

STUDIES ON EXPERIMENTAL PHOSGENE POISONING

I. THE PATHOLOGIC ANATOMY OF PHOSGENE POISONING, WITH SPECIAL REFERENCE TO THE EARLY AND LATE PHASES *

DALE R. COMAN, M.D., H. D. BRUNER, M.D., ROBERT C. HORN, JR., M.D., MELVIN FRIEDMAN, M.D., ROBERT D. BOCHE, Ph.D., MILES D. MCCARTHY, Ph.D.,
MARY H. GIBBON, and JULIUS SCHULTZ, Ph.D.

(From the Harrison Department of Surgical Research and the Department of Pathology, School of Medicine, University of Pennsylvania, Philadelphia 14, Pa.)

Except for sporadic observations, study of the development of the lesions constituting "typical" phosgene poisoning has been neglected, and one of the chief purposes of this report is to close this hiatus. Obviously, a systematic analysis of the sequence of tissue changes from the end of gassing onward is prerequisite to the comprehension of the symptomatology and the abnormal physiology of phosgene poisoning. Another object is to describe both the regressive-reparative and the degenerative processes found in animals surviving the critical 72 hour post-exposure period, which has received more, but still inadequate, attention in the past. The massively edematous lung of acute phosgene poisoning will be treated briefly inasmuch as the present studies add little to what is already in the literature.

It is only in connection with the acute or critical phase of the damage (6 to 72 hours following gassing) that a comparison can be drawn between the findings in men poisoned in industrial accidents or in war and the lesions observed in animals poisoned under controlled conditions. As will be pointed out, there is imperfect agreement between the two, and reasons for this may be traced to one or more of the following: (a) The prevalence of respiratory infections during 1915 to 1920 may have complicated or altered the response of the lung to injury, particularly in men surviving longer than 36 hours. (b) In both accidental and field exposures, it has never been possible to estimate with any reliability the dose to which the victim was exposed, and it is known that exposure to extremely high or low concentrations for a given time will result in anomalous lesions.¹⁻³ (c) Since phosgene was rarely used in World War I,⁴⁻⁶ except in combination with some other gas, descriptions of the lesions found in casualties may not be applicable to pure phosgene injury. (d) The conditions existing during the interval between death and autopsy were not specified in the reports on human material; this stands in direct contrast to experimental work. (e) Species differences may, in part, account for variation in response

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to injury. In this connection it may be significant to the interpretation of the cardiovascular abnormalities that the animal is more resistant to anoxia than is man.⁷⁻⁹ On the whole, however, agreement among the various pathologic data is more satisfactory than that between physiologic experiments and inferences from clinical observation.

The data in this report, it is believed, make it clear that the reaction of the lung to phosgene is a type reaction common to several other injurious agents, rather than a specific response.

MATERIALS AND METHODS

Exposure of the animals to phosgene was carried out in an 850 liter chamber through which specified phosgene-air mixtures were drawn at rates of 300 to 600 liters per minute, depending on the size and number of animals. The concentration of phosgene in the mixture was sampled by absorbing the phosgene from a measured fraction in an alcoholic solution of alkali, subsequently analyzed for total chloride.

Two technics of exposure were used in these studies; they appear to give very similar, if not identical, clinical and pathologic findings:

(1) The desired concentration of phosgene was built up in the chamber, whereupon the caged animals were inserted into the gas mixture via a double door slide arrangement; after a time predetermined to result in a desired mortality at a given phosgene concentration, the animals were withdrawn into a cleansing air current. The phosgene concentration was sampled synchronously with the exposure. This "push-pull" method simulates field exposures and saves time, but causes the operators to work hurriedly in dangerously high concentrations of phosgene; it is not suited for species such as the rabbit and goat which are able to suspend breathing for a considerable time.

(2) The "rise-fall" method was used mainly because of greater convenience and safety. The caged animals were placed in the chamber and then the admixture of phosgene with inflowing air was begun. This results in an exponential rise of concentration which was calculated and found to reach equilibrium in 10 minutes. After a given time at this equilibrium, the phosgene was turned off, whereupon the phosgene concentration in the chamber fell by the same exponent, but reciprocally. The duration of exposure was taken to be the sum of the duration of constant composition plus 10 minutes. The phosgene concentration was sampled throughout the period of constant concentration.

The phosgene used in these experiments was stated to be better than 99.9 per cent pure COCl_2 , the remainder being HCl.

The dose of phosgene is expressed conventionally as the product of mean concentration in mg. per liter of air (C) and duration of exposure in minutes (T). This convention is based on the assumption that minute breathing volume, and hence the intake of gas, is proportional to the metabolism which in turn is a function of the weight; it is comparable to the usual dose system based on body weight.¹⁰ Therefore, the adults of a species, regardless of size, are assumed to receive the same proportional dose of a given CT product. To anticipate the results, analyses of the mortality data support this convention; in any event "individual susceptibility" and behavior during exposure are regarded as more important variables.

The dogs, cats, rabbits, and guinea-pigs employed were adults of mongrel origin, whereas the rats, weighing 150 to 225 gm., were of the genetically homogeneous Wistar strain, obtained from the Institute as needed. The latter were secured in an effort to reduce "individual susceptibility" to a minimum. The other animals were not used until an isolation period had shown them to be free of infection and eating well. All of the small animals of an experiment were gassed simultaneously in individual cages, while the dogs were gassed in pairs or in fours in cages.

The dogs were sacrificed by rapid arteriotomy under amytal or local anesthesia and the small animals by thoracotomy under nembutal anesthesia. A number of ungasped animals of each species were similarly sacrificed for comparison.

The animals were autopsied at once after death (with the exception of a few kept overnight at -4° C.) and representative tissues taken for histologic examination. The lungs were removed *in toto* after ligation at the hilum, and multiple sections, or the whole lung in the case of the rat and guinea-pig, were fixed at once in Helley's fluid. The tissues embedded in paraffin were sectioned at 7.5μ and stained with hematoxylin and eosin or special stains as indicated.

The animals listed in the tables which follow are representative of the larger number which were gassed for histologic study. Further, the data agree with those from more than 1,050 dogs and 2,500 rats used in this laboratory in experiments on phosgene poisoning.

RESULTS

To facilitate description, the course of phosgene poisoning has been divided into three phases, which are somewhat different from those of Winternitz.¹¹ It must be emphasized that such a division is arbitrary, since the sequence of events initiated by exposure to phosgene is con-

TABLE I
Evaluation of Acute Pathologic Changes in the Lungs of Dogs Exposed to a Moderate Concentration of Phosgene (L.D.₅₀) by the "Rise-Fall" Technic

Dog no.	Conc. of CG* (mg./L.)	Time after "CG on" (hours)	Sacrificed (S) or died (D)	Emphysema	Congestion of lung	Alveolar edema	Mucosa of bronchioles; swelling, sloughing, and/or plugging	Bronchiolar constriction	Lung/body weight (X 100)
118	0.49	0:38	S	+ +	o, +	o	±, +	±	1.13
117	0.49	1:38	S	+ +, + + +	o, +	±, +	+	±	1.25
529	0.64	1:39	S	+	o, +	+	+	±	1.20
539	0.56	1:52	S	+ +	o, +	+	+	±	1.60
509	0.52	2:39	S	+ +, + + +	o, +	+ +, + + +	+ +, + + +	+	2.11
728	0.64	2:46	S	+ +, + + +	o, +	+ +, + + +	+ +, + + +	Dil, o	1.36
439	0.82	3:36	S	+ +, + + +	o, +	+	+ +	o	1.45
551	0.58	3:46	S	+ +, + + +	+	+ +, + + +	+ +, + + +	±	1.32
642	0.48	3:52	S	+ +, + + +	+	+ +, + + +	+ +, + + +	±	1.82
566	0.58	3:52	S	+ +, + + +	+	+ +, + + +	+ +, + + +	o	1.46
579	0.67	4:33	S	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	2.24
440	0.45	5:07	S	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	1.89
530	0.64	5:31	S	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	2.80
043	0.37	6:18	D	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	o	3.47
443	0.76	7:32	S	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	2.69
447	0.76	8:17	D	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	2.10
550	0.60	8:35	S	+ +, + + +	+ +, + + +	+ +, + + +	+ +, + + +	Dil, o	3.52

* CG = phosgene. Total theoretical time of exposure = 30 min.

† Beginning "bronchopneumonia" suggested by leukocytic invasion.

‡ Dilated.

TABLE II
Evaluation* of Acute Pathologic Changes in the Lungs of Dogs Exposed to a High Concentration of Phosgene (L.D.₅₀ approx.) by the "Push-Pull" Technic

Dog no.	Conc. of CG† (mg./L.)	Time after "CG on" (hours)	Sacrificed (S) or died (D)	Emphysema	Congestion of lung	Alveolar edema	Mucosa of bronchioles, swelling, sloughing, and/or plugging	Bronchiolar constriction	Lung/body weight (X 100)
815	2.98	0:08	S	++	±	○	○	±	1.04
795	3.30	0:08	S	++	±	○	○	±	1.30
807	3.33	0:20	S	++	±	○	○	±	1.19
819	2.95	0:31	S	++	○	○	○	±	0.92
817	2.98	0:33	S	++	+	○	○	±	1.12
818	2.95	1:01	S	++	++	○	+	±	0.97
816	2.98	1:04	S	++	++	○	++	±	1.06
808	3.33	1:42	S	++	+	○	+	±	1.18
796	3.30	2:04	S	++	+	○	++	±	1.51
820	2.95	4:09	S	++	+	+	++	±	1.82
849	3.33	4:10	S	++	++	++	++	±	2.50
797	3.30	4:20	D	++	++	++	++	Di§	4.65
390	3.55	5:19	D	++	++	++	++	Di	2.50
287	3.31	6:14	D	++	++	++	++	Di	5.91
243	3.22	6:20	D	++	++	++	++	Di	2.92
279	3.22	7:00	D	++	++	++	++	Di	4.26
254	3.25	7:05	D	++	++	++	++	Di	4.48
		8:54	D	++	++	++	++	Di	2.82

* By R. H. only.
 † Time of exposure = 3 min.
 ‡ Beginning "bronchopneumonia" suggested by leukocytic invasion.
 § Dilated.

tinuous and ends either in death or in repair and survival. These three artificial divisions are, chronologically:

1. The incipient phase which extends from gassing up to 2 to 6 hours.
2. The critical phase in which the majority of deaths occur; in survivors this phase ends about 3 days after exposure.
3. The regressive and reparative phase which extends from the fourth day onward; the time of completion of repair is uncertain. The residua of phosgene poisoning are regarded as the terminal stage of repair.

The development of the typical lesions from controlled exposure to pure phosgene has been condensed in Tables I through IV. In the tables 0, \pm , +, ++, and +++ are to be read as none, doubtful, mild, moderate, and severe, respectively. Each designation represents the independent evaluation of the sections by two pathologists (D. R. C. and R. C. H., Jr.), and where they disagreed, both evaluations were entered. Agreement is remarkably close considering that each entry is the summed evaluation of all sections of the lung of an animal. "CG" is the convention for phosgene.

The method involves a sampling procedure and is susceptible to all of the errors inherent in sampling a population, since a given section may constitute but a small portion of a lung. This is important since it has been observed that the periphery of the lung may not show the same degree of radio-opacity as the hilar region.¹²

The Incipient Phase of Phosgene Poisoning

The pulmonary changes in the incipient phase are those which precede clinically-evident pulmonary edema. They are emphysema, necrosis and sloughing of bronchiolar mucosa, perivascular and peribronchial edema, congestion, thickening of the alveolar membranes, and perhaps bronchial-bronchiolar constriction.

Emphysema. As indicated in the tables, emphysema was the earliest prominent lesion in animals exposed to potentially lethal doses of phosgene. Tables I and II dealing with dogs gassed by different techniques indicate that this very early, if not immediate, change is not a technical artifact; the data on the other species confirm this. Not only is it probably the earliest anatomic change, but it appears to attain full development prior to the other changes.

Grossly, emphysema appeared as small pale patches on the surfaces of otherwise unaltered lungs in the earliest specimens. Microscopically (Fig. 1), the distribution of emphysema was patchy and lobular. The alveolar septa were extremely thin and at times fragmented, while the

capillaries were thin and relatively bloodless. Small areas of advanced patchy atelectasis, as seen later, were not apparent in this phase.

Bronchiolar Constriction. The criteria adopted for recognition of constriction of the airways were thickening of the musculature and folding and compression of the mucosa, so as to cause obvious narrowing of the lumen (Fig. 2). On this basis constriction was relatively infrequent (Tables I through IV), but when found it was usually restricted to the finer air passages, in particular, the terminal bronchioles. Of the several species, only the guinea-pig showed conspicuous narrowing. In nearly all instances, the constriction was found only in animals sacrificed within 2 hours after gassing; later the bronchioles were dilated rather than constricted (Fig. 3). Thus, in general, bronchiolar constriction, to whatever degree it did occur, was transient and soon supplanted by dilatation.

Necrosis and Sloughing of the Bronchiolar Mucosa. Swelling of the mucosa of the small and medium-sized bronchioles with sloughing of the epithelium to form plugs in the lumina was found in the earliest stages. It was constantly present, although overshadowed by emphysema. The epithelium sloughed in shreds and irregular patches, and some areas which had not sloughed showed signs of incipient necrosis. The slough together with mucus formed more or less solid masses which were mobile, since a mass might be found to plug the lumen of an intact bronchiole (Fig. 4) or an air passage might be free of all mucous membrane. Such lesions were usually confined to bronchioles proximal to the respiratory bronchioles.

The number of plugged air passages varied from section to section and from animal to animal. Correlation of the location of such plugs with emphysematous lobules was not feasible without serial sections and this was not attempted. The sloughs were believed not to be artifacts.

Perivascular and Peribronchial Edema. Lace-like expansions of the connective tissue around the medium and larger blood vessels and air tubes was another constant early change (Fig. 5). These cuffs were formed by distention of the interstices of the connective tissue with a lightly staining eosinophilic material. These lacunoid spaces were distinct from the lymphatics, which were not particularly distended in this phase. The site of origin of this fluid was not detected, but it clearly was not alveolar because the cuffs faded out as the vessels became finer and were found prior to alveolar edema. Causal relations of this extra-alveolar edema with other anatomic changes could not be established.

Congestion and Alveolar Edema. Dilatation and engorgement of

TABLE III
*Evaluation of the Acute Pathologic Changes in the Lungs of Rats after Exposure to
 L.D.₅₀₋₁₀₀ CXT's of Phosgene by the "Push-Pull" Technic*

C-T data	Time after "CG on" (hours)	Sacrificed (S) or died (D)	Emphysema	Congestion of lung	Alveolar edema	Mucosa of bronchioles; swelling, sloughing, and/or plugging	Bronchiolar constriction	Lung/body weight (X 100)
Rat group 38 C=0.30 mg./L. T=13.5 min.	0:16	S	++	o	o	+	o, ±	1.04
	2:13	D	+++	±, ++	±, +	++	o, ±	1.10
	4:13	D	+++	+++	+++	+++	o, ±	3.46
	5:13	D	+++	+++	+++	+++	o	3.28
	9:13	D	+++	+++	+++	+++	o	3.27
Rat group 51 C=0.31 mg./L. T=10.5 min.	0:15	S	+++	o	o	+	o, ±	0.85
	0:25	S	+++	++	+	+	o, ±	0.84
	0:50	S	+++	+++	+	+	o	0.91
	1:10	S	+++	+++	+	+	o	0.73
	1:40	S	+++	+++	o	+	o, ±	0.88
	2:10	S	+++	+++	+++	+++	o, ±	2.11
2:40	S	+++	+++	+++	+++	o	2.11	
5:10	D	+++	+++	+++	+++	o	3.21	
Rat group 58 C=1.21 mg./L. T=3.5 min.	0:06	S	++	o	o	Sw*, +	o, ±	1.10
	0:33	S	++	o	o	Sw, +	o	1.27
	1:33	S	+	o	o	±	o	1.21
	3:03	S	+++	+++	+++	+++	o	1.00
4:33	D	+++	+++	+++	+++	o	3.58	
Rat group 59 C=0.082 mg./L. T=57 min.	1:01	S	+++	+	o	+	o, ±	1.01
	1:12	S	+++	+	o	+	o	1.40
	1:27	S	+++	+	o	+	o	1.03
	1:57	S	+++	+	+	+	o	1.18
	2:27	S	+++	+	+	+	o	1.26
	2:57	S	+++	+++	++	+++	o	1.46
	3:57	S	+++	+++	+++	+++	o	1.63
	4:57	S	+++	+++	+++	+++	o	2.59
	5:57	S	+++	+++	+++	+++	o	2.12
	7:00-12:00	D	+++	+++	+++	+++	o	3.45

* Sw = Swelling only.
 † Beginning "bronchopneumonia" suggested by leukocytic invasion.

TABLE IV
*Evaluation of Acute Pathologic Changes in the Lungs of Cats, Rabbits, and Guinea-Pigs
 after Exposure to an L.D.₅₀ of Phosgene*

C-T data	Time after "CG on" (hours)	Sacrificed (S) or died (D)	Emphysema	Congestion of lung	Alveolar edema	Mucosa of bronchioles; swelling, sloughing, and/or plugging	Bronchiolar constriction	Lung/body weight (X 100)
Cats C=0.20 mg./L. T=13 min. "Push-pull" technic	0:16	S	+	o	o	o, +	o, +	0.74
	0:43	S	++	o, +	o	o, ++	o, +	0.99
	1:13	S	+++	o, ++	+	o, +++	+	1.17
	2:13	S	++++	+, ++	++	+, +++	o	1.25
	4:13	S	++++	+, ++	+++	+, +++	o	2.92
	6:28	S	++++	+, ++	+++	+, +++	o	3.35
8:13	D	++++	+, ++	+++	+++	+	3.93	
Rabbits C=0.62 mg./L. T=35 min. "Rise-fall" technic	0:40	S	o	+	o	o	o	0.57
	0:55	S	+	+	o	+	o	0.69
	1:03	S	++	+	+	o, +	o, ±	0.75
	1:35	S	+++	+	++	o, ++	o	1.46
	1:46	D	++++	+	+++	+, ++	o	1.76
	2:06	D	++++	+	+++	+, ++	o	1.56
2:46	D	++++	+	+++	+, ++	o	1.07	
Guinea-pigs C=0.34 mg./L. T=9 min. "Push-pull" technic	0:12	S	o	o	o	o	o, ±	0.78
	0:24	S	+	o, +	o	o	+	0.81
	0:39	S	+	o, ++	+	Sw†	+	1.18
	1:09	S	++	o, +	o, +	Sw, +	+	1.13
	2:09	S	+++	+	+	Sw, ++	+	1.54
	3:09	S	++++	+	+	+, ++	o, ±	3.22
3:39	S	++++	+	+	+, ++	o	3.47	
4:24	S	++++	+	+	+, ++	o	2.92	

* These two rabbits by "push-pull" technic; C X T's were the same.
 † Sw = Swelling most prominent.
 ‡ Beginning "bronchopneumonia" as suggested by leukocytic invasion.

blood vessels became distinguishable first in the capillaries of the alveolar membranes and perhaps the smaller veins. This congestion coincided with, or possibly preceded, the alveolar edema; but definitely followed the changes mentioned above.

Alveolar edema was detected first as a thickening of the septal strands; eosinophilic material in the alveoli was found later. Apparently the fluid distending the septal strands escaped into the alveoli. The tabulated data make it clear that alveolar edema is the last to appear of the several changes of phosgene poisoning.

The lung $\times 100$ /body weight ratios in the tables are customarily employed as measures of the degree of congestion and edema; they indicate here that edema fluid does not accumulate in appreciable amounts until after the other elements of the "typical" phosgene lung are well developed. The upper limit of normal lung $\times 100$ /body weight ratios for dogs is approximately 1.25; for other species, 1.0 or less.

Neither bronchiolar plugs nor emphysema could be related spatially with alveolar edema and all lesions in this phase tended to be without preferential localization. There is no way of deciding whether the fluid in a given alveolus arose from surrounding or more distant capillaries.

In animals poisoned by smaller doses of phosgene, identical lesions developed in the order outlined, with equally spotty distribution. The rate of development, however, was appreciably slower and the reaction appeared less intense.

No lesions were found in extrapulmonary tissues in this incipient phase.

Histologic evidence of damage to the capillary endothelial cells was never found in these sections (compare Daly *et al.*¹³).

The Critical Phase of Phosgene Poisoning

The anatomic picture in the critical phase is the well known "phosgene-poisoned lung." Therefore, the points noted below are only those which warrant emphasis.

In animals which died during the first 48 hours after exposure, the trachea was usually filled with froth, while the bronchi contained mainly fluid; this finding is related to the abrupt release of as much as 500 cc. of fluid via the trachea immediately before death. The mucosal surfaces of the trachea and larger bronchi were usually smooth, and pale or slightly pink. Rarely was there free fluid in the pleural cavities.

The lungs were large and coarsely mottled with alternating dark red and pale yellowish patches of doughy consistency and only slightly crepitant. The sectioned lung presented a smooth wet surface from

which fluid escaped freely; the contrasting surface patches extended throughout the lung.

The heart was usually dilated, especially the right side, but other than an occasional subendocardial or subepicardial hemorrhage no gross abnormalities were encountered. The liver, spleen, kidneys, intestines, and bone marrow were dusky with congestion. The adrenal glands occasionally showed small hemorrhages in the medulla or at the corticomedullary junction. At times the brain was somewhat hyperemic and edematous; other lesions were not found. Essentially, therefore, the extrapulmonary organs showed congestion with occasional, irregularly distributed focal hemorrhages.

The microscopic pulmonary lesions of this phase are shown in the last few entries of Tables I through IV. The lesions were identical, regardless of species and the varying conditions of exposure, and appear to represent merely full development of the earlier changes. The pathologic evaluation did not always agree completely with the clinical state, since in addition to two instances in the tables, many animals sacrificed before being *in extremis* showed lesions as fully developed as those in animals which had died.

Most alveoli were filled with an eosinophilic granular material presumed to be from the fluid in the unfixed lung (Fig. 6). This was found in alveoli of the usual size, in emphysematously distended alveoli, and in atelectatic areas. The fluid contained fibrin, sometimes in large amounts, which tended to be condensed along the alveolar walls. The alveolar capillaries were dilated and engorged except in the emphysematous areas where they were relatively empty. Small hemorrhages were found but were never a conspicuous feature.

Necrosis and sloughing of the bronchiolar epithelium were now obvious and the bronchioles were clearly dilated (Fig. 7). The mucous membrane of the larger air passages and trachea was relatively intact, but covered with mucus and scattered polymorphonuclear leukocytes. More intense inflammatory lesions were seen in the bronchioles which contained necrotic epithelium, plugs of necrotic tissue, and exuded cells; such bronchioles sometimes formed the center of an inflammatory focus extending into the adjoining parenchyma (Fig. 8). This early pneumonia (pneumonitis) was variable in extent, sometimes being absent. Generally it was focal, but occasionally it was diffuse with scattered cellular and fibrinous exudate.

In animals which survived until the third day, regression of the edema and congestion appeared to have begun, while the cellular exudate frequently increased in severity and extent. In addition to the types of cells previously found, mononuclear phagocytes began to

be prominent in the alveoli. The pneumonia at this time usually had assumed a more or less lobular pattern and was termed bronchopneumonia. The high lung/body weight ratios were maintained.

Microscopic examination of organs other than the lung confirmed the gross finding of congestion and showed occasional tiny hemorrhages. In every instance the lesions were of the types customarily associated with circulatory derangement.

In Table V are summarized the terminal findings in dogs poisoned by oxygen, vagotomized under local anesthesia, or subjected to drugs or vagotomy before or after gassing. These data show first that the phosgene picture is not specific and secondarily that procedures designed to interrupt or facilitate bronchomotor reflexes fail to influence the pathologic changes.

The Regressive and Reparative Phase of Phosgene Poisoning

Data concerning the regressive and reparative phase were obtained from 121 dogs dying or sacrificed between 4 and 138 days after exposure to doses of phosgene which had killed initially between 70 and 99 per cent of the groups they survived. The majority had served as controls in various experiments but some had been used for innocuous therapeutic trials. The dogs were kept in individual indoor kennels on a diet of Purina "checkers," supplemented by cooked horse meat. Although this diet proved to be adequate for normal dogs, inanition was a frequent finding in deaths during the first month after exposure.

Originally an attempt was made to distinguish a regressive stage from a reparative stage, but this was abandoned when it became apparent that: (a) The two processes overlapped not only from animal to animal, but also within various areas of the lungs of one animal. (b) Dogs which made good clinical recoveries showed earlier predominance of reparative processes and more rapid regression of edema, and vice versa. (c) The pneumonic process which had begun in the critical phase varied in degree and persistence; often it obscured the regressive process and probably interfered with repair. In some instances the pneumonic changes were so severe as to appear to be the immediate cause of death. By the third week after exposure, however, the reparative processes predominated, because animals showing little tendency toward repair had died.

Typically, the regressive changes consisted of a gradual diminution of the amount of fluid in the alveoli and reduction of congestion, so that by the end of 2 weeks after gassing the lungs failed to drip fluid on section. Microscopically, the eosinophilic alveolar material took a deeper stain and by the end of the third week had practically disappeared. The trachea and bronchi appeared normal; the mucosa lining

TABLE V
Evaluation of Pathologic Changes in the Lungs of Dogs Subjected to Various Procedures

Dog no.	C.T. and technic (mg. per min. per L.)	Procedure	Sacrificed (S) or died (D)	Time after "CG on" (hours)	Emphysema	Congestion of lung	Alveolar edema	Mucosa of bronchioles: swelling, sloughing, and/or plugging	Bronchiolar constriction	Lung/body weight (X 100)
61	14.6	Bilat. vagotomy* before CG	D	2:35	+	+	+	+	o, ±	3.98
2	14.6	Bilat. vagotomy* before CG	D	4:35	+	+	+	+	o	3.95
42	11.0	Bilat. vagotomy* before CG	D	7:13	+	+	+	+	o	3.47
164	17.9	Bilat. vagotomy* after CG	D	4:40	+	+	+	+	o	2.06
101	17.9	Bilat. vagotomy* after CG	D	5:50	+	+	+	+	o	4.23
44	None	Bilat. vagotomy only	D	23†	+	+	+	+	o	3.10
45	None	Bilat. vagotomy only	D	23†	+	+	+	+	o	3.05
50	None	Bilat. vagotomy only	D	12 to 18†	+	+	+	+	o	3.41
51	None	Bilat. vagotomy only	D	30 to 36†	+	+	+	+	o	3.04
442	18.6	Atropinet before CG	D	4:30	+	+	+	+	o	3.14
643	14.5	Atropinet after CG	S	4:00	+	+	+	+	o	3.10
798	19.4	Atropinet after CG	D	7:08	+	+	+	+	o	5.02
000	13.7	Eserinet before and after CG	D	6:46	+	+	+	+	o	2.75
909	11.7	Ergotominet before CG	S	4:14	+	+	+	+	o	2.34
913	11.7	Ergotominet after CG	S	4:01	+	+	+	+	o	1.50
620	None	95 + % O ₂ for 48:30 hrs.	D		+	+	+	+	o	4.09
623	None	95 + % O ₂ for 47:00 hrs.	D		+	+	+	+	o	3.95
622	None	95 + % O ₂ for 48:30 hrs.	D		+	+	+	+	o	3.50
621	None	95 + % O ₂ for 48:30 hrs.	S		+	+	+	+	Dilated	1.53

* Performed under procaine anesthesia.
 † Drug in dose sufficient to exhibit action.
 ‡ Time of survival after operation: not gassed.
 § Multiple hemorrhages in alveoli.
 || Beginning "bronchopneumonia," suggested by leukocytic invasion.

the trachea and bronchi either had sustained no damage, or had regenerated perfectly.

Leukocytic infiltration, or bronchopneumonia, generally became more dense during the first week and changed into foci of consolidation. This reached its peak about 10 to 14 days after exposure in sacrificed animals which probably would have recovered; in those which were obviously moribund the infiltration, in general, was heavier and confluent.

In the gross specimen, elevated, irregular, pale gray patches studded the pleural and cut surfaces of the lung, being more numerous on the former. Beads of purulent material could be expressed from these foci; larger patches had the turgor of early abscesses. Microscopically, the lesions, composed of polymorphonuclear leukocytes, lymphocytes, erythrocytes, and fibrin, resembled a purulent bronchopneumonia (Fig. 9). Generally these lesions were situated in connection with a fine bronchiole, the process spreading distally or laterally to involve varying areas of alveolar tissue. Destruction of alveolar partitions was apparent at times, while in other instances the alveolar walls were infiltrated with monocytes and fibroblasts which extended into the alveolar exudate.

The lung/body weight ratios continued high during this pneumonic process. A return toward normal ratios was associated with resolution of the pneumonia or with minimal infiltration. In other areas of the lung, fibroblastic proliferation was active, forming organized masses which frequently obstructed the bronchioles; sometimes this granulation tissue was found to extend along the airways into alveoli (Fig. 10). During this period the abdominal viscera remained somewhat congested and scattered petechial hemorrhages were still to be found.

It was not possible to establish a relationship between the foci of pneumonia and the early mucosal lesions, although both were essentially bronchiolar. The stained sections of the foci failed to disclose bacteria in the exudate or leukocytes; bacteriologic studies were not carried out.

The fibroblastic proliferation noted above appears to be the means of repair of the alveolar structure since in animals which survived for 1 month after gassing, emphysema, atelectasis, and fibrous scars dominated the picture (Fig. 11). The pneumonic process was still to be found, but it became less and less extensive and active with the passage of time. While the pneumonic foci appeared to heal by scar formation, fibroblastic proliferation also took place in areas free of pneumonia. The bronchiolar epithelium commonly regenerated as cuboid or elongated cells (Fig. 12).

Grossly, the lungs of an animal about 60 days after exposure showed

only emphysema. They offered resistance to sectioning which may be ascribed to condensed fibrous tissue. This scarring, together with scattered emphysema and foci of atelectasis, was seen constantly in the sections. Occasional findings were bronchiectasis, especially in the smaller bronchioles, chronic bronchitis, and tiny pulmonary abscesses.

Various combinations of these lesions persisted in dogs sacrificed more than 6 months after gassing and hence may be regarded as permanent residua of phosgene poisoning. Except for moderate emphysema, scars, and occasional small patches of atelectasis, the lungs were grossly normal. The pleural and bronchial surfaces were smooth. In the sections emphysema and fibrous scarring of the bronchioles were present constantly; small, dense nodules of scar tissue were seen less frequently. Epithelial cells, arranged in single, cuboid, or truly cylindrical layers, had regenerated over or through such scar tissue. Some bronchioles were entirely obliterated by scar tissue, and many alveolar walls were thickened by fibrous connective tissue. Occasionally, small areas of atelectasis containing a few lymphocytes were encountered. The most prominent constant change was distention and fragmentation of alveoli into irregularly enlarged chambers; this may be termed chronic lobular emphysema. It is important, however, that even in lungs with the most extensive residua, there were large amounts of apparently normal alveolar tissue.

SUMMARY OF THE ANATOMIC CHANGES FOLLOWING EXPOSURE TO PHOSGENE

Emphysema, lobular in distribution, was found constantly in animals sacrificed at once after exposure to doses which killed between 70 to 99 per cent of the animals. An equally constant, but less obvious concurrent finding was sloughing of the bronchiolar mucosa with formation of intraluminal plugs. Shortly thereafter there developed perivascular and peribronchial edema which preceded the alveolar edema. Bronchiolar constriction was found regularly in only one of the several species examined and even in this species constriction was soon supplanted by dilatation.

These changes gradually but steadily progressed, producing finally the typical lung of phosgene poisoning. The alveolar edema contained a high content of protein which by analysis was approximately equal to plasma protein levels.^{12,14} Leukocytic infiltration, particularly in the bronchiolar regions, began during the early part of this critical phase and became more prominent the longer the animal survived. Frequently, during regression of the congestion and edema, the infiltration gave rise to a picture almost identical with bronchopneumonia.

In animals with the least pneumonitis, repair of the damage was

most rapid and widespread, but even where infiltration was so extensive as to be considered the immediate cause of death, some evidence of repair was found. Repair consisted of fibroblastic ingrowth which finally gave rise to scar tissue; the process apparently proceeded regardless of complicating pneumonitis. The bronchiolar surfaces were relined by cuboid or cylindrical epithelium.

The lungs of clinically recovered animals showed residua consisting chiefly of foci of scar tissue and lobular emphysema, but tiny patches of atelectasis and cellular infiltration occasionally were still present.

Changes in tissues other than the lungs resembled closely those seen in cardiovascular disease, and had no unique characteristics. Petechial hemorrhages were found frequently but were inconstant in distribution and extent. Evidence of primary damage to the heart and central nervous system was lacking.

DISCUSSION

Since there are no data on the lesions in man during the incipient or developmental phase, it is impossible to compare these changes in man and animals. Tentatively, it may be assumed that man would respond like several other species and show a comparable sequence of lesions. The findings reported above are in essential agreement with three recent experimental studies,¹⁵⁻¹⁷ although differences in emphasis on predominance and rate of development of the various lesions are to be found. These differences seem minor, however, in view of variations in histologic technic (dissecting microscope, vital staining) and variation in gassing methods and concentrations. The older reports on animals sacrificed sporadically in this phase provide inadequate information.^{2,11,18}

The findings in man during the critical phase are in general similar to those in experimental animals, but certain inconsistencies warrant closer comparison. In the Hamburg disaster,¹⁹ in which pure phosgene escaped, the pulmonary findings were almost identical with those described in our animals, although the cellular inflammatory lesions appeared earlier and the fibrin later than is usual in experimental poisoning. Outside the lung, however, there were found lesions which seldom or never have been recorded in animals: Focal necrosis of the adrenals, thrombosis of large vessels, subarachnoid hemorrhages, cellular degeneration of the gray matter and a generalized hyperemia, said to extend only to the white matter. Other observers have reported "ring-hemorrhages" in the brain.^{6,20,21} In contrast, the autopsy reports on two men who died 19 and 22 hours after accidental exposure²² stressed edema, emphysema, cardiac dilatation, and necrosis with

sloughing of the laryngeal, tracheal, and bronchial mucosa. This extrapulmonary sloughing suggests exposure to extraordinarily high concentrations of phosgene, but death was not sufficiently prompt to bear this out.

The autopsy reports of 105 soldiers of World War I,⁶ who were reputedly gassed with phosgene, contain records of pleural effusion; this also has been recorded by others.^{23,24} Effusion was noted rarely in dogs and cats, but it was not uncommon in rodents when autopsy was delayed. Other frequent findings were subendocardial and subpericardial hemorrhages, thrombosis of the pulmonary vessels with thrombi attached to the cardiac valves, and edema and extreme congestion of the brain. Hemorrhages in various parts of the central nervous system were seen only in men who died 36 hours or more after exposure. "Bronchopneumonia" was stated to have been present as early as 12 hours after exposure.⁶

These examples are representative of the pathologic details in the literature on phosgene poisoning in man in the acute stage.^{1,4,5,14-21,23-28} In general, the pulmonary lesions do not differ essentially from those recorded on animals poisoned under controlled conditions;^{2,11,17,18,29,30} the variations in detail and emphasis are probably attributable in large part to the factors outlined in the introduction. The extrapulmonary lesions, with the exception of congestion, seem much more prominent in man than in animals, but it is questionable whether this constitutes a real difference in the reaction to phosgene. Because the extrapulmonary lesions resemble those found in death from circulatory failure, and since circulatory insufficiency from blood volume loss is present in phosgene poisoning, it is illogical to postulate the formation *in vivo* of specific humoral toxic agents which might cause these lesions.^{6,17,20}

Records of thrombosis or other obstructions to the pulmonary circulation in both man and animals in the older literature^{6,11,31,32} have no counterpart in the data reported here and the reason for this discrepancy is not known. In any event, it is probable that pulmonary obstruction has little if any significance in the pathogenesis of this edema, since, in addition to the negative evidence, we have found that completely heparinized animals follow the typical phosgene course, with the same sequence of changes.¹²

Autopsy data on man in the regressive and reparative phase are fragmentary and described mainly in terms of "bronchopneumonia."^{6,11,33} In a man who died 11½ days after exposure¹⁹ the combination of fibroblastic proliferation, macrophages in the alveoli, chronic bronchitis and bronchiectasis, and residual edema is almost

identical with that in dogs which died at a comparable interval after gassing. Also the findings in a man who died 3 months after exposure³⁴ are very similar to those in dogs dying about 21 days after exposure. Thus it is reasonable to assume that the reparative processes in human survivors take the same course that has been described for dogs. Evidence corroborating this view is the pulmonary fibrosis, chronic bronchial inflammation, and emphysema detected by x-ray and physical examination.^{23,35-38}

It will be noted that the concentration of phosgene may be varied reciprocally with duration of exposure by a factor of 10, without detectably affecting the pathologic and physiologic findings. The data bear out the assumptions on which the dosage system is based, which in turn is the basis for a systematic experimental study of phosgene poisoning. The range of reciprocity is probably much greater than 10.

According to the above data, certain physiologic and clinical concepts of phosgene poisoning need revision. The "latent" period of phosgene poisoning, the more or less asymptomatic interval between exposure and the onset of detectable edema, is clearly a fallacy since the anatomic pulmonary damage, begun during gassing, steadily progresses. The clinical problem in phosgene poisoning (and similar toxic agents) must lie in the application of measures designed to minimize its progress. Clearly the time for treatment is before, not after, edema has appeared, but because such therapy is unknown, one is confined to providing whatever symptomatic relief is indicated.

We never have predicted successfully the probable outcome from clinical observations alone. Dogs poisoned by doses of phosgene killing 70 to 99 per cent of the group immediately showed bradycardia, a general lassitude, motor activity of the colon and bladder, a flared chest, and a rapid shallow type of restricted breathing; there was no relation between the severity of these signs and survival. Later when râles could be heard, the tachycardia, leaden cyanosis, asthmatoïd breathing, and prostration were merely confirmatory evidence of the degree of involvement of the lungs. However, because the edema fluid is practically plasma, it was possible to estimate the rate of development and ultimate degree of edema by frequent hematocrit determinations. In general it was observed that the slower the onset and rate of hemoconcentration, or the longer the interval between gassing and clinically detectable edema, the better was the prognosis.

The question of bronchoconstriction, or bronchiolar constriction, in phosgene poisoning needs re-examination. In the past, assumption of this condition was based on subjective substernal constriction and similarity of the breathing to that in asthma.⁵ Histologic evidence support-

ing this^{1,11} was not qualified with regard to the fact that the fixed tissue might not represent the living state. The present data, thus qualified, suggest that constriction, if present, is transitory and not significant in the critical phase of poisoning when the breathing is most analogous to that of asthma. It may be important that in the one species, the guinea-pig, in which histologic bronchoconstriction was seen, the bronchial smooth muscle is arranged like that in man.³⁹ Experiments on dogs and rats¹² have led to the conclusion that the asthmatoïd breathing is not of constrictor origin, since: (a) In hot weather panting may alternate with periods of asthmatoïd breathing. (b) Administration of CO₂ immediately converts the breathing into free, rapid, deep movements. (c) Pressure on the larynx removes the expiratory grunt without shortening the expiratory effort. (d) None of the sympathomimetic, parasympatholytic, or myotropic antispasmodic drugs which are effective in asthma exerted more than a transitory effect on breathing. Unequivocal evidence of relaxation of bronchospasm was not seen. Eserine did not exaggerate the asthmatoïd breathing, and vagotomy before or after gassing resulted in breathing characteristic of the un-gassed animal, slow and deep with prolonged inspiration. Drugs which act on the heart peripherally (and vagotomy) readily modified the reflex bradycardia without materially changing the breathing. The data in Table V show that the characteristic findings were unchanged by the two procedures most likely to accent or minimize reflex bronchoconstriction. The evidence obtained from gassed lung preparations designed to demonstrate bronchoconstriction is equivocal.^{2,13,15}

Nevertheless, evidence of subnormal ventilation is found in the transitory arterial anoxemia and the CO₂ retention and respiratory acidosis seen during the incipient phase.^{12,16} Two possible causes of this, other than bronchoconstriction, are (a) obstruction of the airways by the plugs of sloughed epithelium and (b) edema of the remaining bronchiolar epithelium, which is supplied by the bronchial artery, in connection with which the earliest edema was noted. The intrabronchial emboli have been observed before^{11,18} but were not assigned a significant rôle. Their occurrence, synchronous with the emphysema, suggests a causal relation which has not been demonstrated. In the gassed dog-lung preparation desquamation of the bronchial mucosa has been observed, although bronchial emboli were not described.¹³ Experiments with balloon models indicated that the alveoli supplied by unblocked bronchioles are those which would stretch and rupture under negative pressure.¹² It is tempting to postulate that sloughing of the bronchiolar mucous membrane with plugging of the lumen

causes the unbarricaded alveoli to rupture as they follow the expansion of the chest, which is induced during gassing and may be maintained reflexly. When sufficient edema is present another form of bronchial obstruction probably develops which nullifies all inhalational therapy. As the edema fluid moves about via the bronchial system it mixes with air to form a moderately stiff foam which produces a water lock proximal to otherwise functional alveoli.

In the healing process some bronchial plugs are recanalized, but if they should be replaced by scar tissue the result would be atelectasis, as was observed. The emphysema seems to persist much as it first appeared and it is doubtful that such areas are functionally active. This "vesicular" emphysema has been described as a common aftermath of poisoning by any of the pulmonary irritant gases and it has been implicated in the etiology of the "effort syndrome" found in gas casualties.^{28,37,40-42} Psychic factors have been assigned the major rôle in this condition⁴³ but abnormalities of pulmonary ventilation recently have been detected.⁴⁴

It is improbable that the plugs and emphysema bear a causal relation to the edema, chiefly because in exposure to very low phosgene concentrations edema appears without emphysema or significant bronchiolar changes.^{3,45} The hemodynamics of the pulmonary circulation are not grossly disturbed in phosgene poisoning^{46,47} and so it must be assumed that the capillaries are damaged functionally by the gas. It is obvious, therefore, that this study has merely reaffirmed that available histologic methods are inadequate to demonstrate the abnormal functional state of the capillary endothelium. Capillary congestion does precede the alveolar edema, but there is no reason to assume that congestion causes loss of normal permeability. Because the hemoconcentration was arrested and reversed in dogs 15 to 35 hours after exposure, it is probable that restoration of normal capillary permeability began in that period.

The majority of dogs poisoned with the doses used in these experiments died of respiratory failure before or near the peak of hemoconcentration. The type of death indicates functional disintegration of the central nervous system, prior to that of other essential organs such as the heart. Since movement of plasma into the alveoli is responsible for both the major defects, the anoxic anoxia and the shock-like hemodynamics, it seems beside the point to insist that one or the other of these two secondary features is the more lethal. Moreover, both these defects set up vicious cycles which are interlocking and supplementary. It is of interest, however, that the rabbit, a "wet" animal, dies of

typical pulmonary edema without significant hemoconcentration, and therefore without stagnant anoxia.^{12,14}

The resorption of edema fluid appears to take place slowly, presumably because of its high protein content.⁴⁸⁻⁵⁰ Some fluid is removed by the lymphatics^{14,39,51} but the chief mode of regression of the edema seems to be degradation of the protein into diffusible molecules by the macrophages and leukocytes, which were observed to migrate in. It is still not clear whether this inflammatory reaction is of bacterial origin or is a further manifestation of the original chemical damage by phosgene. The different susceptibility of the lungs of dog and man to bacterial invasion warrants caution in extending these interpretations of the inflammatory reaction to man.

In addition to failure of pulmonary function due to residual edema and infiltration, death in the early reparative phase may result from functional failure of key organs such as the kidney, which have been devitalized by the previous prolonged anoxia.^{52,53} A few dogs in which death was delayed for 3 or 4 weeks after exposure showed inanition clinically in conjunction with an apparently more gradual progression of the inflammatory response.

This healing process seems to consist of regeneration of a more or less normal epithelial layer and scar tissue formation, regardless of whether the initial damage had progressed into a focal or confluent inflammatory reaction. This method of healing and the residua are common to lungs poisoned by phosgene, chlorpicrin, lewisite, and mustard vapor.^{17,54,56} Evidence of a type reaction on the part of the lung is seen also in the fact that the acute lesions of phosgene poisoning are identical in many respects with the acute lung damage produced by exposure to chlorine and chlorpicrin,¹¹ nitric oxides,^{55,56} ketene,¹⁵ high oxygen tensions, and following deep x-ray therapy,⁵⁷ bilateral vagotomy,⁵⁸ anaphylaxis in certain species,⁵⁹ and the hot gasses of the Cocoanut Grove fire.⁶⁰

SUMMARY

1. The pathologic anatomy of dogs and other species was investigated after experimental exposure to median doses of phosgene. Particular attention was placed on the sequence of development of the lesions and on the anatomic changes found in animals that survived the acute or critical phase in which the majority died.

2. Extensive emphysema, sloughing of the bronchiolar mucosa, and questionable bronchiolar constriction were found at once after gassing. Peribronchial edema, pulmonary congestion, and alveolar edema de-

veloped subsequently and in that order. The rapidity of development and extensiveness of these lesions were roughly proportional to the severity of the exposure.

3. Recovery from the massively edematous lung of "typical" phosgene poisoning was found to be primarily a process of resorption of edema and scarring. A moderate cellular inflammatory reaction accompanied this process, but sometimes it became so excessive as to be indistinguishable from bronchopneumonia.

4. The residua of phosgene poisoning consisted of pulmonary scarring, lobular emphysema, and small, irregular areas of atelectasis and bronchitis.

5. Comparison of the data with the scanty and somewhat unsatisfactory data on man leads to the conclusion that the processes in man and animals appear to be similar.

6. The findings reported here indicate that certain present concepts of phosgene poisoning need revision.

7. Study of the pathologic anatomy of phosgene leads to the view that the response of the lung to phosgene is a type reaction common to several other agents.

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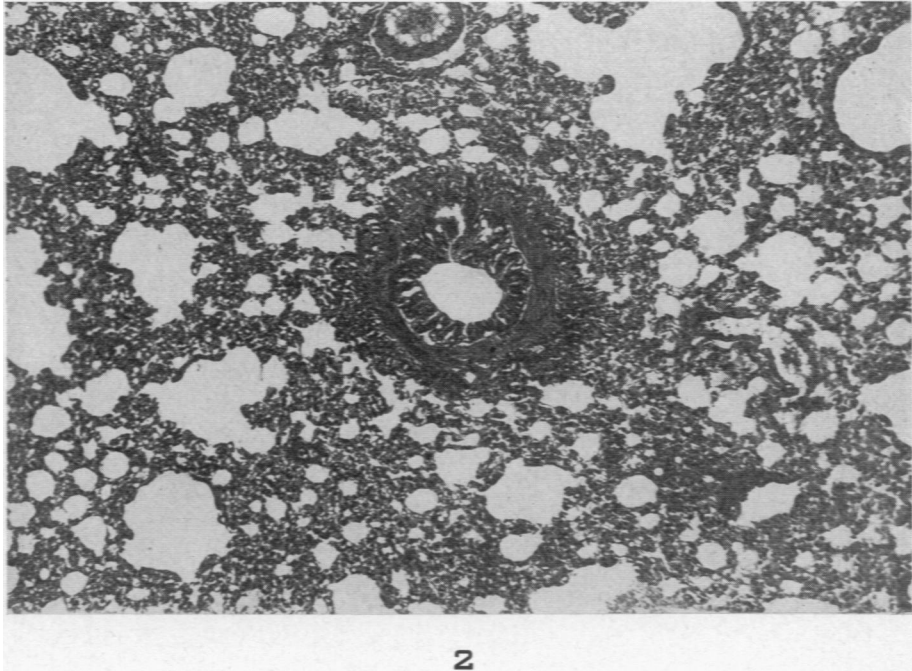
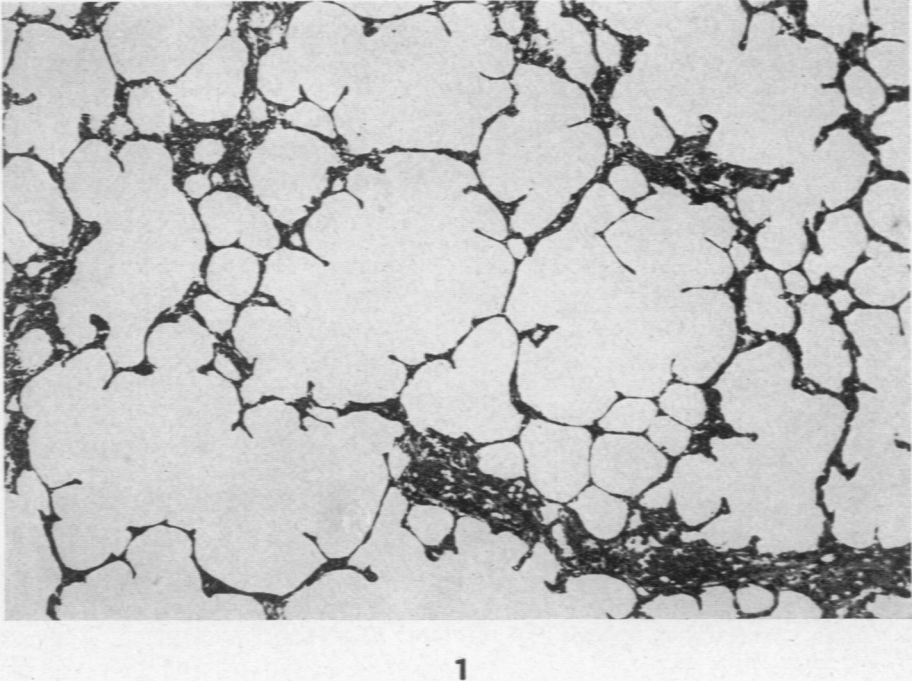
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[Illustrations follow]

DESCRIPTION OF PLATES

PLATE 151

- FIG. 1.** Emphysema in the lung of a dog, showing thinning of the alveolar septa. Animal sacrificed 38 minutes after beginning of exposure to phosgene; Concentration of phosgene (C) = 0.49 mg. per liter of air. Duration of exposure (T) = 30 minutes. $\times 92$.
- FIG. 2.** Bronchiolar constriction. The mucosa is compressed and the lumen is obviously narrowed. Dog sacrificed 8 minutes after beginning of exposure. C = 2.98 mg. per liter; T = 3 minutes. $\times 92$.

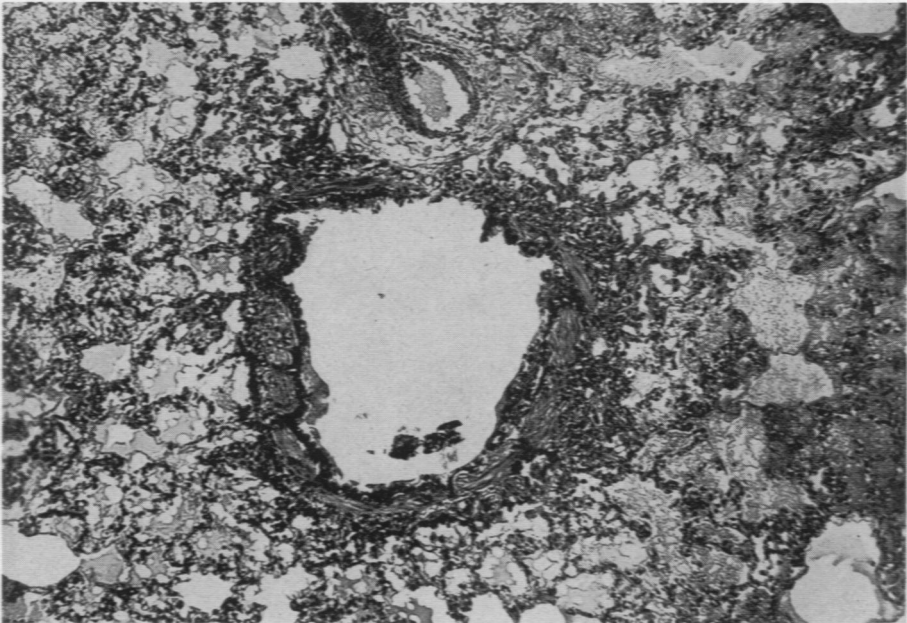


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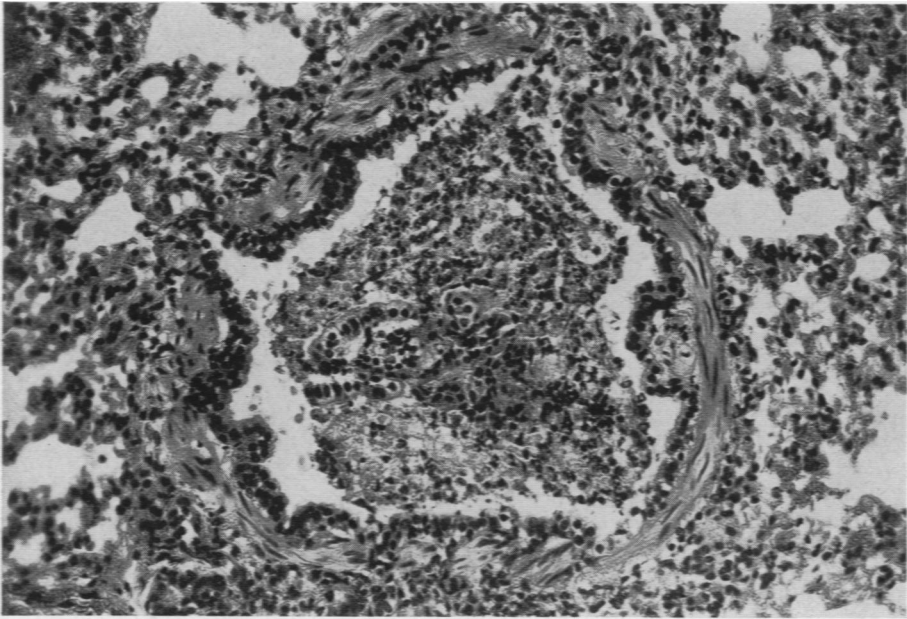
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PLATE 152

- FIG. 3. Widely dilated bronchiole, found in later stage. The mucosa has sloughed away and the surrounding alveoli are edematous. Dog sacrificed 4 hours and 10 minutes after beginning of exposure. C = 3.33 mg. per liter; T = 3 minutes. $\times 92$.
- FIG. 4. Bronchiole containing a plug of desquamated epithelium which has been transported from elsewhere, since the bronchiolar mucosa at this point is still intact. Dog sacrificed 1 hour after beginning of exposure. C = 2.98 mg. per liter; T = 3 minutes. $\times 200$.



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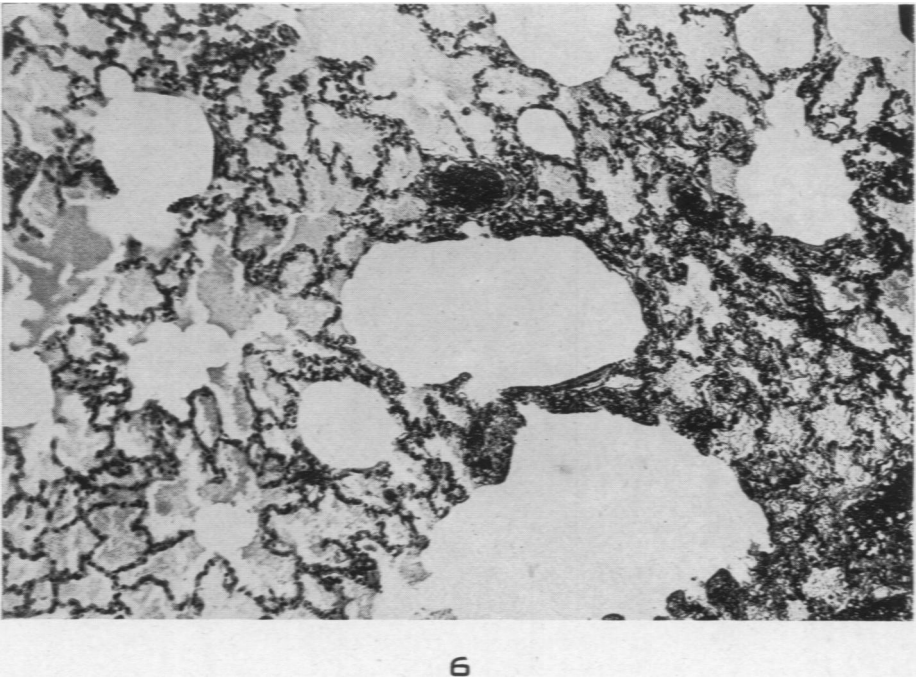
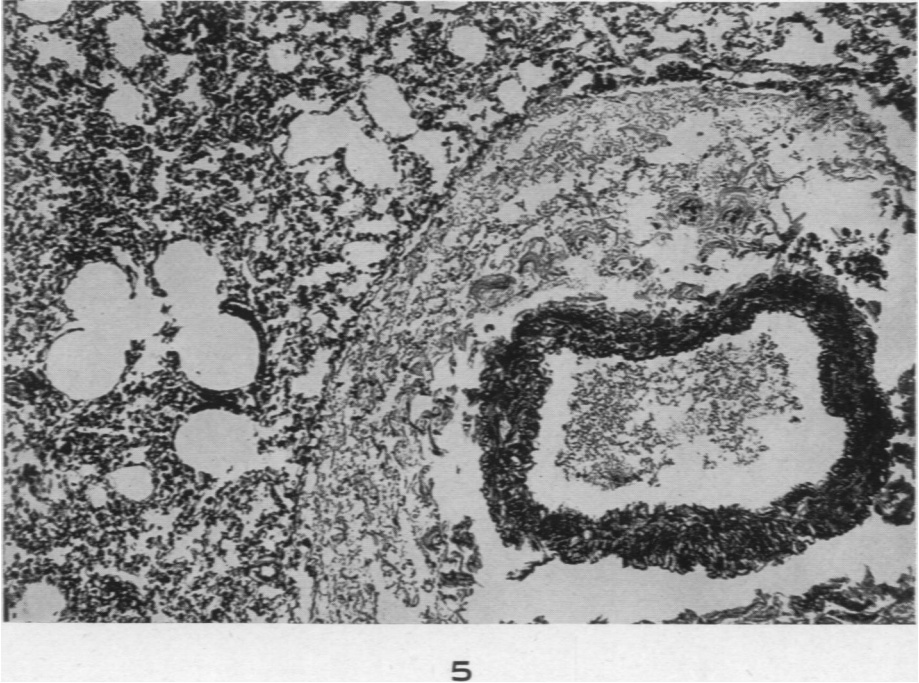
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PLATE 153

FIG. 5. A wide lace-like cuff surrounding a vessel, indicative of perivascular edema. The adjacent alveoli contain no fluid. Dog sacrificed 2 hours and 4 minutes after exposure. C = 3.30 mg. per liter; T = 3 minutes. $\times 20$.

FIG. 6. Typical alveolar edema in the critical phase. Of note is the patchy emphysema. Dog died 7 hours after exposure. C = 3.22 mg. per liter; T = 3½ minutes. $\times 92$.



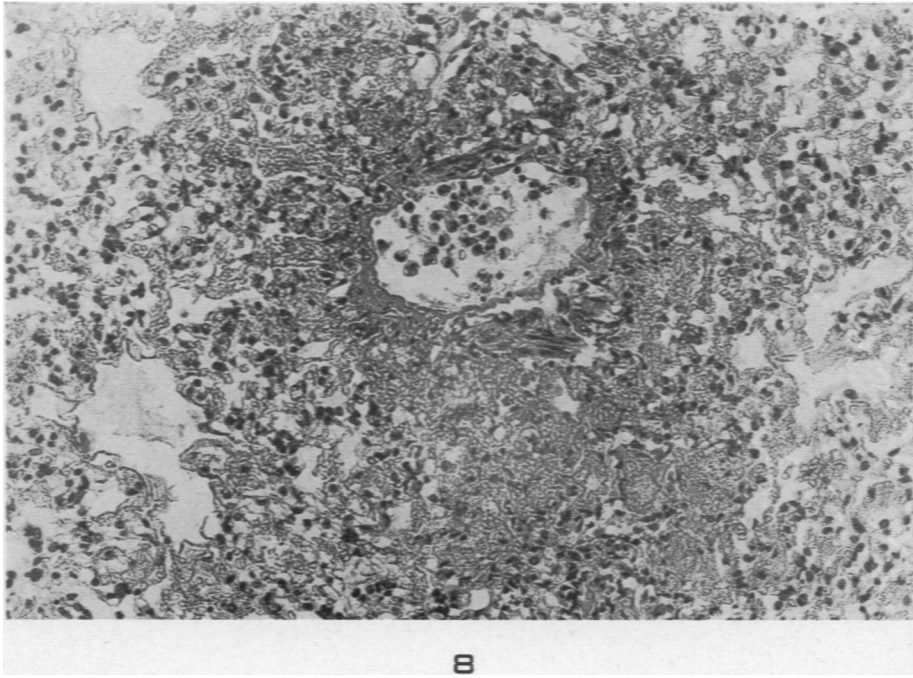
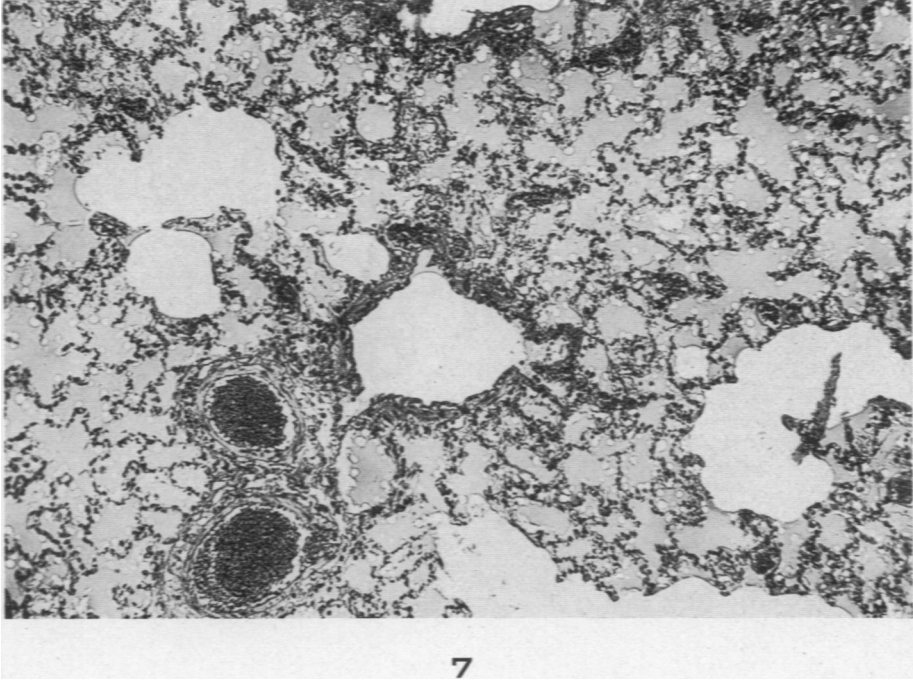
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PLATE 154

FIG. 7. A widely dilated bronchus from which the mucosa has sloughed, together with alveolar edema and emphysema, in the critical phase of phosgene poisoning. Dog died 8 hours and 17 minutes after exposure. C = 0.759 mg. per liter; T = 30 minutes. $\times 92$.

FIG. 8. A denuded bronchiole containing polymorphonuclear leukocytes which forms the center of an inflammatory focus extending into the surrounding alveoli. The exudate consists of fibrin and scattered polymorphonuclear leukocytes and lymphocytes. Dog died 1 2½ hours after exposure. C = 0.263 mg. per liter; T = 30 minutes. $\times 180$.



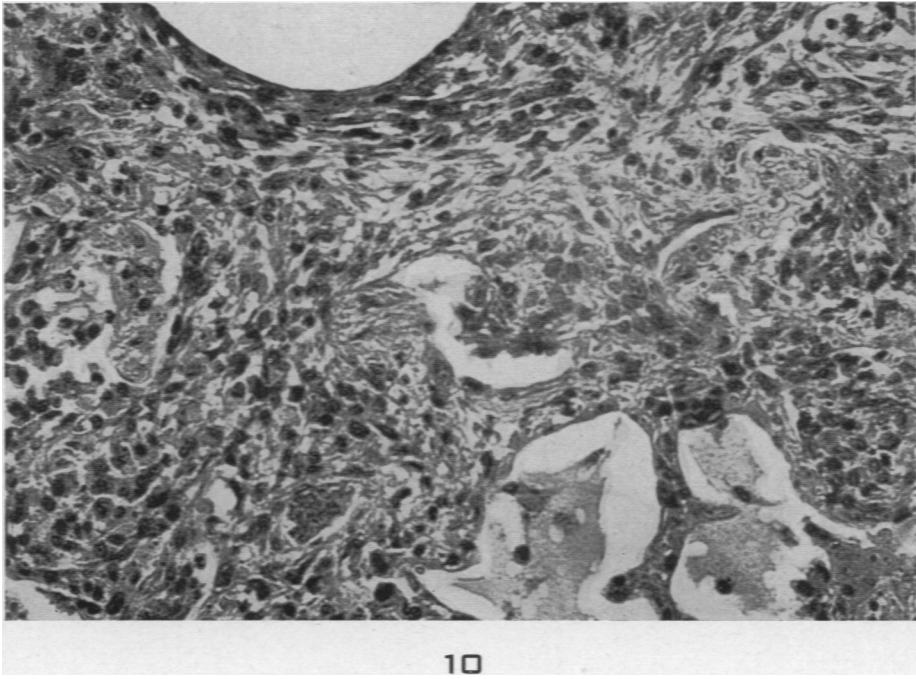
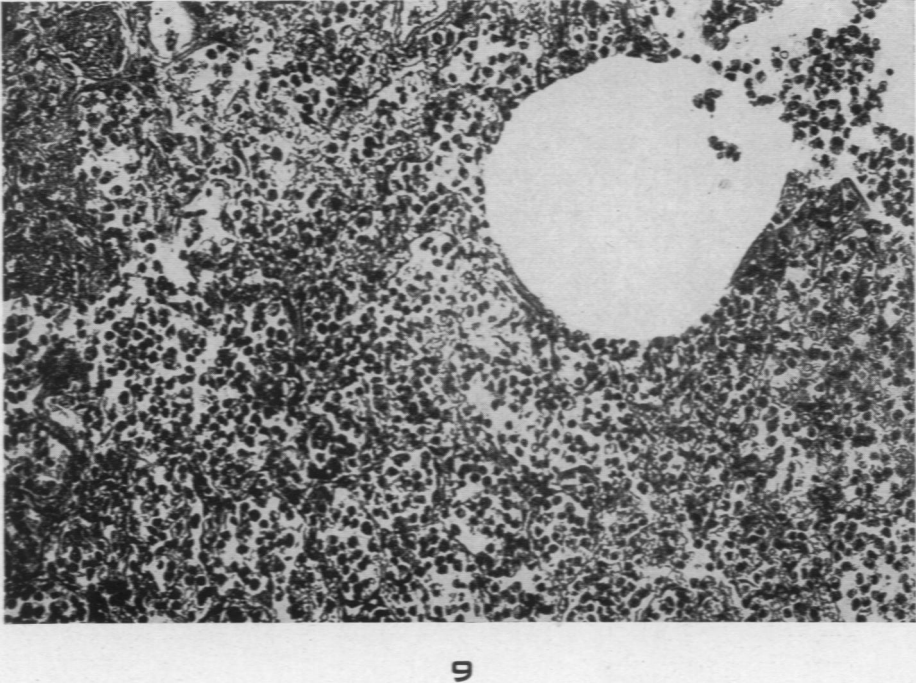
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PLATE 155

FIG. 9. Advanced bronchopneumonia in the lung of a dog dying 20 days after exposure to phosgene. The alveoli are filled with polymorphonuclear leukocytes, lymphocytes, fibrin, and a few red cells. C = 0.238 mg. per liter; T = 30 minutes. $\times 180$.

FIG. 10. Granulation tissue replacing alveoli in the lung of a dog that died 72 hours after exposure. C = 0.264 mg. per liter; T = 30 minutes. $\times 300$.



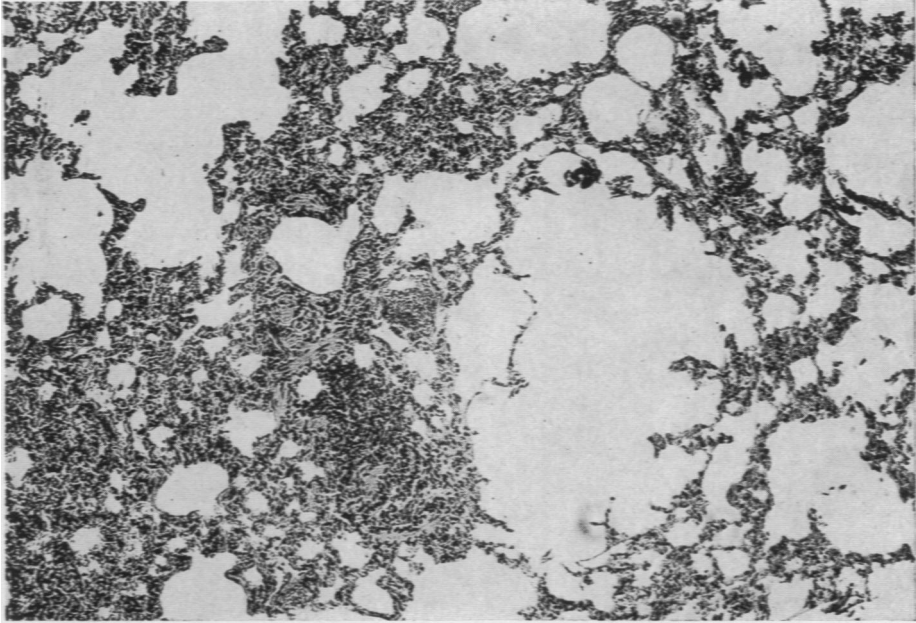
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Experimental Phosgene Poisoning

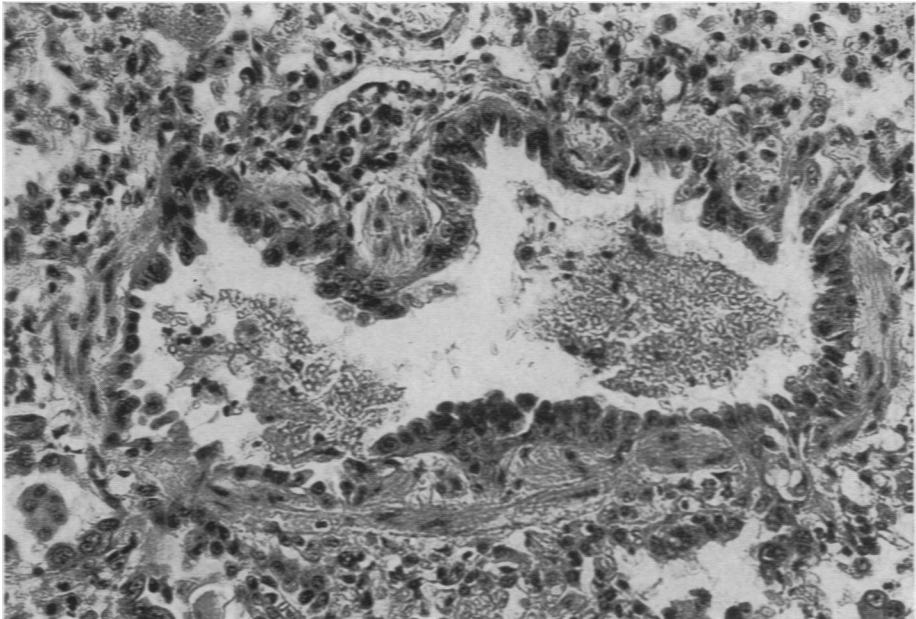
PLATE 156

FIG. 11. Section of the lung of a dog sacrificed 27 days after exposure to phosgene. The emphysema persists and parts of the lung are atelectatic; patches of fibrosis are apparent. C = 0.295 mg. per liter; T = 30 minutes. $\times 83$.

FIG. 12. Regeneration of bronchiolar mucosa. The lining cells are cuboidal in some areas, elongated in others. Dog died $6\frac{1}{2}$ days after exposure to phosgene. C = 0.295 mg. per liter; T = 30 minutes. $\times 300$.



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