rather shallow.

Temp.100.6; pulse 100; resp. 28; B.P. 160/100.

14 hours The patient's condition remained unchanged. Breathing was still very shallow, but regular, and he was bringing up a good deal of sputum. The skin was still pale with cyanosis of the lips and

ears, and he was perspiring freely. Examination of the lungs revealed no change.

Temp.101; pulse 100; resp. 28; B.P. 156/100.

Instructions were given for oxygen therapy to be continued during the night.

22 hours By the following morning the patient stated that he felt much better and he had slept for intervals during the night. The breathing was much easier and there was now no sign of cyanosis or pallor. The headache and tightness in the chest had both disappeared.

Examination of the lungs revealed some deficiency in air entry at the left base but the percussion note in that region could not be regarded as abnormal. Moist sounds were now very sparse and audible only at the bases. Cough had greatly diminished and the production of sputum was very much less.

Temp.99.8; pulse 86; resp.22; B.P.140/90.

26 Hours Examination of the chest now showed only an occasional moist sound at the bases with some rhonchi scattered throughout the lungs. The patient stated that he felt very comfortable. Oxygen therapy was now stopped.

Temp.98.6; pulse 83; resp.20; B.P.140/90.

30 hours Cough and expectoration now only occurred at long intervals and appeared to be in the nature of clearing the throat rather than due to a more deeply seated cause. The patient's condition had been entirely satisfactory during the previous four hours, in which he had not had any oxygen inhalation.

On examination, a few crepitations were detected over both bases, and

rhonchi as before, with air entry quite unimpaired at any part.

As the patient was very anxious to get home, he was taken there by car and his own doctor was notified.

Temp. 98.6; pulse 90; resp. 20; B.P. 130/90.

Nine days after exposure the patient returned to work, bringing a certificate from his own doctor that he had had an acute bronchitis. However, recovery had been complete, and the patient, free from all abnormality, was allowed to return to his former occupation.

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A serial record of blood-pressure, pulse rate, respiration rate and body temperature changes in the seven severely affected cases described above will be found in Table 2.

TABLE 2. SEVERELY AFFECTED CASES.

Case No.	Normal+ Blood Pressure		First X Reporting for Treat-ment	HOURS SUBSEQUENT			AFTER ZERO							
S.1. S.H.A.	132/90	Time	0	1	5	13	16	18	22	32	36 ⊖	50 ⊖	68 ¥	100
		B.P.	150/90	135/90	210/110	240/110	160/130	170/130	180/132	140/110	140/115	138/112	132/110	136/90
		Pulse	70	72	80	100	116	118	118	100	96	80	82	70
		Temp.	96.4	98.2	99.2	-	97.6	97.6	96.4	97.0	97.6	97.6	97.8	98.2
		Resp.	36	22	24	30	32	40	34	26	28	24	22	20
S.2 D.McA.	122/86	Time	0	1	3	5	6	8	10	15	24 ⊖ ¥	32		
		B.P.	178/118	164/118	150/110	180/120	176/120	160/118	146/110	146/120	128/96	150/116		
		Pulse	128	124	102	100	96	90	92	86	84	74		
		Temp.	-	97	99	98.8	98.6	98.0	98.0	98.0	97.2	97.4		
		Resp.	24	22	24	28	30	28	22	20	18	18		
S.3 P.P.	140/86	Time	0	1	3	5	6	8	10	23 ¥				
		B.P.	170/110	152/100	140/96	160/100	150/84	140/84	140/80	140/84				
		Pulse	78	72	80	80	88	70	70	74				
		Temp.	98.4	98.6	98.8	99.0	99.4	97.4	97.6	98.0				
		Resp.	20	22	22	24	22	20	20	20				
S.4 F.B.	126/76	Time	15	16	18	26	32							
		B.P.	150/105	150/105	140/110	170/124	160/130							
		Pulse	100	104	112	120	120							
		Temp.	98.2	99.2	101.2	100.2	99.4							
		Resp.	28	26	26	24	28							
S.5 H.McA.	120/80	Time	12	14	16	20	28	30 ¥	36					
		B.P.	260/86	260/96	166/100	146/86	148/90	150/108	136/96					
		Pulse	84	84	84	78	70	60	74					
		Temp.	97.4	97.8	99.0	98.0	97.6	97.0	97.2					
		Resp.	24	26	26	22	20	20	20					
S.6 A.T.	128/74	Time	10	12	13	17	24 ⊖	32 ¥						
		B.P.	260/220	260/200	160/100	140/80	150/98	142/80						
		Pulse	150	122	94	92	80	78						
		Temp.	100	99.2	99.0	97.8	97.2	97.6						
		Resp.	30	12	28	22	20	20						
S.7 J.K.	130/90	Time	10	12	14	22	⊖ 26 ¥	30						
		B.P.	160/100	160/100	156/100	140/90	140/90	130/90						
		Pulse	110	100	100	86	88	90						
		Temp.	99.0	100.6	101	99.8	98.6	98.6						
		Resp.	26	28	28	22	20	20						

+ Recorded at pre-employment examination.

X All accidents occurred and exposure ceased at zero hours.

⊖ Oxygen flow reduced or administered intermittently

¥ Oxygen therapy finally stopped.

COMMENTARY ON SEVERELY AFFECTED CASES

It is desired to draw attention particularly to the following points in connection with this group of patients:-

1. As will be seen from table 2, elevation of the blood pressure is a constant feature among the severely affected cases. Each exhibits it in a definite and marked degree, the actual extent of the rise being greater in the more serious casualties, and tends to be highest at the height of the illness.

2. In some instances, if not all, there is a transient rise in blood pressure immediately following exposure, followed quickly by a drop and then by a secondary rise as the patient's clinical condition worsens. The initial rise is probably purely emotional in origin, and is well shown in cases 1, 2 and 3. In the other cases it is not apparent, since they were not seen until a considerably later stage of the illness. The secondary rise occurring at the height of the illness is apparent in all the cases described, and it is this one which is typical of severe phosgene poisoning.

3. The body temperature is elevated at some stage of the illness in every case, and this occurs quite irrespective of the development of infective lung complications. The pyrexia, however, quickly subsided in all cases, save in the instance of case S.4, where it persisted for many hours, and merged into the pyrexia of a developing pneumonia.

4. In general it may be stated that patients receiving treatment immediately after exposure recovered more quickly, did not develop infective complications, and were absent a shorter time from work.

5. Dyspnoea was a constant feature of the severe cases and took the form of rapid shallow breathing.

6. The colour of the severely gassed patient is constantly a generalised leaden grey. This is seen to be made up of a mixture of intense pallor and ordinary cyanosis. On the normally better coloured parts of the body, especially the lips and ears, the cyanosis is the usual blue type, unmixed or but little mixed with pallor. The generalised blue and congested type of case recorded in the literature has not been seen.

7. Between the cessation of exposure and the development of serious symptoms, especially lung oedema, there is a period of several hours when the patient remains comparatively well. This is the well known "latent period" of phosgene poisoning, and is mentioned constantly throughout the literature, and it is shown by all the cases described above.

These and the other main features of phosgene gassing will be severally considered during a detailed discussion of the condition in the next and subsequent chapters.

CHAPTER III

Discussion of Phosgene Poisoning

Aetiology

There is no doubt but that this gas acts clinically as a lung irritant. Hitherto it has been generally accepted that this action is solely a local and direct one, but it is hoped to show in the present study that this explanation cannot be accepted as altogether complete and correct. In the literature there is general agreement that among fatal cases the commonest cause of death is pulmonary oedema. This oedema is known to be due to the escape of plasma from the lung capillaries into the alveolar spaces. Although I have not had the opportunity of observing directly the phenomena of plasma exudation from the membranes of the respiratory tract, I have seen them in varying degrees of severity, in the conjunctiva of the eye. These observations have already been described in the case histories presented. It seems reasonable then to accept that a similar exudative process also takes place in the pulmonary tissues and is the proximate cause of the lung oedema that is such a prominent feature of the severer cases of phosgene poisoning.

On the assumption that the pulmonary oedema is caused solely by a local effect upon the tissues of the lung, two possible modes of action of the gas have been suggested. Some writers believe that the substance is inherently a strong irritant, capable of causing severe damage to certain tissues, particularly those of the lungs, which are richly endowed with a network of comparatively superficial and hence readily damaged capillary blood-vessels. Others state that the gas owes its irritant properties to the fact that it hydrolyses in the presence of moisture

to produce carbon dioxide and hydrochloric acid, and that it is the latter substance which causes the actual damage to the blood vessels and tissues. There are, however, very serious objections to both of these mechanisms suggested for the production of lung oedema by phosgene gassing. These objections will be described and discussed more conveniently in subsequent sections, where it is hoped to show that the action of phosgene in producing oedema of the lung cannot be entirely a local one.

Pathology

A.MORBID ANATOMY

Before entering upon a discussion of the chemical or physiological pathology of phosgene poisoning, it is necessary to have some clear picture of the anatomical changes that take place in the lungs. In the present series of cases there have been no deaths, and hence no opportunity of observing personally the morbid anatomy of the condition. The subject has, however, been well covered by other writers.

According to the Medical Manual of Chemical Warfare (23), the essential lesions are pulmonary oedema, rupture of the alveoli and concentration of the blood, with increased viscosity and a tendency to thrombosis. The earlier that death occurs after exposure, the greater the degree of pulmonary oedema. In the early stages the lungs are voluminous, oedematous, and congested with blood, while aerated patches of emphysema alternate with patches of collapse, particularly at the lung edges. Frothy serous fluid mingled with blood drips from the cut surface of the lungs and peticehial haemorrhages may be present

in the surface of the pleura. The pleural cavity itself usually contains a small amount of blood stained effusion. In later cases that come to autopsy there is less pulmonary oedema, and commencing bronchopneumonia may indicate that bacterial invasion has taken place.

Shaw Dunn (24) states that "the lesion produced by phosgene must be "relegated to the category of acute inflammation ... Initial damage is "very uniform in distribution; much more so than in lesions arising from "bacterial infection." The same author further states that "... death "during the first 48 hours is associated with extreme degrees of "pulmonary oedema, and the greater part of the respiratory area is out "of action purely as a result of fluid in the alveolar spaces" ..." it "is the bulk of this fluid which constitutes the grave factor in the "average case. It acts in mechanical fashion by filling up the alveoli "to the exclusion of air." The picture thus presented is one in which death is due to anoxia consequent upon the patient drowning in his own secretion.

Further light has recently been thrown on the pathology of phosgene gassing by McGibbon (25), while investigating the effects of bronchoscopic aspiration of secretions and bronchoscopic insufflation of oxygen and carbon dioxide in goats subjected to phosgene gassing. The common finding in those animals which died or were killed at the expiration of three days, was a variable degree of "consolidation" of the lungs. It was established that two types of inflammatory fluid are produced in the lower respiratory tract as a result of phosgene acting on the tracheobronchial mucous glands and on the epithelium of the

"respiratory unit." Greatly increased mucous secretion occurs in the proximal airways, and an excessive outpouring of clear oedema fluid in the more distal "respiratory unit" spaces. From bronchoscopic observation and from the effects of bronchoscopic aspiration or post-mortem examination it is suggested that the mucous secretion forms plugs in the smaller bronchi and bronchioles which, possibly aided by swelling of the mucous membrane and by bronchiolar spasm, cause obstruction and retention of the oedema fluid in the lung spaces. This condition of fluid retention is referred to by the author as "consolidation." He found that in phosgene poisoning the obstructive agent is tough mucus, whereas in chlorine and "blistering gas" poisoning the obstruction is caused by shed and necrotic mucous membrane.

A similar type of bronchial obstruction in pneumonia has been described by Coryllos (26), and the development of "consolidation" in the undrained portion of the lung in acute bronchiolitis in children by Hubble and Osborn (27). Such analogies between pneumonic conditions and phosgene irritation of the lungs ~~is~~ *are* in agreement with Shaw Dunn's statement, already quoted, that "the effect of phosgene gassing must be relegated to the category of acute inflammation."

B. PHYSIOLOGICAL AND CHEMICAL PATHOLOGY

The inhalation of phosgene gas produces a well defined clinical picture, varying of course to some extent with the degree of exposure. Certain major features of this clinical picture provide the bases on which the physiological and chemical pathology of phosgene gassing are

most easily discussed. These cardinal features are:

1) The latent period between exposure and the development of the typical symptoms;

2) Pulmonary oedema: its production and development;

3) Changes in the peripheral circulation and in the blood pressure;

4) Cyanosis, anoxia and dyspnoea;

5) Alterations in the body temperature;

6) The deleterious effect of exercise.

To these must be added, for completeness, a brief consideration of the process by which pulmonary exudates undergo resolution.

1. The Latent Period:

One of the peculiarities of phosgene poisoning remarked by all writers on the subject is the so-called "Latent Period." By this is meant the interval of several hours, usually 4-12, or even as long as 24, that elapses between exposure and the onset of severe pulmonary symptoms, especially lung oedema. It must, however, be recalled, in this connexion, that owing to the insidious nature of the gas, exposure may have continued, in certain circumstances, for some considerable time before the patient becomes aware of his exposure from the appearance of the initial symptoms. But it is not to this period of delayed action that the designation of "Latent Period" strictly applies. Even after exposure has ceased, the further development of symptoms will take place, and these may not reach their full severity for many hours. It is to this interval between cessation of exposure and development of symptoms that the term "Latent Period" is properly given. In general it may be said that the exact duration of this latent period depends

on the severity of the exposure - the greater the exposure, the shorter the latent period.

That such an interval exists is not, of course, to say that the patient is entirely free from symptoms during this time. Indeed, he is a sick man from the outset and cannot but continue to be aware of having been exposed to the gas. Headache, usually frontal, a foul taste in the mouth, particularly noticeable on attempting to smoke tobacco, a slight irritation or feeling of dryness in the throat, a laryngeal "tickle" accompanied by some degree of unproductive cough, are all present, as a rule, from the beginning, and become more marked as the latent period elapses, till finally they are severe and merge with additionally developed symptoms into the typical syndrome of severe phosgene poisoning.

The reason for this latent period has never been adequately explained. It is customarily stated to be due to hydrolysis of phosgene within the alveoli, with the production of carbon dioxide and hydrochloric acid, and that the latter damages the alveolar walls and allows plasma to escape. It is also assumed that this damage takes some time to develop and that until the injury to the alveolar walls and capillaries reaches a certain stage oedema does not ensue (28, 29). At first sight, such an explanation seems to be an entirely satisfactory one, but further consideration and thought shows that it is quite untenable.

Effects in the lung of Hydrolysis and Hydrochloric Acid Formation

Of all the mineral acids, hydrochloric is the least reactive on the human skin, and yet the application of a 40% solution of the acid in

water will cause cutaneous hyperaemia in 30 seconds (3) - and the skin is a highly resistant organ as compared with the pulmonary epithelium. The rate of development of the lesion of course depends both on the strength of the acid and the site of its action. In this connexion one can profitably recall how a splash into the eye of 0.1 N or even 0.01 N hydrochloric acid, such as is used in clinical laboratories, soon causes pain, congestion and watering of the eye unless it is immediately and thoroughly washed out. It is, then, very difficult to believe that such a delicate, thin and sensitive structure as the alveolar wall is so insusceptible to burning by hydrochloric acid that it takes anything up to 24 hours for a lesion to develop. Moreover, the symptoms of dryness i the throat, laryngeal irritation and cough, as mentioned above, are also attributed to the same acid effect; yet they are present from the beginning and many hours before the signs or symptoms of alveolar damage make their appearance. Again, any acid that might be formed from hydrolysis within the alveoli would certainly not be more dilute than that formed in the upper respiratory passages, for the latter contain a very great deal of moisture which would dilute at once, and to a very considerable degree, the acid products of hydrolysis, whereas the alveolar spaces tend normally to dryness and any acid formed therein would remain in a much more concentrated state. As long ago as 1856 this natural tendency to dryness of the alveoli was well demonstrated by Colin (31) who succeeded in administering 21 litres of water intratracheally to a horse in $3\frac{1}{2}$ hours. He describes the experiment thus:-

"After having fixed within the trachea of a horse, by means of an

opening through one of the tracheal rings, a tube of 1 cm. diameter, I poured in warm water (30° - 35° C.) at the rate of 6 litres per hour. The animal panted and respiration was deepened throughout the 3½ hours' duration of the experiment. Subsequently the animal was sacrificed; the trachea and bronchi were empty, all the liquid injected had disappeared.

"In like manner I instilled into the respiratory passages of a second horse 25 litres of water in 6 hours, performing at the same time three venesections at two-hourly intervals and withdrew 6 kilos of blood. The respiratory mucosa absorbed all this quantity of fluid without the animal seeming greatly embarrassed by it."

The explanation of this natural tendency to dryness in the alveoli has been adequately given by Drinker (32). Throughout the body, both in systemic and pulmonary vessels, the osmotic pressure of the blood colloids is about 25-30 mm. of mercury; this osmotic pressure tends to draw fluid from the tissue spaces into the lumen of the vessel. In the systemic circulation the capillary blood pressure tending to force fluid out of the vessel into the tissue spaces is of the same order, i.e. 25 - 30 mm. of mercury. Thus there is in effect no preponderance in the flow of fluid in either direction between capillaries and tissues. In the pulmonary circulation, however, a different set of circumstances obtains. Here the osmotic attraction of fluid into the lung capillaries still corresponds to a mercury pressure of 25 - 30 mm. while the capillary blood pressure tending to force fluid out of the vessels and into the pulmonary tissues is found to be only about 10 mm. of mercury.

Even allowing for the negative pressure or suction action of the lung during ordinary respiration as being -5 to -10 mm. of mercury, the balance is still in favour of dryness of the alveolar spaces.

The nett result of this inherent tendency to dryness in the alveoli is twofold. Firstly, any hydrolysis of phosgene taking place in the alveoli must be minimal under the less favourable conditions existing there, and most of the hydrolysis, if not all, will take place in the moist upper respiratory passages. Secondly, any acid that is formed within the alveoli cannot be diluted to the same extent as will occur in the upper respiratory tract; yet the latter shows earliest the signs and symptoms of acid irritation. It would therefore appear that the common theory of the hydrolysis of phosgene to an irritant acid neither explains the course of the pulmonary lesions, nor takes into account the existence of the well recognised "latent period."

Solubility Factors in relation to Lung Irritants

In considering the action of lung irritant gases, the question of solubility is a fundamental one. In their monograph on the Noxious Gases (p.112 et seq.), Henderson and Haggard (15) remark:

"To exert its action, an irritant gas must be taken up by the surface "tissues and be dissolved in the fluid which bathes them. The severity "of the effect is greatest upon the surfaces which are most easily "penetrated and particularly upon those which are moist ... Any gaseous "irritant which is highly soluble in water is absorbed from the inspired "air by the first moist tissue which it reaches in the respiratory "passages. As a consequence, the upper tract bears the brunt of the

"action; the lungs are relatively little affected since the "concentration of irritant which reaches them is greatly reduced by "absorption in the upper passages. With those gases which have a low "solubility, the upper respiratory passages suffer little, for little is "absorbed, and the main damage is deep in the lungs. A gas of moderate "solubility exerts its action more or less uniformly throughout the "entire respiratory tract. Thus as a general rule the irritant gases "are dangerous inversely to their solubilities; the less soluble any of "them is, the more insidious its action."

After describing briefly some experiments in support of the above statements, these authors continue.

"The principles defined here as to the locus of action in relation to "solubility do not apply to irritants which are absorbed without "alteration, such as the vapours of ethyl ether. The greater part of "the irritant action occurs in the upper respiratory passages, bronchi and "bronchioles, while the lung alveoli and atria are relatively little "affected. Such amounts of gas as reach the lungs themselves are "absorbed and are the cause of systemic but not of pulmonary symptoms. "The sparing of the deeper portions of the lungs is due to the active "absorption into the blood which prevents the accumulation of the "irritant in the alveoli and so maintains there a lower concentration "than in the upper respiratory passages."

In view of the obvious importance of these general principles, further brief consideration must be given to such physical and chemical properties of phosgene as might have a bearing on the application of these principles to cases of phosgene gassing.

Concerning the solubility of the gas in water, the exact coefficient has not been determined (33) on account of the significant amount of hydrolysis that takes place when the gas is brought into prolonged and intimate contact with a great excess of water in the liquid phaze. This effect so complicates the experimental determination of the solubility coefficient as to render inaccurate any figure that might be obtained, for such a figure would represent the solubility of phosgene together with its degradation products, rather than of the gas itself. That is not to say, however, that phosgene undergoes almost instantaneous hydrolysis when in contact with water, as is so commonly believed. Indeed, the gas can be bubbled through water at ordinary temperatures with very little loss, as has been personally observed. The solubility of phosgene in water is slight, and though the rate of hydrolysis may be appreciable, it is far from being instantaneous. Where it is desired to neutralise or absorb phosgene during chemical experiments or manufacturing processes, it is quite useless to attempt this merely by passing the gas into water in an effort to hydrolyse or dissolve it; a solution of caustic soda or similar strong alkali, which breaks down the molecule and neutralises its constituents, is necessary for the purpose.

Fate of Inspired Phosgene

Following the inhalation of phosgene a certain amount of hydrolysis must undoubtedly take place, but this will be mainly in the wetness of the upper respiratory passage where, indeed, acid irritation is experienced relatively soon after exposure commences. The process of hydrolysis being,

however, very far from complete, one is forced to conclude that most of the inspired gas reaches the alveolar spaces unchanged to mingle with the alveolar air and become, for a time, at any rate, a simple constituent of it. Moreover, on account of the relative dryness of the alveoli, and because the gas cannot remain there for an indefinitely prolonged period, little or no further hydrolysis can take place. Yet the action of phosgene is upon these deep tissues of the lung, and one might therefore be tempted to assume that the substance is, of its very nature, a primary lung irritant of low solubility and that it thus acts in accordance with the principles as set forth by Henderson and Haggard, and quoted above. This conclusion that the phosgene molecule acts by directly damaging the alveolar wall appears to be an erroneous one, for the following reasons:-

Once exposure to the vapour has ceased, the amount of phosgene present in the alveoli will diminish rapidly and disappear; some of it will be expired in the breath and the remainder will behave with the other respiratory gases - transgressing the alveolar wall to combine with or dissolve in the blood of the pulmonary circulation. Yet many hours will elapse before its final and complete disappearance from the alveoli and the development of lung oedema. Thus the gas is either <u>not</u> a primary lung irritant in spite of the fact that it produces maximum damage deep in the lung, or, being a true primary irritant, there must be something inherently peculiar in the very essence of a substance that causes a lesion to develop long after the substance itself has left the site of operation. In the latter case, no farther explanation of the Latent

Period is needed, for none is possible. If the former be true, then some reason must be sought that will explain how phosgene produces its effect on the lung in spite of the fact that it cannot be a primary irritant. This new problem will become a subject for discussion in a subsequent section. The question that presents itself at the moment is why the effect should be delayed.

Fate of Phosgene in the Alveoli

So far as the fate of phosgene in the alveoli is concerned, it appears then to behave rather in the manner of the anaesthetic vapours to which we have previously referred. Substances such as ether and chloroform, poorly soluble in water though they are, irritate primarily the upper respiratory passages and spare the alveoli because they diffuse quickly through the walls to dissolve in the lipoids of the blood and are thus rapidly carried away to produce a systemic effect. Their accumulation in the alveoli is thereby prevented, and their concentration there and capacity for irritation is, at any moment, less than in the upper respiratory tract. Phosgene appears to behave in a somewhat similar fashion. This is not, however, surprising in view of the solvent properties it has in common with the anaesthetic vapours mentioned - a high degree of miscibility with organic liquids such as toluene, benzene, and carbon tetrachloride (1) as well as a ready solubility in lipoids, fats and oils (1). In view of this, and of the points discussed before, the possible fate of phosgene that has reached the alveoli, apart from being exhaled in the breath, must fall under one or more of the following headings:-

(1) A small portion may conceivably undergo hydrolysis within the alveoli, liberating hydrochloric acid and carbon dioxide. The first mentioned acid could then act directly upon the alveolar walls and damage them. This effect would be rapid, as on other tissues, and would not require the long duration of the latent period for its full development. Such a process of hydrolysis within the alveoli, as we have seen, must in any case be minimal, if indeed it does take place to any significant degree at all.

(2) A portion of the alveolar phosgene that transgresses the respiratory membrane may enter at once into direct chemical combination with one or more constituents of the blood. This possibility will be further examined in detail at a later stage.

(3) In view of its very ready solubility in lipoids and fats, part of the phosgene within the alveoli (and probably the greater part) will behave like an anaesthetic vapour and pass into solution in the lipoids of the blood and tissue fluids. It is inevitable, however, that phosgene which has thus entered into solution in the lipoids must eventually and by a gradual process diffuse evenly throughout the fluids of the blood and tissues, there to be hydrolysed, or in virtue of its considerable reactive powers, to enter into chemical combinations as pre-supposed in (2) above. The nett result would be a gradual development, over a period of time and even after exposure had ceased, of the various chemical reactions that may take place between phosgene and the constituents of the body fluids, especially the blood. Such a sequence of events would adequately explain the phenomenon of the latent period if it can also be shown that these resulting chemical reactions would in fact cause a

pulmonary oedema to develop. Before attempting to do so it will be necessary first of all to discuss the various pathological mechanisms that are concerned in the production of lung oedema.

2a. ACUTE PULMONARY OEDEMA. Its Production and Development

In severe or fatal cases of phosgene gassing the most serious and most constant feature of the pathological process is the development of pulmonary oedema. As previously stated, this event has in the past been attributed to damaging of the alveolar walls by the acid products of phosgene hydrolysis permitting the escape of plasma into the alveolar spaces. Yet as this theory has proved incompatible with the phenomenon of the latent period, so too is it untenable as an explanation of the origin and onset of lung oedema, and for much the same reasons. Indeed, the factors responsible for the existence of the latent period and for the production of pulmonary oedema are so inextricably mixed and so interdependent that they may be almost regarded as but two aspects of the same problem, for if all were known of the one it would pre-suppose a more or less complete understanding of the other. Apart from the physical, physiological and chemical objections already raised in discussing the latent period, there are additional objections that may be raised against the theory in connexion with the production of pulmonary oedema.

In the chemical factories with which the writer has been associated, he has from time to time seen persons whose lungs have been affected by various irritant gases, as for example, hydrochloric acid and sulphur dioxide, yet neither of these have produced oedema of the lung,

clinically detectable, even in the most severely affected cases. Chlorine, on the other hand, has usually caused some degree of "wetness" of the lungs, though cases of frank oedema have not been personally observed, probably because this vapour is an overpowering respiratory irritant and the immediate painful stimulation ensures that exposure will be short. Bronchitis and bronchopneumonia have, however, been common sequelae in cases of exposure to any of the three gases just mentioned. From the figures quoted in table 3 which sets forth the comparative solubilities of these gases in water (34), it will be seen that it is the relatively insoluble chlorine which tends to cause lung oedema, while the two more soluble gases do not. This of course is fully in conformity with the general principles laid down by Henderson and Haggard (15) and quoted at some length in the previous section.

Gas:	cc.s of gas soluble in 1 cc. of water at 20° C.
Hydrochloric acid. HCl.	442.0 c.c.
Sulphur dioxide SO_2	39.4 c.c.
Chlorine. Cl_2	2.26 c.c.

TABLE 3.

Yet in view of the foregoing observations on relative solubilities it is most remarkable that neither the vapour of mustard gas nor that of lewisite, both very powerful vesicants, have ever been seen to produce lung oedema among the many cases of inhalation personally observed. The respiratory symptoms have varied from those of mild laryngitis to acute tracheo-bronchitis and even broncho-pneumonia, but in spite of their powerfully irritant and destructive nature, these substances apparently do not produce lung oedema. The solubility of mustard gas is extremely low, being only 0.069% according to Wilson and his co-workers (35). On the grounds of solubility alone the highly irritant mustard gas should produce pulmonary oedema many times more readily than does chlorine, if low solubility were the sole determining factor for the production of pulmonary oedema by an irritant. Obviously, then, it cannot be so. This clinical observation is, moreover, in agreement with the recorded experience with vesicant gases during the war of 1914, and this peculiarity was commented upon by an editorial article in the British Medical Journal (36) in the early days of the recent war. In this article reference was made to cases of mustard gas poisoning so severe as to produce the most destructive necrosis of tissue, extending from the larynx to the smallest bronchioles and permitting secondary bacterial invasion with septic pneumonia - but never causing pulmonary oedema. There must then be more than purely chemical irritation or burning of lung tissue required for the production of lung oedema.

For a proper understanding of the problem it may be helpful to enquire into the production of acute pulmonary oedema in other conditions

and diseases. Outstanding among such morbid states is the one known variously as cardiac asthma, acute pulmonary oedema or nocturnal paroxysmal dyspnoea according to the predominating feature of the particular case. This disease condition has many features in common with phosgene poisoning. These include the sudden onset of lung oedema, the dyspnoea, leaden coloured cyanosis, sweating, elevation of blood pressure and body temperature and the often inexplicable onset of these symptoms while the patient is at rest.

Acute Pulmonary Oedema or Cardiac Asthma

On the general manifestations of these attacks, and the conditions necessary for their occurrence, all authorities are agreed. They occur as a rule in patients suffering from high blood pressure and always in those with a damaged left ventricle. The commonest cause of a damaged left ventricle is of course hypertension, either the so-called essential type or the secondary form due to various causes, especially chronic nephritis.

According to classical theory these attacks are attributable to acute failure of the left ventricle in transferring blood from the pulmonary to the systemic circulation. This leads to stasis in the lungs, and after an interval, to the transudation of plasma from the engorged lung capillaries, thereby producing pulmonary oedema. This explanation still finds authoritative support (37a, b, c), but there is a very considerable and growing weight of evidence against this simple theory.

A recent annotation in the British Medical Journal (38) drew attention to the fact that the classical theory of backward pressure in the lungs

can no longer be considered as established, and cites the work of Luisada (39), who emphasises that pulmonary oedema cannot be produced experimentally by overloading the left ventricle, nor by any mechanical procedure that might be expected to cause pulmonary congestion. Luisada moreover suggests that the primary factor is a neurogenic one, and that only when this is present can simple mechanical changes in the cardio-vascular system produce pulmonary oedema. This observation is supported by the records of previous authors who have observed the development of pulmonary oedema in patients suffering from various lesions of the nervous system. Langeron (40) reports its occurrence in an epileptic, probably neurosyphilitic, and reviews 16 similar cases in the literature where attacks of pulmonary oedema occurred in epileptics, many of them definitely suffering from neurosyphilis. Moutier (41) also reports its occurrence in soldiers with non-penetrating injuries to the skull, and Farber (42) observed it in a series of children with encephalitis, polioencephalitis, meningitis and brain abscess and tumour, while Weisman (43) found it in 70% of his patients dying of intracranial haemorrhage, traumatic or otherwise. According to Kaufmann (44), acute pulmonary oedema is a well recognised complication of head injury. Luisada (39) concludes that there is a neurogenic factor operative in cases of pulmonary oedema following exposure to irritant gases, and that the condition is not due solely to direct damage to the lung capillaries. More recently Wasserman and Goodman (45), in an experimental review of the subject, also came to the conclusion that a neurogenic factor is of fundamental importance in the production of an attack of cardiac asthma or acute pulmonary oedema.

Moreover, it must be remembered that attacks of cardiac asthma - pulmonary oedema are recurrent. Seltzer (46) reports a case where "during "the entire seven months period of the terminal illness the patient "underwent 146 attacks of acute left ventricular failure, characterised "by pulmonary oedema of great degree and its accompanying symptoms and "physical signs." It is difficult to believe that acute failure of the left ventricular muscle precipitates these attacks, for this would mean that acute ventricular failure must suddenly occur at each separate episode and that such a heart can repeatedly, and in rapid succession, alternately fail and recover normal function. In addition there must be taken into consideration the often recorded fact that during the attack there is a remarkable rise in the systolic blood pressure (47a,b) which is very constant and which does not readily fit in with the concept of a left ventricle that is supposed to be failing acutely. Christie (48) regards this phenomenon of greatly increased pressure in a heart supposedly strained to breaking point as being "a rather "extraordinary fact."

A very excellent discussion on the etiology of acute pulmonary oedema, or paroxysmal nocturnal dyspnoea as they more frequently call it, and one that throws considerable light on the nature and locus of action of the postulated neurogenic factor, is contained in the monograph on Cardiovascular Diseases by Scherf and Boyd (49). Against the classical conception of lung oedema produced by stasis and congestion they adduce the following evidence.

(1) The attacks occur usually at night while the patient is sleeping,

and when there is least strain on his damaged left ventricle.

(2) If pulmonary oedema were due to stasis in the lungs these attacks should be very frequent in advanced mitral stenosis with congestive cardiac failure, whereas in fact they very rarely appear; if they do occur in this disease it is during a period of exertion and never while the patient is quiet at night.

(3) "If acute weakness of the left ventricle actually released these attacks one would expect the blood pressure to fall during the episode, or where compensatory regulations were instituted to remain unaltered. However, both systolic and diastolic pressure rises in the attack and this increase occurs so regularly that an attack in which the blood pressure remains unaltered or actually falls is a sure indication that terminal oedema is present, or that an attack of cardiac asthma - pulmonary oedema co-exists with a recent coronary thrombosis or a profoundly damaged myocardium."

(4) While morphia has a most beneficial effect in these attacks it has no direct or beneficial effect on the muscle of the left ventricle.

Having thus raised serious objections to the classical theory of backward pressure, stasis and congestion as the cause of an attack of pulmonary oedema, Scherf and Boyd go on to propound a newer concept of the mechanism, summed up in the proposition that "paroxysmal nocturnal "dyspnoea originates in an abnormal state and abnormal function of the "respiratory centres." Their evidence in favour of such a 'respiratory centre theory' may be briefly stated as follows:

(1) The excellent effects of morphia both in the attack and prophylactically;

(2) The occurrence of cardiac asthma and pulmonary oedema in organic cerebral lesions, especially skull trauma;

(3) The attacks are independent of the degree of pulmonary stasis present, and within certain limits, independent of other signs of decompensation;

(4) Cardiac asthma occurs exclusively in the same conditions as those a in which Cheyne-Stokes breathing is found and this is known to be due to a disturbance of the respiratory centre;

(5) The manifestations of the attack, particularly the very sudden onset and the apparent purposelessness of the gasping respiration exhibit an entirely different character from the dyspnoea of pulmonary stasis;

(6) A normal oxygen saturation of the blood and absolutely no excess of carbon dioxide in the blood, either during the attacks or in the intervals between them, indicates that the conditions in the lungs are normal. (It is of interest to note that Christie (50) and Haldane and Priestley (51) have drawn attention to the fact that the same state of affairs obtains in cases of phosgene gassing - namely, that there is no retention of carbon dioxide; indeed, it is usually below normal unless death is imminent);

(7) The pallor, anxiety, sweating and other accompanying phenomena as well as the frequent absence of other signs of cardiac weakness and their sudden appearance in individuals at rest and who are entirely free from complaints during the day also deserve notice.

Consideration of the above points in favour of the "respiratory centre theory" of causation of acute pulmonary oedema adds further light

on the etiology of the condition. Since it is generally accepted that paroxysmal nocturnal dyspnoea occurs in cases of left ventricular failure it is well to consider how left ventricular failure can bring about these changes in the respiratory centre responsible for initiating the attack.

The left ventricle supplies blood and oxygen to the tissues and removes metabolites from them. Failure of the left ventricle therefore results in an accumulation of metabolites in the tissues because blood flow is deficient. The deficiency in blood flow also results in an excessive formation of metabolites, in that metabolism in the tissues is incomplete because of deficient oxygen supply, the nett outcome being the accumulation in the tissues of excessive amounts of acid breakdown products mainly non-volatile acids, such as lactic and pyruvic acid. That this state of affairs exists in cases of left ventricular failure is recognised by Sherf and Boyd (loc.cit., p.10) in these words:

"In decompensated patients, not only a decrease in the minute volume but "an accumulation of non-oxidised metabolic products and a disturbance of "the metabolic status of the tissues can be demonstrated."

Moreover, in this disease the lungs are normal between attacks and gaseous interchanges at the alveoli take place normally. The rate of blood flow is reduced by the failing left ventricle; tissue oxidation processes are slowed and incomplete, and an alteration towards tissue acidity takes place. In short, it is not the quality of the blood that produces tissue alterations in cases of ventricular failure, but rather the rate of flow. Of course, in other morbid processes the same effect of altering tissue acidity might well be produced by changes in the quality of the blood, and not by any diminution in its rate of flow.

In either instance the final result could be the same - an increase of tissue acidity leading to the development of an attack of cardiac asthma or acute pulmonary oedema. That the same type of mechanism operates for the production of lung oedema in cases of phosgene gassing seems reasonable to expect. The probable changes in the blood chemistry, following the inhalation of phosgene, that would bring about this state of affairs, will be discussed, however, at a later stage.

So far as the actual precipitation of the attack is concerned, the nocturnal nature of the episodes provides the clue, and adds further confirmation to the theory that the fundamental cause is an increase in tissue acidity. Normally carbon dioxide (CO_2) accumulates in the body during sleep because of altered irritability (sensitivity) of the respiratory centre. This normal increase in blood CO_2 (i.e. alteration of the blood towards the side of acidity) may be sufficient to tip the scales and precipitate an attack, when taken in conjunction with the already present excess acidity due to increased presence of metabolites, as outlined above. It is further noteworthy that the sensitivity of the respiratory centre to carbon dioxide is greatly increased by the local accumulation of excess of acid substances, so that in left ventricular failure the respiratory centre becomes unduly sensitive to the normal increase of CO_2 during sleep, thereby further enhancing the facility with which a very small increase in acidity may alter the respiratory centre and precipitate an attack.

Before leaving this question of ventricular failure and decrease in the rate of blood flow, it must be noted in parenthesis that in all cardiac conditions producing an increase in the circulation time ~~tissue~~ the rate of

flow through the lungs is much more altered than the rate of flow in the systemic circulation. Considerable investigations have been made into this point by various authors (52a, b, c, d), and all of them show that in cardiac failure in general, and left ventricular failure in particular, the prolongation of the circulation time in the lesser circulation is relatively greater than in the major circulatory system. This observation may have a bearing on cases of phosgene gassing in that, if the blood were altered in such a way that it would exert a local effect upon the capillaries, circumstances might cause the brunt of such effect to fall mainly on the pulmonary vessels, both because of their being the site of prior action from any phosgene-blood compound so formed and because of their longer exposure to it.

Anoxic and Other Factors influencing the Production of Lung Oedema.

Of paramount importance in research into the production of pulmonary oedema is the work of Drinker, extending over many years, and comprehensively epitomised in his recently published monograph (53). His studies are not so much concerned with the primary cause of the condition, but rather with the actual mechanism of fluid production and of resolution of pulmonary exudates. One factor that he does stress, however, and which he regards as being of the highest importance, is the part played by anoxia, and more particularly, by anoxia of the pulmonary capillaries. Not only does oxygen lack cause increased capillary permeability everywhere in the body, but Drinker has shown that the minute vessels of the lung are especially susceptible to anoxia.

Thus not only is anoxia capable of producing pulmonary oedema, but the oedema fluid once formed (whatever the cause of its initial production may be) prevents oxygen from reaching the capillaries and this leads to the development of further oedema and anoxia, the process tending to continue in a vicious circle. In this connexion it is important to remember just how dependent are the lung capillaries on the alveolar air for the supply of oxygen to meet their normal requirements. The tiny vessels themselves contain venous blood. In normal resting conditions the intracapillary venous blood may still contain sufficient oxygen for the viability of the capillaries themselves, even with blocked or partially blocked alveoli surrounding them; any further stripping of oxygen from the venous blood, as by exercise, for example, may so tip the scale as to produce a significant anoxia of the capillaries, causing them to become dilated and permeable, permitting the transudation of plasma and allowing the development of further lung oedema to take place.

While the work of Drinker rightly stresses the importance of local anoxia of the lung tissues in the production of pulmonary oedema this does not as a rule cast much light upon the primary cause. Anoxia may beget anoxia and tend to keep going the process of oedema formation; it does not, however, initiate the process except in the rare case of pure anoxic asphyxia. For the induction of pulmonary oedema in experimental animals Drinker describes in his book the use of a drug which, when given by mouth or injected subcutaneously, intramuscularly, intravenously or intraperitoneally quickly produces an acute and even fatal oedema of the lungs and nothing else.

Post-mortem examination reveals no change in any organ; the animal is apparently normal in every way, except that it has died of a pure, acute pulmonary oedema. Though the nature of the drug is not disclosed in his monograph, the substance is in fact alpha naphthyl thiourea, a substance derived from urea: discovered during the recent war, its constitution could not be disclosed at the time of publication of this work on account of National Security Regulations (54). The substance is, however, now widely used as a rat poison, and acts entirely in the manner described.

Anoxia, however, is not the only factor acting locally that can cause capillary permeability and the escape of fluid into the tissues. Thus according to Samson Wright (55) "it is brought about by the products of tissue activity, i.e. metabolites ... maybe CO_2 or increased H^+ ion concentration." (loc.cit., p.461), by chemicals such as urethane (ibid., p.482) and by increased intracapillary pressure (ibid., p.474), though Drinker (53) does not believe that this plays a significant part in the case of pulmonary oedema. Sjerning (56) has actually induced pulmonary oedema in cats and dogs by the intravenous injection of chloramine and subsequent injection of urethane. The amount of fluid actually present in the lung at the time is also of importance. Thus in congestive heart failure from mitral stenosis there is no pulmonary oedema, for the lungs contain less fluid than normal (the "dry lung" of pathologists), and in addition, the membranes of the lung are probably less permeable on account of chronic fibrosis.

To summarise, the factors influencing the production of lung oedema, and of possible significance in phosgene poisoning, are these:

(1) An abnormal response of the respiratory centre to the accumulation of acid substances.

(2) Anoxia of the respiratory centre enhancing the effects of (1) above.

(3) Local anoxia of the lung capillaries leading to increased permeability, transudation of fluid, blockage of the alveoli and the begetting of further anoxia.

(4) The local action of acid substances on the lung capillaries.

(5) The specific action of chemicals, such as urethane and alpha-naphthyl thiourea, upon the capillaries.

(6) The existence of suitable conditions in the lungs such as normal or increased fluid content and permeability of the alveolar tissues.

2b. PHOSGENE IN THE PRODUCTION OF PULMONARY OEDEMA

In discussing the Latent Period in cases of phosgene gassing a chain of events was postulated that would adequately explain this phenomenon if it could be shown that the resulting chemical reactions between the blood or tissue fluids and the phosgene that had transgressed the respiratory epithelium mixed with the alveolar air, could in fact cause pulmonary oedema to develop. In order to show that the possible chemical reactions could indeed initiate the process of oedema formation, it will first of all be necessary to consider a little of the chemistry of phosgene and its related compounds or derivatives, together with their relevant physiological actions where known, and from this to derive something of the possible reactions between the gas and the normal constituents of the blood.

Chemical Reactions of Phosgene and Related Substances

Structurally the phosgene molecule is represented by the formula $O=C\begin{matrix}Cl\\Cl\end{matrix}$ and the substance may therefore be regarded as the acid chloride of carbonic acid $O=C\begin{matrix}OH\\OH\end{matrix}$, more familiarly represented by its empiric formula H_2CO_3.

Acid chlorides are formed by replacing with Cl the OH radicle of an acid. As can be seen, this is the relationship between phosgene and carbonic acid.

All acid chlorides still retain, but in an enhanced degree, some of the reactions of the parent acid in that they can combine, for example, with alcohols and phenols to form esters with the evolution of hydrochloric acid. The following examples will make this clear.

(1) $CH_3CO.Cl + C_2H_5OH = CH_3COOC_2H_5 + HCl$
acetyl chloride — ethyl alcohol — ethyl acetate

(2) $CO.Cl_2 + 2\ C_2H_5OH = (C_2H_5)_2CO_3 + 2HCl$
phosgene — ethyl carbonate

Usually the acid chlorides are prepared by the interaction of an acid with phosphorus pentachloride, thus

$CH_3COOH + PCl_5 = CH_3COCl + POCl_3 + HCl$
acetic acid — acetyl chloride

Phosphorus trichloride, a gas, may however be more conveniently used in place of the solid pentachloride for this purpose. Alternatively, acid chlorides are frequently prepared from the parent acid and thionyl chloride $SOCl_2$, the latter being structurally analogous to phosgene in the formula $O = S\begin{smallmatrix}Cl\\Cl\end{smallmatrix}$. Thionyl chloride is of course itself the acid chloride of sulphurous acid $O = S\begin{smallmatrix}OH\\OH\end{smallmatrix}$, more familiarly written H_2SO_3. The preparation of acid chlorides by the use of thionyl chloride is exemplified in the following reaction:

$$CH_3COOH + SOCl_2 = CH_3COCl + SO_2 + HCl$$

The above reaction is a particularly useful one in that the bye-products are both gaseous and can be driven off to leave the pure acid chloride behind.

As would be expected, phosgene can take the place of thionyl chloride in the above reaction, thus:

$$CH_3COOH + COCl_2 = CH_3COCl + CO_2 + HCl.$$

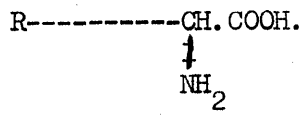
Indeed, acetyl chloride, used for the manufacture of aspirin, has been prepared commercially by means of this reaction involving the use of phosgene (9). It should be particularly noted that in this method of preparing the highly reactive acid chloride a free acid and an acid anhydride are evolved in the process.

By means of any of the above reactions, including the one where phosgene is used, the acid chlorides of amino-acids can also be formed at ordinary temperatures. In the case of amino-acids, however, the amino group also takes part in the reaction and the hydrochloride of the amino-acid chloride is actually produced, instead of the amino-acid chloride itself (57). The reaction may be regarded as taking place in two stages:-

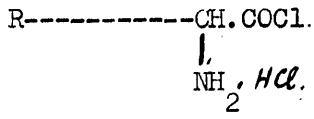
(i) the formation of an amino-acid chloride with the evolution of hydrochloric acid, and

(ii) the attachment of the hydrochloric acid so formed to the free amino group to produce the hydrochloride of the amino-acid chloride.

This type of compound in relation to the parent amino-acid is shown below:

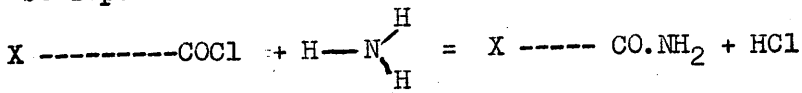


Amino acid



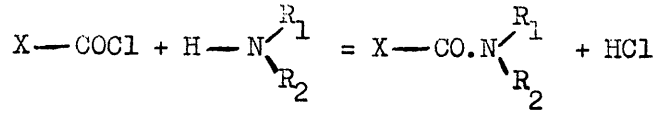
Hydrochloride of amino-acid chloride

Furthermore, like any other acid halide, phosgene reacts with ammonia (or a substituted ammonia) to form an acid amide (or substituted acid amide). The general reaction between an acid chloride and ammonia may be represented thus:

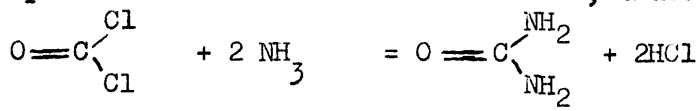


acid chloride ammonia acid amide

With a substituted ammonia the reaction would be:

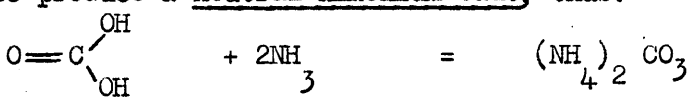


In common with the other acid chlorides phosgene reacts thus with ammonia to form the acid amide. Both chlorine radicles are replaced, and the compound so formed is carbamide or urea, thus:-



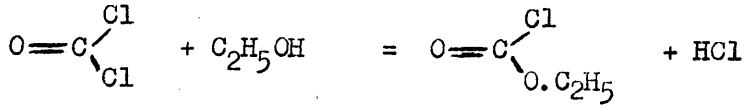
acid chloride (phosgene) ammonia urea

It should be particularly noted that <u>acid halides</u> (which include acid chlorides) reacting with ammonia or a substituted ammonia, form an entirely new group of compounds - the <u>acid amides</u> - with the evolution of <u>free hydrochloric acid</u>, as exemplified above; the <u>parent acid</u>, on the other hand, reacts with ammonia or a substituted ammonia simply by adding it on - to produce a <u>neutral ammonium salt</u>, thus:



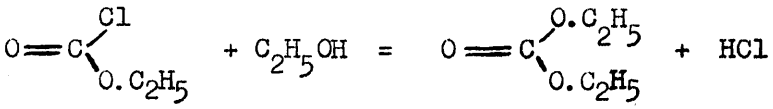
parent acid (carbonic) neutral ammonium salt (ammonium carbonate)

As previously mentioned, acid chlorides react with alcohols or phenolic hydroxyl groups to form esters. Phosgene gives this reaction, but being a dichloride gives the reaction in two stages, first forming ethyl chloroformate - the half ester, half acid chloride, thus:-

1st stage: 

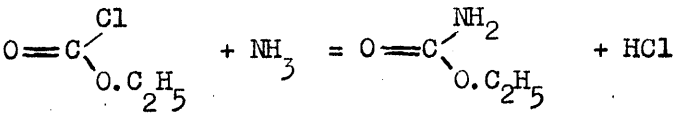
ethyl alcohol — ethyl chloroformate

and under more drastic conditions then proceeds to form the complete ester, namely, diethyl carbonate.

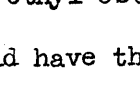
2nd stage: 

diethyl carbonate

The second stage of the above reaction can, however, be replaced by the reaction with ammonia, as previously described, to form ethyl carbamate - the half ester, half acid amide - thus:

(2nd stage) 

ethyl carbamate (urethane)

Ethyl carbamate is the ethyl ester of a hypothetical carbamic acid which, if it were stable, would have the formula  but it is not known to exist in the free state. The <u>salts</u> of this acid are, however, well known under the name of carbamates and its esters are generically known as the <u>urethanes</u>, the ethyl ester being the common urethane of the Pharmacopoeia.

The important points to be noted from the foregoing discussion on the chemical reactions of phosgene are, firstly, that it is an extremely reactive substance, and secondly, that in all its reactions free hydrochloric acid and sometimes also the acid anhydride , carbon dioxide, are liberated. Thus phosgene not only reacts with and neutralises basic substances but actually evolves acid compounds in so doing.

Chemical Reactions of Phosgene in the Blood

It has previously been shown that once phosgene vapour has reached the alveoli little or no further hydrolysis can take place and that it must therefore behave as a component of the alveolar gases, crossing with them into the blood. Some of it may undergo hydrolysis, and some may react immediately with certain chemical constituents of the blood, while the third, and probably very considerable part, may remain unchanged for a time, dissolved in the lipoids of the body fluids, from which it will gradually diffuse and react with the basic substances of the blood. The principal basic substances are, of course, the sodium bicarbonate and the amphoteric amino-acids. From a knowledge of the chemical properties and activity of phosgene already described, the various reactions theoretically possible between it and the principal blood bases include the following:-

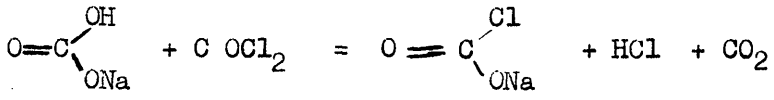
A. Reactions with Bicarbonate Base

1) Some of the phosgene is hydrolyzed by the body fluids to hydrochloric acid and carbon dioxide; the hydrochloric acid then reacts with bicarbonate to form sodium chloride and more carbon dioxide, thus

$$2NaHCO_3 + COCl_2 + H_2O \rightarrow 2NaHCO_3 + 2HCl + CO_2 \rightarrow 2NaCl + 2H_2O + 3CO_2$$

One molecule of phosgene has thus neutralised two molecules of bicarbonate base, and in addition has produced three molecules of the anhydride of the dibasic carbonic acid.

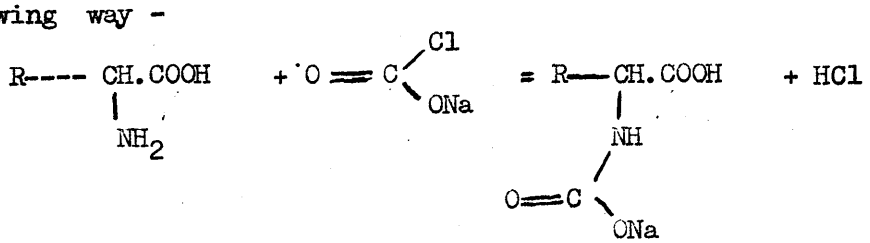
2) The phosgene may react directly with the bicarbonate to produce sodium chloroformate.



bicarbonate chloroformate

In this reaction one molecule of phosgene has neutralised one molecule of bicarbonate base and in addition has produced one molecule of the monobasic hydrochloric acid and one molecule of the acid anhydride of the dibasic carbonic acid. The free hydrochloric acid will then neutralise a further amount of bicarbonate with the evolution of carbon dioxide or may react with and neutralise the basic amino radicle of the amphoteric amino-acids.

3) Sodium chloroformate as formed in the previous reaction may then react with amino groups, the chlorine radicle of the chloroformate combining with a hydrogen atom of the amino radicle. The amino groups are those of the amino-acids. This type of reaction would take place in the following way -

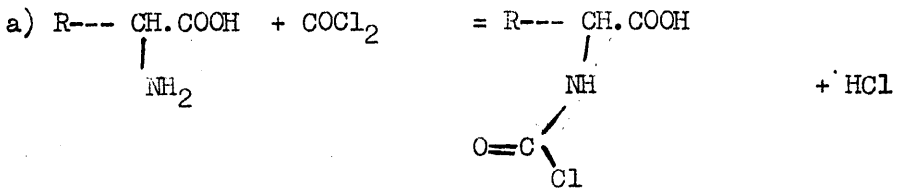


amino-acid chloroformate

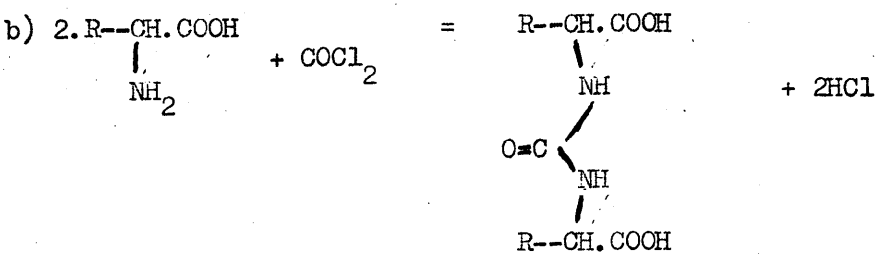
It will be noticed that the side chain of the amino-acid has in effect become a carbamate and such types of compounds may well exhibit the urethane effect of increasing capillary dilatation and permeability. Furthermore, this type of reaction has neutralised the alkaline amino radicle of the amino-acid, leaving it with a free carboxylic acid group and has also produced a further molecule of hydrochloric acid. Both these acids are then free for the further neutralising of available base.

B. Direct Reactions with Amino-acids

1) Phosgene may combine directly with amino-acids in two ways, one molecule of phosgene reacting with either one or two molecules of amino-acid, thus:

a) 

Almost certainly, however, such a reaction would proceed a stage further, for the chlorine radicle of the compound formed is available for reacting with more base - amino groups for preference, thus:

b) 

Complex symmetrical urea derivative.

By reacting with two amino-acids not of the same composition the resulting compound would, of course, be an unsymmetrical urea derivative.
Of all the reactions described under the headings A and B above, those involving combination with free amino groups will probably take place preferentially to those reactions between phosgene and water or inorganic base. The hydrochloric acid formed in these reactions, however, will probably react preferentially with inorganic base.

3) It is also theoretically possible that phosgene may combine directly with a single amino-acid to form the hydrochloride of the amino-acid chloride, as previously described in the general chemistry of acid-chlorides, thus:-

$$R - \underset{\underset{NH_2}{|}}{CH.COOH} + COCl_2 = R - \underset{\underset{NH_2HCl}{|}}{CH.COCl} + CO_2$$

In such a reaction the amino acid not only loses its amphoteric basic properties, but it becomes a free acid chloride capable of further reaction with basic substances and at the same time the acid anhydride of carbonic acid is also formed.

The reactions between phosgene and the basic substances of the blood as described above are not intended to be exhaustive nor to represent precisely the chemical changes that take place. Rather are they intended to typify the sort of reactions that one can expect or predict. Of all the types described, those occurring under heading B.1, and especially

the completed form under heading B.1b, would be by far the commonest, the most easily produced and certainly the most interesting. Chemical changes of this type resulting in the formation of complex urea derivatives are not unknown in medicine. Indeed, they are used in the preparation of symmetrical urea derivatives such as Suramin B.P.(11) and S.U.P.36 and similar drugs (58). Unsymmetrical urea derivatives formed by the same type of reaction are represented by urethane B.P.(59) and by alpha-naphthyl thiourea, both these drugs being known to cause marked capillary permeability leading to the escape of plasma into the tissues, and the latter as having a specific effect upon the vessels of the lung leading to the development of a gross and even fatal pulmonary oedema (53, 54).

At any rate, whatever be the exact nature of the chemical reactions produced by phosgene in the body, the following very important general conclusions may be drawn:-

1. Whether by hydrolysis <u>in the blood stream</u> or by direct chemical combination with basic substances in the body, hydrochloric acid is formed and sometimes also the acid anhydride CO_2.
2. The acids so formed are free to react with further available base.
3. By reacting with the amino radicle of the amphoteric amino-acids their basic properties are destroyed and they become free organic acids adding farther to the "acidity" of the blood.
4. <u>One</u> molecule of phosgene may react to produce <u>several</u> molecules of acid, i.e., liberate several acid radicles which absorb farther amounts of base for their neutralisation.
5. Some of the compounds formed are themselves acid chlorides and will react farther, with neutralisation of additional base. Moreover, the

acid chlorides, including phosgene, are all irritants capable of causing vasodilatation and increased capillary permeability by their local action on blood vessels, as can be appreciated from direct observation of their behaviour as lachrymators and eye irritants.

6. Other compounds formed may be of the urethane type. Urethane itself has been used in experimental physiology for the production of lung oedema, and other compounds of the same type may well have similar properties.

7. In virtue of its powers of linking amino-acids together very complex bodies may be formed by the action of phosgene in the blood. Complex urea derivatives chemically analogous to alpha naphthyl thiourea and possibly having the same specific properties of producing pulmonary oedema may be formed. Likewise, complex linkages between amino-acids will result in the formation of compounds in the nature of peptides and peptones, and such compounds are well known to produce increased capillary permeability and oedema. (Consider allergic and "shock therapy" reactions that may be produced by peptones).

8. No matter in what way phosgene may react with the constituents of the blood it will always result in a very profound disturbance of the acid/base equilibrium. This disturbance will produce many physiological reactions, especially on the acid sensitive respiratory and vaso-motor centres. There is also a very great deal of evidence to show that such disturbances result directly in the formation of pulmonary oedema.

Reaction of Phosgene on Blood Pigments

While there is no clinical evidence that the blood pigments are in any way altered in cases of phosgene poisoning, it has been claimed that the gas does, in fact, modify the blood pigment in some degree. Thus Meyer (60) states that part of the circulating haemoglobin is disrupted to form haematin. He identified this substance spectroscopically in the blood of 56 patients examined during the Hamburg disaster of 1928, and quotes the works of several other German authors who had previously detected the pigment in cases of phosgene gassing during the 1914 war.

Haematin (acid haematin) is formed according to Whitby and Britton (61) by the action of dilute hydrochloric acid on haemoglobin. The presence of this pigment in the circulation in cases of phosgene gassing therefore adds further proof that phosgene must reach the blood stream and give rise to the formation of hydrochloric acid and other chlorine compounds therein.

3. BLOOD PRESSURE ALTERATIONS

Among the cases of phosgene gassing described in this thesis one of the most constant and notable clinical features is the alteration that takes place in the level of the blood pressure. This alteration is particularly marked and of greater significance among the severely affected cases. Before proceeding to discuss these matters, however, it would be profitable to review briefly the mechanisms for normal vasomotor and blood pressure control. The following account is based upon that of Samson Wright in his textbook of Applied Physiology (62).

Regulation of Normal Blood Pressure

Blood pressure varies directly as the product of cardiac output and peripheral resistance: increase in either of them produces a rise in tension, and decrease produces a fall. The mechanisms are mainly chemical, but nerve reflexes also play their part. Of the two factors, it may be stated here, in parenthesis, that alterations in peripheral resistance are of greater importance for producing blood pressure changes in phosgene gassing, and it is to peripheral factors that greater attention must therefore be paid.

The principal nerve centre for the control of blood pressure lies in the vaso-motor area of the medulla. Stimulation of this centre is effected normally by any rise in the carbon dioxide (CO_2) tension or hydrogen ion (H^+ ion) concentration of the blood. This stimulus is then transmitted to the peripheral arterioles, via the vaso-motor nerves, and produces arteriolar constriction. Such constriction of vessels increases peripheral resistance and the blood pressure consequently rises. A similar effect of increasing peripheral resistance is also produced indirectly from the action of increased CO_2 tension, or acid ion concentration, of the blood upon the chemo-receptors of the carotid and aortic bodies. From these chemo-receptors the stimulus is relayed along the sino-aortic nerves to the vaso-motor centre in the medulla, and thence transmitted to the periphery as before. It is probable, however, that this effect is ordinarily of less importance than the direct one.

In addition to the central effect it is important to note that an increase in the CO_2 tension of the blood exerts a direct action upon the

walls of the arterioles themselves. This peripheral action of CO_2 is antagonistic to the central one. It tends to produce vasodilatation from relaxation of the muscle coat of the arterioles, and the effect may be very obvious in the skin and mucous membranes. The peripheral action of carbon dioxide has been well shown by perfusion experiments in animals, and its effect can also be demonstrated in the human subject who is made to breathe in and out of a closed bag, thereby gradually raising the CO_2 tension in his alveolar air and blood. After a short while generalised flushing takes place and the vessels of the skin become thus obviously dilated. Because of this vasodilatation and the accompanying decrease in peripheral resistance, the blood pressure should tend to fall, though in man the central and peripheral effects of CO_2 may neutralise one another to a considerable extent. In any case, according to Wright, excess of carbon dioxide only raises the blood pressure after a latent period, during which it has gradually been accumulating until its tension in the blood has become very high. Thus, retention of carbon dioxide or acid ions may first cause vasodilatation, fall in blood pressure and flushing of the skin, but farther increase always produces vasoconstriction, elevated blood pressure and intense pallor.

Considering next the part played by oxygen (O_2), excess of this substance has no effect upon the vaso-motor centre. On the other hand, a severe decrease in the oxygen tension of the blood sensitizes the vaso-motor centre to the action of CO_2 or H^+ions, though prolongation of anoxia for any length of time depresses the heart muscle and thus causes a profound fall in blood pressure. The lesser degrees of anoxia are, however, accompanied by changes in the respiration and heart rates and

in the blood pressure, these changes being most frequently, according to Schneider (63) an increase in respiratory and pulse rates and an elevation in blood pressure. In the asphyxia of throttling, for example, there is retention of CO_2 combined with increasing anoxia. For a time the blood pressure rises to great heights, for the vasomotor centre, like the respiratory centre, is stimulated by the increasing venous character of the blood (64); finally there is a profound fall in blood pressure as the heart fails and death supervenes from deprivation of the cardiac muscle. In contrast, pure anoxia, as from the respiration of an inert gas, causes rapid and increasing fall in blood pressure and death, the blood vessels remaining tonically constricted throughout. In these circumstances no CO_2 retention accompanies the anoxia; indeed, carbon dioxide saturation falls far below normal as that substance is freely washed away during respiration of the inert atmosphere. That anoxia has caused death from deprivation of the cardiac muscle and not from failure of the vasomotor centre is shown by the persistence of vasoconstriction even post mortem. Oxygen lack may, then, sensitise the vasomotor centre to the action of CO_2 and acid ions, but does not produce a direct stimulation of it.

BLOOD PRESSURE CHANGES IN PHOSGENE POISONING

Among the seriously affected cases described in a previous section of this paper, a rise in blood pressure was found to be a constant feature, and, as a rule, it was of very considerable degree. It must be emphasised, however, that the blood pressure recordings ~~we have~~ I made were all taken while the patient was having continuous inhalations of oxygen. This form of treatment was adopted in an attempt to keep at normal level the oxygen

tension of the patients' blood. If these inhalations produced excessive oxygenation the increased O_2 tension would, of course, have no effect whatsoever upon the level of blood pressure, as stated above. On the other hand, if in spite of the continuous administration of oxygen some degree of anoxia persisted (and this we believe to have happened) the result would have been to sensitize the vasomotor centre to other factors causing the rise in blood pressure, or in more extreme cases to have caused a serious fall in blood pressure owing to deprivation of the heart muscle.

That the administration of an excess of oxygen causes no alteration whatsoever in the blood pressure of normal human subjects has been adequately confirmed by the work of Benedict and Higgins (65) and again very recently by Comroe and his co-workers (66). Both these publications, however, draw attention to the fact that it does produce a remarkable slowing of the pulse. This effect was seen in several of the mild cases of phosgene gassing previously described and more particularly towards the end of treatment when recovery was more or less complete, with return to normality. In one particular instance (case M.4,, C.H.) the pulse rate fell as low as 50 beats per minute.

Anoxia if at all severe or prolonged leads, as we have seen, to a serious fall in blood pressure. Therefore, even if a considerable degree of anoxia were actually present in the cases that have been already described, there must have been some other factors present and capable of far outweighing any tendency to hypotension from this cause ~~in order~~ if one is to account for the great rise in blood pressure actually observed.

These preliminary remarks are made for the purpose of showing that the recorded elevations in blood pressure cannot be attributed to the fact that oxygen was being administered at the time when these determinations were made, and this irrespective of whether or not the method of administration of oxygen was efficient and whether some degree of anoxia co-existed or not. It remains now to consider in some detail the other factors which must be responsible for the alterations in blood pressure as actually observed. This can most readily be done under the two clinical headings used for the description of the cases themselves.

Mildly Affected Cases

In the mildly affected cases there was little exposure to phosgene vapour and therefore little of the gas entering the bloodstream to exert there an acidifying effect. Compensatory mechanisms by way of chemical buffering and an increase of pulmonary ventilation to wash out excess of carbon dioxide soon offsets the action of the phosgene on these patients. Until such times, however, as the compensatory mechanisms become established, carbon dioxide and acid ions liberated by the interaction of inspired phosgene and the basic substances of the blood are temporarily free to exert an effect. At first such an effect will normally be a peripheral one, producing dilatation of capillaries and arterioles. Flushing of the skin and a fall in blood pressure due to the decreased peripheral resistance tend automatically to follow. Only at a later stage with further increase of acid formation would the central effect predominate and the blood pressure rise, but owing to the slighter degree of exposure, this later stage is never reached and the case remains mild throughout. Smoothly and efficiently the respiratory centre responds by

increasing ventilation (for this centre is even more readily stimulated by the same elements as act upon the vaso-motor one) and very soon the acid/base equilibrium of the blood is restored to normal. The capillaries and arterioles regain their normal tone and the blood pressure resumes its former level.

In some instances, however, the fall in blood pressure that might have been anticipated from the obvious state of generalised vaso-dilatation of the cutaneous vessels at least, has not in fact appeared, or has even been replaced by a slight rise. This may reasonably be attributed to the natural fears of the patient, who knows that he has been gassed by a highly dangerous vapour. The emotional response of the heart is to accelerate and increase its output which may counterbalance, or more than counterbalance, the fall in peripheral resistance, and as the blood pressure is proportional to the product of cardiac output and peripheral resistance it will find its level accordingly. The possibility that a certain amount of vaso-constriction of the internal organs such as the kidney may contribute to a compensating or overcompensating rise in blood pressure cannot, of course, be excluded from the evidence available. It is, however, probably true to say that it is the emotional alteration of the heart's rate and output that contributes most to the effect observed.

Severely Affected Cases

In severe cases the greater amounts of phosgene inhaled permits the upset of acid/base equilibrium in the blood to develop to a much greater extent and to outstrip, for a time at least, the compensatory mechanisms that the body so quickly attempts to establish. Not only may there be an

overwhelming amount of liberated acid substances for the body to deal with, but, with the onset of pulmonary oedema gaseous exchanges in the lung may be so impaired as to render impossible the ready and full oxygenation of the blood. Remembering that pulmonary oedema has to be present in a very marked degree before it is clinically detectable one can appreciate that lesser amounts will exist for a long time before its presence can be determined with certainty. Yet even the minor degrees of exudation into the alveoli, if at all general, must exert a considerable effect in impeding the passage of oxygen across the alveolar membrane. Such anoxia as may be thus produced will not only enhance the sensitivity of the vaso-motor centre to its chemical stimulants and thereby add to the increasing spasm of the arterioles and consequent rise in blood pressure, but will also delay the oxidation or destruction of metabolites and acid or toxic phosgene derivatives already present or being formed in the body. In this way the abnormal conditions tend to become very prolonged and persistent.

As the formation of pulmonary oedema progresses in these severer phosgene casualties the carbon dioxide tension in the blood is diminished (50) and indeed falls far below normal unless death is imminent (51), while according to Cordier (67) the hydrogen ion concentration gradually increases. This decrease in the CO_2 tension has been well explained by Haldane (68) who drew attention to the fact that carbon dioxide is about 25 times more soluble in water when compared against oxygen. In a lung flooded with oedema fluid carbon dioxide may thus readily diffuse out of the circulation although oxygen cannot at all readily pass in. The less soluble and non-volatile acid substances derived from the chemical

combination of phosgene with the constituents of the blood will however persist, since they cannot readily diffuse out, and will continue to exert their effects upon the respiratory and vaso-motor centres.

Another factor adding to the state of anoxia and its sensitization of the vaso-motor centre is the effect produced by irritation of the bronchioles by the phosgene vapour, or more likely, by the products of the hydrolysis that it undergoes in these normally moist respiratory tubes. Bronchiolar spasm and obstruction of the smaller tubules by mucoid secretion cuts off from their normal air supply the alveoli with which they are connected. In this way, even alveoli that are not yet directly affected by an accumulation of oedema fluid may be virtually functionless, and comparatively large areas of relatively undamaged lung tissue may thus be functionally cut off.

In severely affected cases the peripheral action of increased CO_2 tension or H^+ion concentration in causing a degree of hypotension and a generalised flushing may be present in the early stages. As the latent period elapses and the acid substances accumulate this gives way to increasing hypertension with generalised pallor and arteriolar constriction. In some cases, especially where exposure has been particularly severe, these early hypotensive phenomena may be entirely absent, or in other instances may be completely masked by the emotional disturbances commonly and naturally associated with this type of accident.

4. CYANOSIS, ANOXIA AND DYSPNOEA

Cyanosis, anoxia and dyspnoea are three prominent features of phosgene poisoning. While it may be true to say that anoxia is the fundamental symptom and, in some degree at least, responsible for the development of both cyanosis and dyspnoea, the three symptoms are sufficiently interdependent as to make it difficult to discuss fully any one of them without some reference to the others. Nevertheless, an attempt will be made to describe them under separate headings and to elucidate their mode of production, in order to show that they are due to the same type of mechanisms as are responsible for the other main symptoms of phosgene gassing already discussed.

Cyanosis

In the severe and more advanced and consequently more typical cases of phosgene poisoning the patient's skin becomes discoloured by a leaden grey cyanosis as the illness approaches its height. The integument over the entire body is affected in some degree, though the intensity varies from part to part. Generally speaking, the patient's colour gives the impression of greyness which on closer examination is found to be due to an intense pallor on a bluish background. The skin is cold and clammy to touch, the clamminess being replaced at times by visible beads and pools of unevaporated perspiration that has accumulated upon a cold and bloodless skin. At those parts of the body which normally exhibit some degree of redness, such as the lips, the ears and finger tips, the cyanotic blueness is deeper, as a rule, though still accompanied by an element of pallor. Further consideration of the causes behind these components and accompaniments of cyanosis shows that they are but confirmatory symptoms

and signs of those conditions which we already know phosgene produces in the other systems of the body.

The blood coloration of the normal skin is due mainly to the blood in the network of capillary venules in the sub-papillary layers of the dermis. Pallor is produced by a diminution in the amount of haemoglobin held within these vessels, either because of a deficiency in the quantity of the pigment itself or because of a diminution in the calibre of the individual vessels. Cyanosis, or blueness, on the other hand, is due to the presence of abnormal amounts of reduced (i.e. unoxygenated) haemoglobin, of any type and from various causes, within the lumen of these minute vessels of the skin.

The typical greyness of the phosgene casualty is made up, as we have seen, in part by pallor and partly of blue cyanosis. In other words, the blueness of the cyanosis is due to alteration in the circulating haemoglobin and is modified by the state of the vessels that contain it.

Considering first the contractile state of the vessels, it will be recalled that both the capillaries and arterioles in the integument have powers of contraction and dilatation and that either type of vessel may react independently of the other. Furthermore, the arterioles regulate the rate of entry of blood into the skin and the rate of blood flow through the skin, while the capillaries control the amount of blood within the skin. When the rate of blood flow through the skin is brisk the part will be warm; with slowing of the rate the skin becomes cold. The temperature of the skin is thus an index of the state of contraction or dilatation of the arterioles supplying it. Thus the coldness of the skin in phosgene gassing is but another indication of the arteriolar

constriction which we already know to exist in the splanchnic vessels and which account for the increased peripheral resistance and raised blood pressure.

So far as the capillaries are concerned the matter is a little more complex. Two factors must be taken into account, the amount of blood entering the vessels and the state of the walls of the vessels themselves. Capillary constriction, which in its extreme form is tantamount to a physiological and temporary occlusion of the vessels, causes less blood to be actually held within the skin, and what there is to be very thinly spread, as it were, over the whole skin area under consideration. The result will be pallor and this will be most intense if at the same time arteriolar constriction diminishes the amount of blood entering the capillary bed.

Following from the diminished amount of blood entering the skin because of arteriolar constriction the integument will gradually become cooler, for less heat is being brought to it. This cooling produces in turn a varying degree of cyanosis which will, of course, be combined with the pallor due to the constricted state of the vessels. In his monograph upon the blood vessels of the skin Sir Thomas Lewis (69) shows that the blood tends to be deficient in meeting the full needs of the skin whenever the skin temperature comes to lie within the critical range between 15° and 20°C, and that the haemoglobin is then more completely stripped of its oxygen (as estimated by the O_2 tension of the venous blood leaving the part), with the result that cyanosis (blueness) develops. At this critical range of temperature the capillaries become contracted, an

observation confirmed by Carrier (70), who observed the phenomenon directly by means of a microscope while the skin was being gradually cooled. He reported that when a temperature of 20°C was reached, "The (blood) stream became granular, the capillaries contracted and there was "soon a very slow stream in only a few capillaries and stasis in the "remaining vessels. The arterioles had disappeared."

It is interesting to note that the critical range of temperature involved in this phenomenon (15°-20°C = 59°-68°F) is the average room temperature to which the skin would tend to fall once the amount of blood and warmth reaching it had been reduced by arteriolar constriction.

Having thus accounted for the element of pallor which is such a marked feature of phosgene poisoning it is now necessary to add a little about the blueness which accompanies it.

The term cyanosis indicates no more than a blue coloration of the skin due to the chemical state of the haemoglobin circulating therein. The commonest type of cyanosis, and the one with which we are primarily concerned in cases of phosgene poisoning, is the type due to the presence within the vessels of an abnormal amount of haemoglobin in the reduced state. According to Lundsgard and Van Slyke (71), cyanosis of this type appears when the amount of haemoglobin in the superficial capillaries is more than 5 Gms. of unsaturated haemoglobin per 100 c.c. of blood. It therefore follows that cyanosis indicates anoxaemia, or rather anoxia, since all the tissues become involved. The absence of cyanosis does not, of course, preclude the presence of anoxia, for this may exist, though not to the critical degree necessary for the production of cyanosis.

This is important in that the indications for the relief of anoxia, as by oxygen therapy, may be present even before cyanosis develops. However, apart from the comparatively unusual histotoxic type of anoxia and some forms of anaemic anoxia, neither of which produce cyanosis, the presence of this sign indicates a state of anoxia well advanced in degree though it gives no clue, of course, as to the precise cause of the oxygen deficiency.

In phosgene poisoning the types of anoxia responsible for the production of cyanosis are the anoxic and stagnant varieties. Not only is the blood insufficiently oxygenated in the lungs on account of the pulmonary oedema that is present (anoxic anoxia), but its stagnation within the constricted capillaries allows it to be more completely stripped of its oxygen content, thereby enhancing further the degree of oxygen unsaturation of the haemoglobin present in the vessels (stagnant anoxia).

Other modifications of the haemoglobin, apart from the presence of the de-oxygenated pigment, can of course produce cyanosis. Thus methaemoglobinaemia and sulphaemoglobinaemia can cause it. Whether or not there is any chemically modified pigment that contributes to the cyanosis of phosgene poisoning has not been determined in this present investigation. It is unlikely, however, that abnormal derivatives of haemoglobin contribute much to the colouration of the skin in these cases, for the amounts of the abnormal pigment haematin found by Meyer (60) and the other German workers in a number of cases of phosgene gassing was extremely small, and could have but little influence on the clinical appearances of the grey and cyanotic skin.

Anoxia

A certain amount has already been written on the subject of anoxia in previous sections, and it remains only to sum up those features previously mentioned, and to add one or two relevant details.

Physiologists customarily divide anoxia into four types, stagnant, anoxic, anaemic and histotoxic, and these provide convenient headings under which the subject may be discussed.

Histotoxic anoxia is a comparatively rare type and is due to blocking of the enzyme systems of the tissues so that they cannot use the oxygen transported to them normally in the blood. An example of this type of anoxia is to be found in cyanide poisoning, where death is due to deprivation of the vital tissues, although the blood remains fully saturated with oxygen even to the end. Nothing is known of the possible occurrence of this type of anoxia in phosgene poisoning, nor is there anything to suggest that it is one of the factors producing anoxia in this condition.

Anaemic anoxia is due to a reduction in the carrying capacity of the blood as after severe haemorrhage or in conditions such as carboxy-haemoglobinaemia where part of the blood pigment is fixed in an irreversible or almost irreversible chemical combination and not available for the transport of oxygen. Although haemoconcentration occurs in phosgene poisoning (as seen in cases S.1, S.2), and has been reported by various authors (72, 73, 23), there is no actual blood loss. The alteration of haemoglobin by disruption of the molecule, as previously reported (60), is of slight degree, even if it occurs in all cases affected by the gas, and can play but little part in the production of

anoxia. It is therefore apparent that the stagnant and anoxic factors, discussed to some extent in previous sections, account for the severe anoxia found in the more serious cases. The mechanisms by which their effects are produced are briefly as follows.

Anoxic anoxia is due to reduced partial pressure of oxygen in the arterial blood brought about by altered conditions in the lungs preventing the blood from being adequately oxygenated in its passage through them. In the earlier stages of phosgene gassing, before pulmonary oedema has become clinically detectable, there is probably some degree of swelling of the alveolar walls due to interstitial oedema, or there may be some degree of fibrinous exudate present, either of which will greatly reduce the permeability of the alveolar epithelium and make gaseous interchanges more difficult and incomplete. Later, when the alveolar spaces themselves become flooded with oedema fluid there can be very little oxygen present in the affected alveoli, and that will only be in solution. Deoxygenated blood reaching such alveoli from the periphery must continue on its way through the alveolar capillaries and back to the general circulation without having added to its oxygen content by passage through the lungs. Thus the blood leaving the lungs will be a mixture of oxygenated and unoxygenated blood, the exact proportions depending upon the amount of functionally useless and waterlogged alveolar tissue in relation to the amount still capable of carrying on respiratory changes more or less normally. Collapsed areas of lung tissue add farther to the embarrassment, as reported by McGibbon (25), whose experimental gassing of goats showed that the smaller bronchioles become blocked by thick tenacious mucus which prevents further entry of oxygen into the

alveoli that they supply. In due course the air dammed back behind the mucous obstruction will be gradually absorbed from the alveoli, leaving them more or less empty and collapsed and useless. The mode of breathing also contributes to the production of anoxia as well as being caused by it. Shallow and rapid breathing interferes with full oxygenation in the lungs but at the same time allows carbon dioxide to be washed out. Since this type of abnormal breathing is produced by anoxia, the anoxic process tends to move in a vicious circle, confirming from another aspect Drinker's dictum (32) that "anoxia begets anoxia." The subject of abnormal breathing in relation to phosgene poisoning will, however, be discussed more fully under the next heading.

Stagnant anoxia occurs wherever the circulation is defective from cardiac failure or from peripheral causes. Either of these may cause the blood to circulate more slowly in the tissues so that there is more time available for the excessive stripping of oxygen from the haemoglobin. This leads to an increased venosity of the blood for the greater part of its journey through the tissues, and in cases of pulmonary oedema, to the arrival in the lungs of a highly de-oxygenated blood, and this at a time when conditions there would in any case be quite inadequate to secure even normal re-oxygenation of blood much less seriously deficient in oxygen content.

The various factors leading to excessive stripping of oxygen from the haemoglobin in the tissues have already been discussed in some detail when dealing with the subject of cyanosis.

Peripheral Role of CO_2 in Anoxia

So far as the peripheral effect of carbon dioxide in relation to anoxia is concerned, the position is far from clear. As we know, the CO_2 tension in the blood of phosgene casualties with pulmonary oedema is abnormally low. Evidence is increasing that CO_2 does more than play a physiological role in the adjustment of acid/base equilibrium. Thus not only is it known that oxyhaemoglobin gives up its oxygen more readily in the presence of CO_2 (74), but it has also been shown by Evans (75) that carbon dioxide is utilised by animal tissues and that it may, in some manner as yet dimly understood, regulate the rate at which physiological oxidations are carried out in the tissues. The diminution in the amount of carbon dioxide in the blood, whether due to displacement by other acids as in phosgene poisoning or to deficiency from other causes, may thus add to the anoxic state by depriving the tissues of a substance essential for their normal efficiency in using such oxygen as may be available to them.

Dyspnoea

The abnormality of breathing observed in all the presently recorded cases of severe phosgene poisoning was an increase in the respiratory rate and a decrease in the depth of respiration. This shallow and rapid type of respiration is described by all writers recording cases of phosgene gassing and whose works have been consulted in the preparation of this paper. The mechanism involved in the production of this form of dyspnoea is not a simple one and many factors play a part, each adding

its quota to the final result, each modifying or enhancing the part played by the others.

The principal factors causing dyspnoea may be divided into two groups - the central factors, mainly chemical, acting on the respiratory centre and possibly also on accessory centres in the carotid and aortic bodies, and peripheral factors, mainly physical, acting on the lung tissues and their nerve endings. As is well known, emotional activities also play a part in producing dyspnoea, or in enhancing it, and their effect is mainly in the direction of inducing shallow, rapid breathing, as in hysteria and such normal emotional reactions as anger and fear. These psychological components will not, however, be discussed farther in the present paper for their effect is so difficult to assess and apportion in such a general discussion of cases. It is sufficient for our purpose that the existence of these psychological factors be recognised, and it may be reasonably assumed that they always exert some effect, for fear and emotional upset are invariable accompaniments of accidental exposure to a toxic gas.

In his excellent review of the subject Christie (48) points out that uncomplicated anoxaemia does not cause dyspnoea, with the important corollary that dyspnoeic symptoms cannot be regarded as an essential feature of the indications for the need of oxygen therapy. Of course, anoxaemia may play a contributory part in the production of dyspnoea, for oxygen lack in its lesser degrees sensitises the respiratory centre to the stimulating action of CO_2 and acid substances. The severer forms, however, act as depressants and lead eventually to its paralysis. Thus in the present series of cases, though anoxia was undoubtedly present,

it must have been manifest in its lesser degrees, probably because oxygen therapy was started at the onset of the illness and continued for long periods, in the hope that it would avert, as it apparently did, the severer and depressing degrees of anoxia. In other ways, too, it is possible for anoxia to lead indirectly to stimulation of the respiratory centre with production of dyspnoea. By direct action upon the chemo-receptors of the carotid and aortic bodies it is said that oxygen can produce a reflex excitation of the medullary centre, though Christie states that the evidence for this is scarcely conclusive. Oxygen lack, however, does certainly lead to incomplete oxidation and disposal of the acid products of tissue metabolism which accumulate and act upon the respiratory centre to cause alterations in breathing. Such an effect must undoubtedly be present in the case of phosgene poisoning with its accompanying variety of forms of anoxia, and ~~added to the~~ enhancing this increased ~~in the~~ accumulation of acid metabolites there is the factor of increased acid production due to the chemical reactions of the phosgene itself.

The subject of acidaemia is of considerable importance in relation to dyspnoea. Thus Fulton (76) remarks "when the alkali reserve of the body "is depleted either by the ingestion of acid or by the metabolic production "of acid, the respiratory centre becomes more sensitive to CO_2. Pulmonary "ventilation increases and the arterial CO_2 pressure is maintained at a level below normal." This compensatory mechanism is, of course, very efficient but like all compensatory mechanisms can be overloaded and break down. According to Banus and his co-workers (77), the pH of the arterial blood, under normal conditions, is held constant within 0.01 pH unit despite wide variations in the alkali reserve. The breakdown of the

compensating mechanism can be well seen in the case of diabetes mellitus where the pH may fall to 7.1. An increase in blood acidity of this order not only increases the sensitivity of the respiratory centre to such amounts of CO_2 as are present - for these authors belong to the school which holds that only CO_2 is the specific stimulant of the respiratory centre - but it also causes reflex excitation of the centre by stimulating the carotid and aortic chemo-receptors too. Whether one believes that the respiratory centre is specifically stimulated by CO_2 alone, though capable of being sensitized by an increase in hydrogen ion concentration (the stimulating effect of which reaches the respiratory centre only by way of the carotid and aortic chemo-receptors), or whether one holds that increased acidity and increased CO_2 tension are interchangeable stimulants, the nett result must be the same - namely, to produce an increase in respiration amounting in severer cases to actual dyspnoea. Such a train of events following from the increased production of acid seems inevitable in phosgene poisoning. Indeed, speaking of acidosis and dyspnoea Christie (48) states that "Only in Kussmaul's breathing of "diabetic acidosis, in the acid poisonings and in emphysema can dyspnoea be "truly ascribed to acidosis." And, of course, in this connexion phosgene gassing in its physiological effect is strictly equivalent to acid poisoning.

Of the peripheral mechanisms concerned with the production of dyspnoea in these cases, by far the most important is the rigidity and distension of the lungs exerting their effect through the Hering-Breuer reflex. It has long been known that distension of the lungs reflexly inhibits inspiration. This reflex acts by stretch and pressure stimuli

affecting the nerve endings in the pulmonary tissue, these stimuli being transmitted through the vagus nerve to the respiratory centre which then inhibits inspiration. This is the mechanism for the normal control of respiratory rhythm. When the lungs are inflated by the inspiratory act the "stretch receptors" prevent over-distension by discharging impulses that reflexly bring inspiration to an end. In this way the reflex controls respiratory depth. Because of the oedematous state of the lungs in phosgene poisoning, they are already subject to some degree of distension and rigidity on account of the fluid within them. The amount of respiratory inflation necessary to bring the inhibitory reflex into action is greatly reduced, and respiration becomes more shallow. Not only does the reflex thus control respiratory depth but it also exerts an effect upon the respiratory rate, so that, as well as becoming more shallow, the respirations are also more rapid. This effect is well described by Adrian (78) when he says: "The stretch receptors in the "lungs resemble those in muscle in their effect on the central nervous "system. Both influence it to cut short the movement that has stimulated "them, and by so doing prevent the inconvenience or damage that might "come from unrestrained motor activity. But the lungs must be adequately "ventilated, and if the range of movements is restricted the movements must "succeed one another at shorter intervals. Without the vagal mechanisms "the respiratory centre (in the conditions of these experiments) slowly "charges and discharges itself with little variation in rhythm. The "impulse from the stretch receptors quickens the rhythm by cutting short "the discharge, and so hastening the recharging process. They are "inhibitory but they seem to act mainly by raising the discharge

"threshold, not by preventing the accumulation of active material." Thus the inherent rhythmicity of the respiratory centre, which emits impulses at a constant and steady rate, is altered by the Hering-Breuer reflex in such a way that its rhythmic rate is increased, and respiration becomes more rapid in those conditions where the reflex is abnormally stimulated.

In cases of phosgene gassing the stimuli that give rise to this reflex probably rise in two ways, namely, as the result of congestion and of atelectasis. As previously mentioned, some of the lobules of the lung become collapsed due to blockage of the respiratory bronchioles by mucous plugs. The result is that the adjacent parts of the lung are "put on the stretch" and thereby a stimulus is supplied to bring the vagal inhibitory reflex into action. A second group of stimuli is provoked by the congested and oedematous state of the alveolar tissue. Here waterlogging of their walls, engorgement of vessels and distension of the alveolar spaces by oedema fluid all supply a stretch stimulus that will make the breathing more rapid and shallow.

The characteristic dyspnoea of phosgene poisoning is thus accounted for by chemical and physical mechanisms, the latter due to the state of affairs within the lungs themselves, the former due to the altered state of "acidity" in the circulating blood and throughout the tissues.

5. CHANGES IN BODY TEMPERATURE

One of the notable features of the cases described in the clinical part of this thesis is the change that takes place in the body temperatures. In every one of the severe cases the temperature was elevated during the

height of the illness. This rise in temperature was apparent even in the cases that made an uninterrupted recovery and where the pyrexia could not be considered as due to septic or inflammatory or pneumonic complications. The elevation of temperature may have been present for only a few hours, but the fact that it occurred at all requires a word or two of explanation. Not that the explanation would appear to be obscure or that the phenomenon would indeed be an unexpected one when the facts are considered. The point is worth stressing, however, in view of the fact that certain cases of undoubted phosgene poisoning have, to my certain knowledge, been wrongly diagnosed as "influenzal", and this solely because the body temperature was raised by one or two degrees. In other instances the development of even a slight pyrexia has been thought to indicate the onset of septic complications against which the sulphonamides were exhibited and credit given to the drug because the temperature returned to normal in the course of a few hours. Shaw (21) appears from his paper to be unaware that pyrexia is a normal feature of phosgene poisoning and even goes so far as to recommend the use of sulphonamides prophylactically in all cases of phosgene gassing.

While it is true that septic or inflammatory complications will produce the rise in temperature that would be expected in such conditions, the event occurs as a sequel rather than a complication of the original gassing so far as can be judged from the cases personally observed. The rise in temperature due to such sequelae is a secondary rise occurring some time after the initial pyrexia has returned to normal. In all the severe cases of the present series (save in one instance, Case S.4), the

temperature had returned to normal and had remained there for several hours before the patients passed from my care to that of their family doctor. Subsequently, some of these patients may have developed an acute bronchitis (or, for the sake of argument, they might in fact have developed even a bronchopneumonia, so far as is known) during which their temperature could have been very high indeed; but the fact remains that it was not a continuation of the initial pyrexia that is due directly to the effects of phosgene inhalation.

The solitary exception mentioned above is severe case No. S.4, patient F.B., who did not receive any form of treatment until 15 hours had elapsed after exposure. In this instance, the patient exhibited an elevated body temperature when first examined 15 hours after exposure, and he subsequently developed bronchopneumonia, necessitating his transfer to hospital, without his temperature having first returned to normal. This exception may, however, have been more apparent than real, and the pyrexia present when he was first examined may have been in fact a secondary rise due to commencing pneumonic complications. The exposure of this particular patient had not been so severe as in other instances where, at most, a mild bronchitis had ensued some time after the initial rise in temperature had fallen again to normal; the difference probably lies in the fact that the other more severely affected cases had commenced treatment, especially oxygen therapy, immediately after exposure. No doubt an oedematous condition of the lung is extremely favourable for the growth and multiplication of the pathogenic organisms normally present in the respiratory tract. If, however, by early and intensive treatment conditions can be rendered less favourable within

a comparatively short time, it may then be too late for these pathogens to become widely and firmly established. In such a case the result must be either that they never gain hold at all and the patient makes a complete and uninterrupted recovery, or that with the rapid development of a less favourable environment and the early recovery of at least part of the patient's powers of resistance, these organisms can establish themselves sufficiently to produce only the milder sequelae.

The primary rise in body temperature seen in the severer degrees of phosgene poisoning is due to interference with the normal loss of heat from the body. Excess of heat produced by the metabolic processes of the body is normally dispersed by radiation and convexion from the skin, and by vaporisation of water from the lungs, and from the skin, in the form of invisible perspiration. Where greatly excessive amounts of heat are to be dispersed the process of sweating comes into play. Dispersal of heat produced by strenuous exercise, for example, is promoted by all these means. The skin becomes flushed and warm, for arteriolar and capillary dilatation takes place, the amount of blood flow through the skin being greatly increased. Not only do these changes increase the area of the capillary network exposed to the cooling effect of the atmosphere, but at the same time the production of sweat ensues. Secreted by the sweat glands on to the hot flushed skin the liquid sweat is quickly vaporised and carried off, drawing with it from the body the amount of heat necessary for its vaporisation. Thus is provision made for keeping the internal environment at optimum physiological temperature. Even in circumstances which do not cause excessive production of heat for

dispersal a certain amount is normally disposed of by invisible perspiration, though the fluid in this case is believed to exude through the skin by osmosis rather than to be actively secreted by the sweat glands. The production of sweat by these glands is therefore regarded as an emergency mechanism.

In phosgene poisoning the vessels of the body are intensely constricted and blood flow through the skin is greatly reduced. The normal methods of heat disposal are therefore no longer effective and the emergency mechanism is called into play. Sweat is then secreted in copious amounts, but collects in beads and pools on the pale cold skin from which it cannot be evaporated and there it lies unvapourised and ineffective for dispersing the heat that is accumulating within the body. Some heat loss may of course take place, as normally happens, from evaporation of water from the lungs. Even this is strictly limited, for the following reasons. The amount of water that can be vapourised in the lungs is limited by the quantity that is necessary to bring the expired air to full saturation with water vapour. The inspired atmospheric air is already partially saturated and the lungs can only vapourise that quantity that will produce complete saturation of the expired air. A certain amount of heat is also lost from the body in warming up the cool inspired atmospheric gas to the temperature of the expired gases which is nearer that of the body. The quantity of heat that is disposed of in this way will of course be comparatively small. Moreover, in phosgene poisoning a considerable part of the lungs will be out of action through atelectasis and waterlogging of the alveoli. Respiration though rapid is shallow, so that the total effective heat loss from the lungs may be much less

than normal. The normal physiological production of heat and the breakdown in the mechanisms for its disposal therefore leads to a state of heat retention and an increase in body temperature. Only as the condition of the patient improves and the effects of the acid poisoning are neutralised will the vascular state and conditions in the lungs return to normal and allow once again the physiological mechanisms for heat dispersion to come properly into play.

6. THE DELETERIOUS EFFECT OF EXERCISE

The hurtful effect of exercise after exposure to phosgene is well known. Indeed, many cases are on record of persons dying suddenly on attempting exercise a short time after exposure to the gas. In some instances the amount of physical effort involved has been very small, as for example, assuming or maintaining the erect posture, walking a short distance to a first aid station, or climbing into an ambulance. Serious untoward effects from exercise are not apparent among the cases here recorded, for the risk being appreciated, particular care was taken to avoid, so far as possible, the exercising of these patients in any way. So well known, however, is the deleterious effect of exercise upon phosgene casualties that some short reference must be made to the subject for sake of completeness.

The first and most obvious effect of exercise is to raise the cardiac output, which consequently raises the blood pressure. Since a considerable degree of hypertension may already be present on account of increased peripheral resistance, as previously described, any farther burden may prove too great for the heart and consequently death can ensue

from cardiac failure. The degree of exercise necessary to embarrass the heart to this extent will naturally vary in individuals and will depend upon the adequacy of their normal cardiac muscle reserves.

A second and equally obvious effect of exercise is to speed up metabolism and increase the production of acid metabolites. Added to the acidosis already present these substances will further stimulate the respiratory and vasomotor centres, adding thereby to the serious effects of phosgene or acid poisoning already described.

Lastly, and possibly most important of all, is the increase in anoxia that exercise produces in such cases. It will be recalled that anoxia, according to Drinker (32, 53), is the most potent factor causing injury and increased permeability of the lung capillaries. The main source of oxygen supply for the cells forming the walls of the lung capillaries is from the alveolar air with which they come in contact. A thin film of fibrinous exudate or oedema fluid on the alveolar walls (a condition that may exist for some time before frank pulmonary oedema is clinically detectable) will greatly cut down the oxygen supply to the capillary tissues and they will be then dependent upon the oxygen of the blood within the lumen of the capillary itself. But the blood reaching the pulmonary capillaries is venous blood. Under resting conditions the oxygen content of this venous blood, together with what little that may diffuse through the film of oedema fluid, may be sufficient to prevent an increase in capillary tissue anoxia and the greater permeability that it produces, which leads in turn to the development of further pulmonary oedema. Exercise, however, will strip the venous blood more completely of its oxygen in the peripheral tissues so that the blood

reaching the minute vessels of the lungs will contain practically no oxygen at all. The result is to tip the scales and finally deprive the capillary endothelium of the lungs of its last reserve of oxygen supply. The consequent state of anoxia increases permeability and promotes the further progression of pulmonary oedema. This may increase very rapidly indeed, and the patient rapidly drowns in his own secretions. In less severe cases or with smaller amounts of exercise the outcome may not, of course, be fatal, but in any event the increased anoxia cannot but have a most serious effect upon the condition of the patient.

CHAPTER IV

RESOLUTION OF PULMONARY EXUDATES: COLLATERAL RESPIRATION

Having discussed at some length the production of pulmonary oedema, and particularly the formation of lung oedema in cases of phosgene gassing, some consideration must for the sake of completeness be given to the means by which these exudates undergo resolution. Moreover, a fuller understanding of the process of resolution is of great assistance in establishing a rationale of treatment.

Resolution of Lung Exudates

The possible ways in which free alveolar fluid, which invariably contains an amount of plasma protein, may be got rid of are not numerous. They are usually stated to be as follows:

a) The protein may be hydrolysed by enzymes to nitrogenous compounds of smaller molecular size, and these together with water and salts be reabsorbed by the lung capillaries.

b) Proteins, water, and salts may all be reabsorbed by the lymphatics and so return slowly to the blood stream.

c) The fluid may drift up through the bronchioles and bronchi, aided by ciliary action, and eventually be coughed up.

Though all of these mechanisms are theoretically possible, there are good reasons why they are not all equally probable, nor can they for various reasons be equally efficient. Detailed consideration will be given to each mechanism separately.

Reabsorption by Lung Capillaries

This method of resolution must be of little consequence if indeed it takes place at all. The amount of tryptic digestion in the lungs can only be slight and it would not be possible to dispose of much of the protein in the exudate by breaking it into polypeptides or amino-acids for the purpose of securing its reabsorption by the lung capillaries. Moreover, during the time when the exudate is forming the capillaries are pouring forth fluid into the alveolar spaces, and it is not likely that an endothelium which has permitted this exudation can not only so quickly recover its normal integrity, but actually proceed at once to reverse the manner of its functioning. Indeed, the continued presence of fluid in the alveoli leads to a continued anoxia with its consequential increase and persistence of capillary permeability and the further development of pulmonary oedema. Resolution by capillary reabsorption would therefore seem to be an ill-considered theoretical possibility rather than an even probable fact.

Reabsorption by the Lymphatics

In order to appreciate the limitations that apply to resolution of pulmonary oedema by reabsorption of fluid via the lymphatics, a brief recapitulation of the minute structure of the lung will have to be made. The intimate histology of the respiratory unit is classically described by W.S.Miller in his paper first published in 1893 (79) and further elaborated in his later monograph entitled "The Lung" (80).

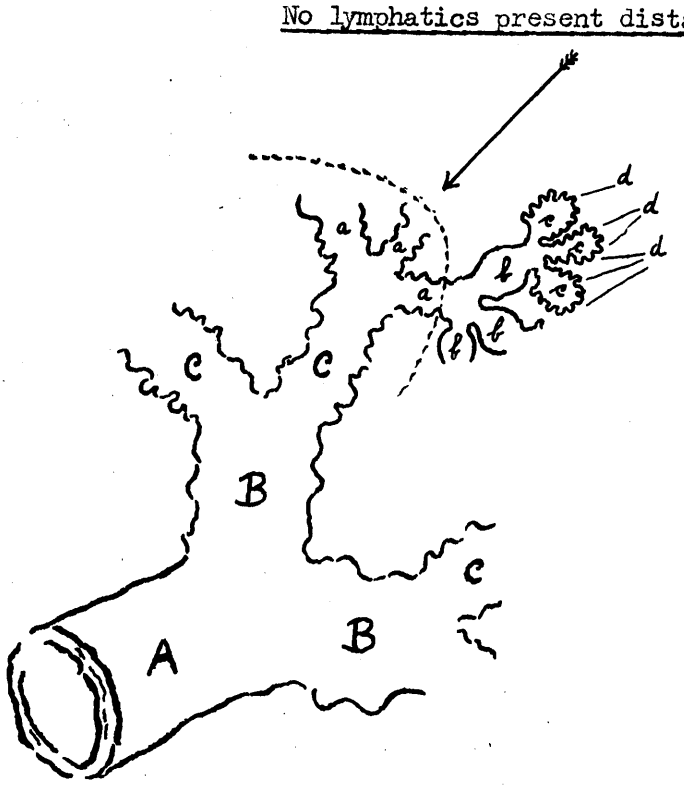
According to this account the bronchial tubes constantly divide to

form smaller and smaller bronchioles till finally the primary respiratory bronchiole is reached. This respiratory bronchiole differs from the ordinary small bronchiole in that it contains no cartilage and has a number of air saccules opening directly off it. The primary respiratory bronchiole then further sub-divides to form two secondary bronchioles very similar to the parent tube except that there is a larger number of air saccules opening from them. At its termination the secondary respiratory bronchiole opens into several alveolar ducts each of which in turn forms several atria or small compartments from which the air saccules arise. The air cells themselves (alveoli) open off the walls of the saccules. The accompanying diagram (p. 135) may help to make this clear; an excellent coloured diagrammatic representation of the respiratory unit will be found, however, on p.41 of Miller's monograph.

The pulmonary artery follows the bronchi and bronchioles until it reaches the last division forming the respiratory bronchiole. Here it penetrates the lobule, dividing into as many little branches as there are atria. From these atrial arteries the terminal arterioles arise and supply the air saccules. Each air sac receives a single artery on its side nearest the centre of the lobule, and this vessel at once breaks up to form the rich capillary network on the walls of the alveoli themselves. The vein returns along the periphery of the lobule, but tends to lie as far away as possible from the artery and bronchiole.

More important for the present purposes, however, is the distribution of the lymphatics. This is described in detail and beautifully

illustrated in another paper by Miller (81), dealing exclusively with the



A. Bronchiole

B. Primary respiratory bronchioles

C. Secondary respiratory bronchioles

a. Alveolar ducts

b. Atria

c. Saccules

d. Air cells or alveoli

lymphatic vessels and lymph flow in the lungs. Briefly, the deep lymphatics that lie within the substance of the lung itself run with either the bronchioles, arteries or veins. These three groups anastomose freely among themselves. The most important point, however, about the distribution of the deep lymphatics of the lung is best stated in the words of White himself, that "no lymphatics are present in the walls of the "air spaces distal to the ductuli alveolares."

In view of this anatomical peculiarity in the distribution of the lymphatic vessels within the lung, it is obvious that the lymphatics do not provide an efficient means of pulmonary drainage. Indeed, they cannot even begin to function until the oedema fluid has flooded the alveoli completely and reached the level of the alveolar ducts where lymphatics are first encountered. Two short quotations from Drinker's monograph (53) more than adequately summarise the situation. Speaking of the experimental production of pulmonary oedema in dogs by the administration of alpha-naphthyl thiourea he says (loc.cit., p.39), "Two important things "may be learned from this experiment; first, that the lung capillaries "possess some quality either of position or anatomical constitution which "renders them uniquely vulnerable to the drug or to some compound "developed in the body as a result of injection; and, secondly, that the "lymphatic system in the lungs is ineffectual for draining off a real "excess of pulmonary tissue fluid." Again he writes (ibid, p.41): "The second and much more definite fact evident from these last "experiments consists in the inadequacy of the lymphatic system in the "lungs to keep pace, in terms of removal, with a reasonably steady and

"rapid production of excess tissue fluid. This is not an agreeable "picture when one contemplates the situation of a man who has inhaled a "dangerous amount, of chlorine, nitrogen dioxide or phosgene - any one of "which may be encountered in industrial accidents."

Thus, when capillary leakage is excessive and continuous, drainage of the lungs by the lymphatic route becomes inadequate, leaving no outflow except by way of the air passages - a method of removal that tends, of course, to progressive exclusion of air and to eventual death unless removal of the fluid is speeded up and assisted by the massaging action of bodily movements, deep breathing, coughing and the like, all of which tend, in some degree, to promote lymphatic reabsorption as well.

Drainage via the Respiratory Passages

Since the lymphatic system in the lungs is far from able to cope with the disposal of large quantities of alveolar fluid, it is apparent that the greater part of such exudes must be got rid of through the respiratory passages. Drainage of the lung in this way is secured partly by the free flowing of fluid from higher to lower levels, and eventually into the larger tubes from which it is expelled by coughing. The flow of fluid in the smaller tubes is also assisted by the flagellar movements of their ciliated epithelial linings which help to force the fluid along the narrow tubules and away from the alveoli. Similarly, the respiratory and other movements of the chest exert a massaging action which assists in displacement and easy disposal of the secretion.

The principal aid, however, to drainage of the lungs by expectoration

is the reflex process of coughing, by which air behind the blockage in a bronchiole is forced along the tube under considerable pressure and drives the obstructing mucus before it. Moreover, it is generally held that if the bronchiolar obstruction is not soon relieved, air is absorbed from the alveolar spaces distal to the mucus plug so that the whole lobule becomes collapsed and airless. At this stage the cough mechanism is of course no longer effective, and removal of the obstruction from the bronchiole comes to depend entirely upon such factors as liquefaction of the tenacious mucous plug, and its removal by peristaltic wave-like movements of the bronchiolar walls, assisted by ciliary action from the cells that form their lining. In the smaller bronchioles, however, such a mechanism cannot operate, for the lining epithelium is devoid of cilia and peristaltic movements are minimal, if indeed they do take place at all.

Collateral Respiration

For many years no certain answer could be given to the problem of how obstructions in the smallest bronchioles are finally overcome. Recent physiological investigations, particularly those of van Allen and his colleagues (82, 83, 84, 85), have revealed the mechanism by which this seeming impasse is overcome, for they have shown that when a lobule is cut off from the general respiration by blockage of its bronchiole it may yet receive a considerable amount of air by a collateral route. Though it had been for long believed that each lobule was an entirely separate and independent unit, each forming a cul-de-sac at the end of its respiratory bronchiole, it is now apparent that this is not the

case, for it has been repeatedly demonstrated that interalveolar pores, or minute channels of communication, do in fact exist between adjacent lobules. These interalveolar pores are beautifully illustrated by Loosli (86) in a series of very striking photographs that accompany his comprehensive paper on the subject; in this paper is also included a review of the literature and a critical survey of the work of others in the same field, up to the year 1937. It is now apparent that by means of these pores air is able to flow from adjacent functioning units into an alveolus or lobule that has been cut off from its normal supply by blockage of the respiratory bronchiole. In this way sufficient aeration of the lobule may be secured to permit the functioning of the cough reflex and the expulsion of the obstructing secretion.

Moreover, the alveolar pores, or channels of collateral respiration as they have been called, appear to have an economic significance in bronchial obstruction, for they permit an obstructed part of the lung to carry on a considerable ventilation that may be sufficient to oxygenate to a satisfactory degree the venous blood passing through the capillaries in the obstructed area. This function has been clearly assessed by Kindskog and Bradshaw (92), who have shown that an obstructed lobule may breathe through collateral channels at least 10% as much air as it would normally receive through its respiratory bronchiole. Furthermore, these authors state that the volume of collateral air flowing is directly proportional to the depth of respiration, and that when positive pressure breathing is instituted the volume of collateral air flow is increased out of proportion to the depth of respiration. Such observations all

point to the very great benefit that one might expect from the administration of oxygen, especially if under pressure, in cases of pulmonary oedema - an expectation that has been realised in practice and personally confirmed from observation of the clinical cases described in this paper.

In conclusion, the extensive work on the subject of collateral respiration and its tremendous significance in cases of pulmonary obstruction and oedema are most clearly epitomised in the words of van Allen himself, when he writes (82):-

"The principle of respiratory mechanics that has been described (collateral "respiration) would appear to have a broad economic significance in the "functioning of the lower respiratory tract. Considering the exudative "tendency of the bronchial mucosa and the disposition of the lungs to "transudation it is likely that obstruction of the smaller air passages "occurs frequently. The more minute bronchioles possess no ciliary and "little, if any, peristaltic function to assist in elimination. The "lumen, of one of these is so small as to be filled over considerable "length by no more than a droplet of exudate or secretion, and the result "would be completely to isolate the corresponding unit of respiratory "ducts, atria and alveoli, if there were no peripheral interconnections. "Then, unless special respiratory effort were soon instituted to make use "of the air available for expulsion, it would be lost by absorption. "Inspiration, no matter how forceful, would not be able to introduce air "past the column of fluid to replace the absorbed air. Atelectasis must "soon develop and this lobule of parenchyma must then remain functionless

"until the exudate undergoes removal by absorption. Under these "circumstances a night's sleep for an individual with slight bronchial "catarrh would be expected to leave the lungs considerably, perhaps "seriously, handicapped for respiratory space. Indeed, a bronchial tree "made up of blindly terminating branches would be as inefficient as a "blood vascular system consisting of end vessels; even more so, since "respiration operates by ebb and flow rather than by circulation of "air, and since the forces impelling the air in quiet breathing are "comparatively weak. However, as it is, since the bronchial tree has the "function of collateral respiration, air is supplied to an obstructed "lobule as long as the peripheral interconnections remain free and until "such times as the block is eliminated by means of sufficiently forceful "effort or by absorption."

CHAPTER V

DIFFERENTIAL DIAGNOSIS; COMPLICATIONS AND SEQUELAE OF PHOSGENE GASSING; PROGNOSIS.

DIAGNOSIS:

The diagnosis of phosgene poisoning in most instances is not difficult. A history of exposure to the liquid or vapour, followed by the development of typical symptoms of lung oedema after a definite latent period, is conclusive. On the other hand, care must be taken not to attribute symptoms of respiratory disorder to the inhalation of phosgene merely because the patient has been in contact with that substance. Should pulmonary symptoms develop immediately, or within a short interval, after alleged exposure, the true cause must be sought elsewhere, for in phosgene poisoning there is a well marked latent period of several hours' duration. Of course, in view of the existence of this latent period, great caution must be observed before finally excluding a diagnosis of phosgene gassing. Wherever the possibility of committing this error exists, the patient should be kept under observation and at rest while developments are awaited.

During the interval of waiting, it is well to begin oxygen therapy, for this will not prevent a correct diagnosis from being eventually made; moreover, it allays the fears of the patient and anticipates the development of anoxia which may be present for some time, and in some considerable degree, before it can be identified. Serial records of pulse rate, respirations, and temperature, and above all of blood

pressure, should be made during this time as they will be of great assistance in arriving at a correct diagnosis. Moreover, in cases of phosgene poisoning they form a most valuable guide to prognosis, as well as providing definite landmarks along the course of clinical development.

Concerning the differential diagnosis between phosgene poisoning and "constitutional" illness, the only condition with which it might be confused - and that only in the earliest stages and before severe lung oedema develops - is influenza. In this connexion it cannot be too greatly stressed that some elevation of body temperature is the general rule in all cases of phosgene gassing of any severity and that such a rise in temperature has nothing to do with infection. Yet I have known of at least two definite and classical cases of phosgene poisoning wrongly labelled "influenza" by an experienced clinician, unfamiliar with this condition, purely on the grounds that the patients had elevated temperatures together with vague respiratory symptoms, and must therefore be suffering from an infective process. The point is of great importance and the appearance of pyrexia does not exclude phosgene poisoning, but tends rather to confirm it, and is not necessarily an indication that infective complications are developing. The absence of pain from the back and bones and eyeballs, and of true toxaemia and prostration all help to distinguish phosgene poisoning and influenza. Moreover, leucopoenia is a common finding in the latter condition, while a progressive haemoconcentration, as evidenced by a rise in the red cell count and haemoglobin content of the blood, is typical of the phosgene casualty.

The differential diagnosis between poisoning by phosgene and other

lung irritants, such as chlorine, bromine, or hydrochloric acid gas, need not be discussed here in any detail. It is sufficient to mention that these are all acute, and in severe cases, suffocative poisons. Inhalation of them is accompanied by immediate and severe or even intense pain in the chest, and all the signs of an instantaneous, though possibly progressive, irritation of the respiratory tract, mainly in its upper regions. Solvent vapours may also have lung irritant properties, again of the type that develops immediately and without a latent period. The respiratory symptoms are, however, not as a rule extreme, and are greatly overshadowed by nausea, lethargy or even coma or mental disturbances associated with the anaesthetic properties of the organic solvents. Indeed, all the gases mentioned, and the other respiratory irritant vapours with which I am familiar, may be readily distinguished from phosgene by the rapidity of their action in producing pulmonary irriation. Poisoning by phosgene is milder and more insidious at the onset, with little or no immediate irritation, a long period of development characterised as "the latent period" and leading to the later onset of a progressive lung oedema.

Complications and Sequelae

The complications of phosgene poisoning appear to be confined to the respiratory system. In the series of cases that I have described, where pulmonary complications did occur, they have varied from a mild tracheo-bronchitis to a more severe acute bronchitis and in one instance to a bronchopneumonia. The onset of these inflammatory and

infective complications is marked by the appearance of a secondary rise in body temperature. This has been discussed already in a previous section and so need not be repeated here.

Of late sequelae there have been none. Once the patient has recovered from phosgene poisoning and from such complications as may have accompanied it, he reverts to a condition of normality. No instance of a subsequent hypersensitivity to phosgene vapour has been personally observed, and no record of such an occurrence has been found in the literature. Moreover, I have had the opportunity of questioning and examining clinically some nine or ten men who had been severely affected by phosgene in accidents occurring at a chemical factory from six to ten years ago. No abnormality of any kind was detected clinically among these men, and none gave a history of having become more prone to respiratory or other ailments as a result of his accident; these statements were confirmed by reference to the works' records of absence due to sickness; their records showed no departure from the average either for frequency or type of illness or for duration of absence. It would therefore appear that there are no sequelae attributable to poisoning by phosgene.

PROGNOSIS:

From consideration of the cases herein described one must conclude that the prognosis is, in general, a favourable one, providing that efficient treatment is carried out as early as possible after exposure. Even the most severely affected casualties who have been subjected to massive

concentrations of the gas or large quantities of the liquid can make an uninterrupted and complete recovery when treatment is started at once. The longer the delay in commencing treatment, however, the more likely are complications to develop and the more serious are they liable to be. On the other hand, once recovery has taken place, there are no permanent after-effects in the way of respiratory system weakness or hypersensitivity to the chemical.

Where the patient becomes hot and flushed soon after exposure, and where there is little alteration in the systolic blood pressure or where the change is limited to a fall in blood pressure (but not profound enough to indicate collapse), the case will be a mild one, and recovery should be complete within a few hours.

Grey cyanosis, a mixture of pallor and the ordinary blue cyanosis, indicates that the case is a serious one. Similarly a steadily progressive rise in the systemic blood pressure, mainly the systolic, is indicative of a seriously affected casualty and the height to which the blood pressure rises would seem to be directly proportional to the severity of the condition. The existence of hypertension does, however, indicate that the normal physiological mechanisms are functioning well and that the patient is, for the present at any rate, capable of coping with his illness. Along with increasing improvement in the clinical condition of the patient the blood pressure returns to normal, but does so gradually and by easy stages. Any <u>sudden</u> drop in the abnormally high blood pressure would, of course, be of the most serious import, indicating a rapid failure in the efficiency of the heart muscle and the imminence of death.

An elevation of body temperature is of no prognostic significance and as previously stressed, does not indicate the presence or development of intercurrent respiratory infection. Recurrence of pyrexia after a period of normality, when the other symptoms have disappeared or for the most part subsided, does however indicate respiratory infection. The prognosis in such a case becomes that of the infective condition, whether it be a bronchitis or bronchopneumonia, but will of course be modified by the amount of strain thrown upon the patient by his previous injury from phosgene and the manner in which it has affected him. In rarer instances the symptoms of phosgene poisoning may all but disappear while the initial pyrexia may persist till it merges with the pyrexia of a complicating infection. Amelioration of the other symptoms without an accompanying tendency for the body temperature to revert to normal calls for increased watchfulness and suspicion; it would appear also that this unusual sequence of events is more likely to occur in cases where a very considerable time has elapsed between exposure to phosgene and the beginning of treatment.

CHAPTER VI

TREATMENT OF PHOSGENE POISONING

There is at the present time no specific treatment available for cases of phosgene poisoning. Of all the therapeutic measures that may be employed oxygen therapy is, undoubtedly, by far the most important and valuable. Other general measures may be helpful, and indeed essential in some cases.

Before discussing in detail the various therapeutic measures likely to benefit the individual who has been affected by phosgene vapour, it would be well to stress the importance of beginning treatment at the earliest possible moment after exposure; the longer the delay in starting treatment the longer it will take for recovery to be complete, and the more likely are complications to develop. Details of therapeutic procedures will be described under separate headings, as follows:-

Rest:

As soon as possible after exposure, the patient should be placed completely at rest in bed. Following an accident of any severity the casualty should be brought to the first aid station on a stretcher, however short the distance may be. Mild cases may well walk if the station is within, say, half a mile.

From the beginning, rest should be complete and continuous, in the recumbent or reclining position, whichever be the more comfortable. The patient should not be allowed to undress himself or attend to his own wants. When dyspnoea is severe and when pulmonary oedema is developing the patient becomes orthopnoeic and is more comfortable and less restless if propped up in bed with plenty of pillows. The resting

state should be maintained until recovery is complete, i.e., until the blood pressure is again normal and until there is no cyanosis or dyspnoea, and no signs of pulmonary congestion or oedema. Before allowing the patient to get out of bed, oxygen therapy should have been stopped for some hours, and the patient should be able to move freely in bed, and be able to sit up unsupported and unaided, without discomfort or the return of any symptoms of respiratory or cardio-vascular embarrassment. Exercise should be somewhat restricted for the next 24 hours, and the patient must be instructed to rest at once should symptoms of dyspnoea or palpitation ensue with exercise during this period.

Nursing procedures such as bed bathing should not be permitted until the patient is over the worst. Tepid sponging of face and limbs is sufficiently refreshing and does not have the same exhausting effect.

While lack of observation of the principle of complete rest, from the moment after exposure till recovery is complete, may not result in sudden or unexpected death as frequently as a few authors would have one believe, the present series of cases does show that recovery takes longer, the illness is more severe, and the complications more serious and frequent in cases not rested until some time has elapsed after their exposure to the gas.

Warmth

Being as a rule aware of the evil reputation of phosgene, the patient is usually greatly frightened by his accidental exposure to it, and suffers from a considerable degree of mental shock and agitation, accompanied by a feeling of chilliness or even by actual shivering. At a later stage,

when the cutaneous vessels become constricted and the blood flow through the skin is considerably reduced, this sensation of chilliness is greatly intensified, and the patient can feel very cold indeed, despite the fact that his bodily temperature may actually be elevated. For these reasons, the application of warmth is necessary. Hot water bottles are probably the most convenient in the majority of instances, but the electric blanket or electric cradle may be preferred. The latter appliance has been found to have the advantage - that it will bear the weight of the blankets and thereby free the chest from their restricting weight and permit the fullest possible respiratory movement at the stage when respiratory distress is marked.

Oxygen Therapy

Oxygen therapy should be instituted as soon as the patient has been got to bed, and should be continued, without interruption, for as long as is necessary.

The most convenient method of administering oxygen is by the B.L.B. mask, for this leaves the mouth free and permits the simultaneous administration of fluids or allows for vomiting, which is not uncommon in the early stages. Moreover, the apparatus is a very efficient one, and it enables oxygen to be given in high concentration for long periods, and under slight pressure, which is of additional benefit. Most patients have no objection to this type of mask, whereas with the oro-nasal type they usually complain of a sensation of suffocation, and are constantly trying to remove it.

The patient, of course, requires to be instructed in the use of the

apparatus, the purpose and general functioning of which should be explained to him, as well as the necessity of inhaling the breath only through the nose. Simple explanation and the early encouragement of nasal breathing is well repaid as the critical point in the disease is reached, for confidence has been inspired, so that the patient trusts the efficacy of the apparatus and co-operates in its use. In a short while he has become no longer conscious of the presence of the mask and the regular nasal breathing has become so automatic that it will continue uninterruptedly throughout the crisis when efficient oxygen intake is most necessary, and will be maintained even if he should doze off in sleep.

The nurse or other attendant should also be completely familiar with the principle and operation of the B.L.B.mask, especially the necessity of securing and maintaining its close fitting to the face, and of keeping the rate of oxygen flow at such a level that the rubber bag is not allowed to empty completely at any inspiration. Lack of observation of either of these two fundamental points is undoubtedly the commonest cause of insufficient oxygen being received by the patient, in spite of the high degree of efficiency with which the apparatus is capable of working. Moreover, failure to ensure that the bag is always kept partially inflated destroys the patient's confidence in the apparatus, for his inability to obtain an adequate amount of gas from any inspiratory act makes him feel that the supply of oxygen is restricted or liable to run out, and also adds to his burden and distress because of the increased inspiratory effort that it produces.

The purpose of the air ports should also be clearly in the mind of the attendant or nurse. Since their function is to permit of oxygen from the cylinder being diluted with air from the atmosphere, these ports must be kept closed during the severe phaze of the illness when the patient needs all the oxygen he can get. As recovery advances, they may be gradually opened, the rate of flow of oxygen being simultaneously reduced until the patient is breathing a mixture of which the greater part is atmospheric air. Soon after this stage is reached, the supply of oxygen may be completely withdrawn. The correct use of these air ports is not at all well or readily understood by the untrained or inexperienced attendant. If for any reason reliance has to be placed on the services of such persons instructions should be given that the air ports are to be kept closed until such times as specific orders are given to the contrary. This may result in undiluted oxygen being given for a period when it is not strictly necessary. Yet an adequate supply of oxygen is so essential for the prevention or relief of anoxia and the combatting of pulmonary oedema that it is better that oxygen should be used extravagantly or even wastefully, from an excessively high concentration or rate of flow, than that the patient should receive too little for his needs.

Similarly, the flow meter should not be relied upon as an indication of requirements in oxygen therapy. When the ports are closed and the patient is thus relying entirely upon a supply of oxygen from the cylinder the rate of flow must be such that there is enough entering the bag to meet every need of each inspiration - no matter what the

reading on the flow meter may be. By stressing the necessity for a close fitting face piece and the necessity of adjusting the rate of oxygen flow to keep the bag at all times partly inflated, while maintaining the air ports constantly in the fully closed position, the process of administering oxygen and the working of the apparatus may be greatly simplified for the inexpert attendant such as a member of a first-aid or rescue team. In practice it is found that the rate of consumption of oxygen as gauged by the flow-meter varies between 2 and 10 litres per minute, depending upon the severity of the case and the stage of the illness.

The colour of the patient is not much help in assessing the efficiency of oxygen therapy. There is usually a certain amount of cyanosis, especially marked on the lips, ears, nose and fingertips, that cannot be overcome no matter how far the administration of oxygen is pushed. The degree of cyanosis should, however, be kept to the minimum possible. With the severely affected patient it becomes not so much a question of how much oxygen does he require, but rather how much is it possible for him to use. Persistence of cyanosis may indicate anoxaemia and the need for oxygen, while the oedematous condition of the lungs may preclude the possibility of the body receiving all that it needs, even though oxygen may be made freely and abundantly available to it. Oxygen therapy is efficient if the patient be given all that he can use. In cases of severe pulmonary oedema it is manifestly impossible to give all that the patient requires, else it would always be possible to cause the cyanosis, dyspnoea, and similar anoxic symptoms, and perhaps

even the lung oedema itself, to disappear immediately and completely. It is always possible, however, to make certain that the patient receives all the oxygen that his lungs are capable of using, and this is the ideal to be achieved whenever oxygen therapy is employed.

During the height of the illness, when the patient may be very restless and inclined to pull off or otherwise displace the mask, it has sometimes been found necessary to maintain the facepiece constantly in position by hand, and thus administer oxygen in much the same way as one would an anaesthetic from a Boyle's or similar machine.

As for the gas itself, I have always used pure oxygen unmixed with carbon dioxide, and with entirely satisfactory results. This practice has been based on a belief that the respiratory centre was well enough stimulated by acids present in the blood and that no additional respiratory stimulus was necessary. Indeed, the regular and rapid though shallow breathing would seem to indicate that the respiratory centre is functioning rhythmically, but at an abnormal rate from excessive stimulation, the shallowness of the breathing being attributable to the distended or stretched condition of the lung causing a reflex inhibition through the Hering-Brauer reflex and not in any way connected with carbon dioxide excess or deficiency. There has, however, been considerable controversy (20, 87, 88, 89, 90, 91) on the relative merits of oxygen and oxygen-carbon-dioxide mixtures. Many authors advocate mixtures containing up to 7% of carbon dioxide in all cases, and claim equally effective results, basing their claims, as do Gibbs and his co-workers (87) on a belief that carbon dioxide is the essential specific stimulus of the respiratory centre, and that while the presence

of other acid substances may sensitize the centre to the action of carbon dioxide they cannot, however, replace it. Dumoulin and his colleagues (88) on the other hand, believe that the results of oxygen therapy in experimental phosgene poisoning are equally good whether or not carbon dioxide is added. Cordier (90), however, advocates administration of pure oxygen in cases of phosgene gassing on the grounds that the blood pH is progressively falling and the respiratory centre is adequately stimulated by the acids present. He believes that the addition of CO_2 is indicated only in such conditions as carbon monoxide poisoning, where there is no excess of acid present in the blood, and where the administration of pure oxygen, by washing out the normal CO_2 of the blood, would deprive the respiratory centre of its sole and normal stimulus. Thelwall Jones in his paper (20) appears to favour the use of a mixture containing 7% of carbon dioxide for most forms of industrial gas poisoning. He points out, however, that in the severe case of phosgene gassing included in his report it was necessary to change to pure oxygen in the severer stages of the illness "owing to "the distressingly deep breathing induced by the CO_2." Whatever may be the theoretical considerations, or the relative merit of the various opinions in this controversy, it can only be repeated that the administration of pure oxygen has in practice proved entirely satisfactory for the treatment of the cases that have come under my care.

For successful oxygen therapy, probably the most important point is that it should be started early. Once the exudative condition of the bronchioles and alveoli is well advanced these structures become impervious to oxygen, however efficiently administered. While collateral

respiration and the diffusion of oxygen into collapsed lobules may take place to a limited extent through the alveolar pores (92), a great deal more can be administered with greater ease and certainty if an early start is made. Moreover, adequate supplies of oxygen are necessary for the complete breakdown of acid metabolites (and possibly for other acid compounds in the tissues); if these substances are allowed to accumulate because of a deficiency of oxygen they can only add to the burden of tissue acidity that is such an important feature of phosgene poisoning. The early administration of oxygen, before anoxia has become obvious and extreme, will not only prevent the accumulation of acid metabolites but may even play some part in preventing the formation, or at any rate continued existence, of many other acid compounds. In his authoritative writings on the subject Drinker stresses the fact that once anoxia begins to develop it increases the production of pulmonary oedema which in turn leads to further anoxia; oxygen therapy should therefore begin at the earliest moment. So insistent is he on these two points that he words them in the strongest possible terms: thus in a recent paper (32) he says, "The two principles that this laboratory has "learned are the master words of oxygen therapy: anoxia begets anoxia, "and if real benefit is to be expected from oxygen, it should be used "before the need is certain." This theme he elaborates in his monograph (53) where he states (p.72):

"Two principles emerge from these experiments; 1) oxygen lack is the "most potent and elusive cause of abnormal leakage from the lung "capillaries, and as a consequence administration of oxygen is the

"obvious method of treatment. 2) If oxygen administration is withheld "until the physician is sure pulmonary oedema is present, then fluid will "have reached many alveoli and bronchioles. By this time, though high "tensions of oxygen will be definitely useful, their utility will be "far less than if given earlier when the gas could easily reach lobules "everywhere in the lungs. The lesson, never to be forgotten, is that if "oxygen is to be most helpful it must be used before the physician is "sure it is needed."

Concerning the duration of oxygen treatment, no definite period can be laid down. Each case must be assessed individually, the only criterion being that oxygen must be administered for as long as the patient needs it. No ill effects have been noted in the cases here reported, even where oxygen has been given for upwards of 36 hours on end. As the patient's condition improves, the amount of oxygen should be gradually decreased and a larger proportion of air admitted through the ports of the B.L.B. mask. Eventually the flow of oxygen may be cut off entirely for short intervals, and the effect noted. When total withdrawal is possible without causing the slightest embarrassment to the patient, the need for oxygen therapy has passed, and its administration may be finally stopped. A too speedy and injudicious return to exercise may, however, necessitate its resumption for short intervals in a few cases.

Diet

At the ontset, when the patient feels chilled and shivery, a warm

drink of sweetened tea or coffee is greatly appreciated. At a later stage, when vomiting is a common occurrence and maybe copious and recurrent, half-normal saline suitably flavoured with fruit juice and a little glucose has been found to be helpful. Not only does this assist in replacing the fluid lost by vomiting and sweating, but it appears also to allay the tendency to vomiting, or in any case makes it easier for the patient if vomiting should occur. At no time have fluids been pushed and the matter has been left to the desires of the patient. Although it might be thought that because of the existence of haemo-concentration a large intake of fluid would be desirable in order to counteract it, I have always felt that to accomplish this would only add to the amount of fluid in the circulation and tend to promote advancement of the lung oedema. Moreover, once the blood chemistry has re-established itself to normal, and once the capillary vessels in the lungs have recovered their integrity and no longer permit the leakage of plasma, the existing haemoconcentration will tend to promote more rapid resolution of the lung oedema by drawing upon this available fluid to make good the normal blood volume.

As the patient's condition improves, and when vomiting has ceased, crisp buttered toast, milk, switched egg, custard, junket and milk pudding may gradually be added to the diet. It is most remarkable how soon after the crisis the appetite returns, and the patient expresses a desire for food. Nor is it many hours before he is anxious and fit to return to a normal and mixed light diet.

Sedatives

Only on rare occasions has the use of a sedative been found necessary because of extreme restlessness, amounting in one case to delirium. For this purpose morphine has been used in doses of 1/6 grain administered hypodermically. The drug has proved effective in allaying restlessness and has thereby prevented farther exhaustion or tendency to increased anoxia. In the present series of cases morphine has not been used as a routine treatment for pulmonary oedema. It may well be, however, that the exhibition of morphia to all severe cases would prove beneficial, in view of its sedative effect upon a respiratory centre that is in a state of abnormal excitation, and especially as this is probably one of the main factors in the actual causation of pulmonary oedema. Unfortunately the point did not occur to me for some considerable time, after which no subsequent opportunity arose of giving this method of treatment a proper trial.

As a routine measure to allay the dry irritating cough of the very early stages, a simple linctus was employed.

Stimulants

Only with one patient (Case S.1, W.N.A.), was it deemed necessary to resort to a cardiac stimulant. In this instance, the sudden collapse of the patient during the critical stage of his illness was met by injecting 1.5 c.c. of Coramine (Nikethamide B.P., 25% solution). The response was good and the patient continued on his way to eventual complete recovery. Apart from this solitary instance the need for

emergency stimulation of the heart has never arisen. Such measures, it is felt, may be justifiable on a specific occasion, to tide the heart over a short but difficult interval, but that there is no justification for adopting them as a routine measure, and thereby stimulating to further effort a heart that is already coping adequately with the additional burdens it has to bear.

Sulphonamides

In his paper Shaw (21) suggests the routine administration of a sulphonamide (sulphapyridine) in all cases of phosgene poisoning as a prophylactic against the development of the pulmonary complications that he believes to be imminent on account of the elevated temperature. No justification of this recommendation can be offered here. As already stated, pyrexia is a normal symptom of phosgene poisoning and does not indicate bacterial invasion. The use of sulphonamides as a routine is therefore quite unjustified. They do, of course, have their usual place in the treatment of infective complications. Apart from this use I feel that the sulphonamide drugs are contraindicated in phosgene poisoning for two reasons. Firstly, they are likely to increase nausea and vomiting and add farther to the distress of the patient. Secondly, they may produce a methaemo-globinaemia and thereby reduce further the oxygen-carrying capacity of the blood at a time when this needs to be maintained at as high a level as possible. The cyanotic state of the average phosgene casualty indicates that not all the haemoglobin is functioning as a carrier of oxygen, and it is quite unjustifiable to run the risk of reducing this farther by the exhibition of a drug that can have no

direct effect upon the phosgene poisoning itself.

In the present series of cases the necessity for sulphonamide therapy on account of developing pneumonia arose in only one instance (Case S.4, F.B.).

VENESECTION: TRANSFUSION AND INFUSION

Much has been written on the subject of venesection in cases of phosgene gassing; in every case that I have seen venesection has, however, been contra-indicated. In no instance were the veins engorged nor were there other signs of congestion on the right side of the heart. Haemoconcentration was however present and presumably the circulating volume of blood was therefore reduced. But neither of these is, in itself, an indication for venesection. The absence of congestion in the venous system indicates that the right side of the heart is dealing adequately with the venous circulation in spite of the increased blood viscosity due to haemoconcentration.

Yet many authors recommend venesection for all cases of phosgene gassing (21, 72, 91). This method of treatment was particularly favoured by the American writers of the years immediately following the first World War, and they based it upon their wartime experiences. In most accounts a congestive stage is described where the phosgene casualty is deeply cyanotic and the veins are engorged - the so-called "blue type." It is claimed by this group of authors that such cases responded well to venesection, and quite conceiveably they did. It is probable, however, that this type of war casualty suffered from chlorine or other poisoning as well as from the effects of phosgene - as was

admitted in the Official History of the War (16) - so that a different syndrome was then being seen and treated. A "grey type" of phosgene casualty was also seen and was apparently similar to those described in this thesis. This "grey type" was generally regarded as being the more severely affected, or as indicating a later stage of development of the "blue type." It now seems almost certain, however, that the grey types were, in fact, the only true cases of pure phosgene poisoning. And so it is all the more important to note the point on which all authors are agreed, that when venesection was extended to the grey type of casualty the treatment proved to be exceedingly dangerous and often had fatal results. In such recent official publications as the Medical Manual of Chemical Warfare (23), recognition is made of the fact, for there it is stated that venesection is contra-indicated in the leaden grey casualty. Certainly I have seen no other picture than the grey uncongested one among the many cases of phosgene gassing that I have treated, and in no instance could I find any justification for performing venesection. Moreover, Boycott and Hunt (93) have separately shown, as also has Shaw Dunn (94), that venesection in goats exposed to phosgene makes no difference to the actual state of the lungs as compared with unbled controls.

As for transfusions of blood or infusions of saline or plasma, I have never adopted these procedures for the same reason that I rejected the pushing of fluids by mouth - namely, that any addition to the amount of fluid in the circulation could only add to circulatory embarrassment as well as increasing the amount of fluid available for the production of lung oedema. On the other hand, various authors (72, 91) do

recommend these procedures, either separately or combined with venesection, on the grounds that they will dilute the blood, decrease haemoconcentration and viscosity, and so lessen the burden on the right side of the heart. Yet in all my patients the right side of the heart appeared to be able to cope with its functions, and the desirability of administering intravenous fluid has never impressed itself upon me. Moreover, as has been pointed out in a recent annotation in the Lancet (95), there is now much evidence, both from man and animals, that injected protein solutions usually leave the circulation rapidly, the protein being removed from the bloodstream, as well as the water and salts. Courtice and Foss (96) have also shown recently by experimental studies on dogs and goats poisoned with phosgene, that injected protein solutions (serum or plasma) will not correct the haemoconcentration that follows exposure to the vapour. The animals in these experiments died more quickly after infusion of plasma and serum, presumably, the authors say, from pulmonary oedema, and they conclude that transfusions are definitely detrimental where gross pulmonary oedema is present.

This brief mention of treatment by venesection, transfusion and infusion is included only for completeness and for theoretical discussion, and I have had no practical experience of any of these three forms of therapy in patients poisioned by phosgene.

DRAINAGE OF THE LUNGS

Postural or other forms of lung drainage have also been suggested for the treatment of pulmonary oedema due to the inhalation of phosgene.

Edkins and Tweedy (97) believe that oedema fluid is normally removed from the lungs by evaporation and by drainage through the lymphatics but that removal may also take place via the bronchial airways with the aid of ciliary action, respiration and coughing. They further suggest that postural drainage might be of assistance, but draw attention to the danger of this manoeuvre in that a comparatively sound area of lung might become blocked by the exudate. This method of treatment was never attempted in any of the cases herein described. I have never seen a patient with severe pulmonary oedema who could stand the strain of postural drainage, for the energy that must be expended on maintaining some abnormal posture would be greater than these patients could bear. Moreover, in most instances no particular posture could ever have secured drainage of the lungs, for the oedema process extended throughout, and it was always felt that from the very nature of the condition the oedema fluid could not be unilateral or otherwise localised. To have attempted postural drainage would have meant a very grave risk of flooding with displaced oedema fluid such respiratory units as were still functioning and upon the continued integrity of which the patient's vital processes depended.

Bronchoscopic drainage of the lungs has also been recommended by Jackson (98) for the treatment of these cases, though he gives no indication of whether this recommendation is made on theoretical grounds or is based on actual experience. He states (loc.cit., p.85): "Bronchoscopic oxygen insufflation combined with bronchoscopic "aspiration of the secretions is the best method of treatment for "poisoning by chlorine, asphyxiating, or other war gases."

Speaking of the war gases he later remarks (p.301): "During the

"acute stages bronchoscopy has been deemed of little benefit. Any "tendency towards drowning of the patient in his own secretions calls "for bronchoscopic aspiration."

Piquet and Marchand (99) likewise advocate bronchoscopic drainage as a result of experiments in dogs exposed to chlorine vapour. It has, however, not proved possible to discover any published series of human casualties treated with bronchoscopic drainage. In any case, the procedure is too specialised and technical to be of general application, apart from the fact that it would certainly prove extremely exhausting for the patient and probably necessitate the administration of an anaesthetic. Neither of these very serious disadvantages could be readily outweighed by such small benefit as is likely to accrue from removal of only a very small part of the total secretion by this very difficult and specialised mechanical procedure.

SUMMARY AND CONCLUSIONS

The development of pulmonary oedema following the inhalation of phosgene vapour has been attributed in the past to the formation of hydrochloric acid within the alveoli, and to the action of this acid upon the alveolar walls in damaging the lung capillaries and thereby causing an exudation of plasma to take place. There are, however, both on chemical and physiological grounds, very grave objections to this conception of the pathology of phosgene poisoning. Among the more important of these objections is the fact that hydrochloric acid is known to produce rapid injury of any tissue with which it comes in contact, so that if it were formed within the alveoli it should cause immediate damage to their walls and a very rapid development of pulmonary oedema. But such a speedy onset of lung oedema does not in fact take place. Indeed, one of the most notable features of phosgene gassing is the "latent period" of many hours that must elapse between cessation of exposure to the vapour, and the onset of pulmonary oedema. The conception of alveolar damage due to a local action of hydrochloric acid is apparently an erroneous one.

Consideration of the behaviour of inspired gases, and of the known physical and chemical properties of phosgene, leads to the conclusion that the inhaling of this substance must produce certain chemical changes in <u>all</u> the tissues of the body, and eventually to the conclusion that pulmonary oedema is a local manifestation of a generalised systemic disturbance, and not the result of a purely local damage to the lungs.

Attention has been drawn to the remarkable similarity between

the clinical manifestations of phosgene poisoning and of the condition known as cardiac asthma, or acute pulmonary oedema. A survey of the literature dealing with acute pulmonary oedema shows that it is no longer possible to accept the classical explanation of this condition - namely, that it is a failure on the part of the left ventricle in transferring blood from the pulmonary to the systemic circulation. Most authorities now place emphasis upon the neurogenic nature of the condition, and more recently considerable evidence has been brought forward to show that the site of the neurogenic disturbance is located in the respiratory centre. The modern conception of the causation of the acute pulmonary oedema or cardiac asthma syndrome is that it resides in "an abnormal state and an abnormal function of the respiratory centre", and that this abnormal status and functioning is due to the accumulation of acid metabolites. A great deal of indirect evidence in support of this theory has been adduced by its authors. The fundamental feature of increased tissue acidity has for the most part been based upon theoretical considerations, which show that a gradual and steady accumulation of acid metabolites must inevitably take place throughout the body tissues of those cardiac patients who are prone to develop attacks of acute pulmonary oedema. It is, however, a noteworthy fact that, in contradistinction to the classical theory, this modern concept of the pathology of cardiac asthma does explain all the well known clinical phenomena of the disease.

In the present thesis evidence has been brought forward to show that inspired phosgene vapour passes practically unchanged through

the alveoli into the bloodstream and that it must then gradually enter into chemical combination with various constituents of the blood and tissues. Furthermore, no matter whether these chemical reactions take place by simple or by devious routes, they lead always to the liberation of great quantities of acid. Indeed, one molecule of phosgene entering the bloodstream will be responsible for the production of many molecules of acid and for the simultaneous and independent neutralisation of several additional molecules of base. The acid/base equilibrium of the tissues is thus very profoundly disturbed, and so there is brought about those very same conditions that had previously been postulated as the cause of the attacks of acute pulmonary oedema occurring in certain types of heart disease.

The major symptoms of phosgene poisoning have been discussed in relation to increased acidity of the tissues, and all the symptoms are explainable on this basis. Not only does it account for such phenomena as the greatly elevated blood pressure, the leaden grey cyanosis, the peculiar type of dyspnoea and the very low tension of carbon dioxide in the blood, but it even accounts for the existence of the strange and hitherto unexplained "latent period." Indeed, the latent period is now obviously a mere clinical expression of the fact that tissue acidity goes on progressively increasing for some time after exposure to phosgene, and finally culminates in producing an acute attack of pulmonary oedema.

The relationship between phosgene, its chemical derivatives, and other substances known to have a specific effect in producing lung oedema has also been discussed. The process by which pulmonary oedema undergoes resolution has been considered, as well as the prognosis, diagnosis, and

treatment of the condition. In the matter of treatment great stress has been laid upon early and efficient oxygen therapy, and the beneficial effects have been considered in relation to collateral respiration.

The original purpose of this thesis was simply to attempt to establish a rational chemical pathology of phosgene poisoning. In this attempt one was inevitably driven to the remarkable conclusion that the lung oedema of phosgene gassing, contrary to expectation, is only a local manifestation of what is really a generalised systemic condition, namely, excessive tissue acidity. It is even more remarkable, however, that others should have reached the same conclusion about an entirely unrelated type of lung exudate. At first sight there would seem to be no possible common explanation for two apparently unrelated forms of acute pulmonary oedema, the one due to left ventricular heart disease and the other due to the inhalation of a chemical substance which, so far as is known, has no specific effect upon the left ventricular muscle. But the fact that a common explanation has been found makes it more likely to be the correct one. At the same time, of course, the separate and independent investigations which have suggested the same fundamental pathology for these two apparently dissimilar forms of lung oedema afford some degree of confirmation and support for one another.

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