Phosgene Poisoning as an Example of Neuroparalytic Acute Pulmonary Edema: 
The Sympathetic Vasomotor Reflex Involved*

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SCHMITT AND MEYERS' showed in 1957 that the acute pulmonary edema that follows vagal section is associated with a marked decrease in sympathetic inflow to the lung. It has long been known, on the other hand, that certain forms of acute pulmonary edema are associated with a marked increase in the organism's total level of sympathetic activity.¹ Pursuing this dichotomy as a possible taxonomic principle around which to order the entire syndrome, we have recently succeeded in establishing a rational classification of the many disparate entities of acute pulmonary edema into two grand polar groups, according to certain anatomic, physiologic, pharmacologic, clinical and radiologic criteria which we found empirically to be useful. One group is the hyperactive-sympathetic, characterized (1) anatomi~ically by immediate and generalized lung hyperemia, with evenly distributed capillary and venous engorgement accompanving the alveolar edema;²,³ (2) physiologically by initial high systemic and pulmonary arterial pressure,⁴ as indices of high sympathetic tone; (3) pharmacologically by the ameliorative effect that sympatholytic agents exert on the development and course of the lung lesions;⁵ (4) clinically by hypertension and hypersympathicotonia; and (5) radiologically by uniformly dense lung fields.⁶ This group includes epinephrine toxicity, pheochromocytoma, some asphyxiations, some head injuries, brainstem irritation, some hypothalamic lesions and NH₃ toxicity. The other group is the hypoactive-sympathetic or neuroparalytic, characterized (1) anatomically by a late and patchy type of lung hyperemia in which venous engorgement is not usually observed, and in which randomly distributed areas of alveolar eduate alternate with areas of emphysematous or normal parenchyma;¹,⁷ (2) physiologically by initial normal or low systemic and pulmonary arterial pressure; (3) pharmacologically by the negative effect that sympatholytic agents exert on the lung lesions;¹ (4) clinically by hypotension and shock or a tendency to shock; and (5) radiologically by the eventual development of a reticulo-granular image scattered throughout the lung fields.² This group includes cervical vagal section, silo filler's disease, some bulbular poliomielitides, so-called high altitude pneumonia, hyaline membrane disease of the newborn, explosive recompression and probably paroxysmal nocturnal dyspnea. Phosgene poisoning also fits neatly into the neuroparalytic category.

The present study was made in order to test in intact animals the basic principle underlying the above pragmatic classification, specifically as it applies to the neuroparalytic group of acute pulmonary edema entities. Phosgene poisoning was chosen for this purpose because it is the experimental condition of the neuroparalytic group most easily controlled in a laboratory setting; the neurophysiologic approach was chosen because sympathetic nerve assay provides the most direct, incontrovertible datum of

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sympathetic activity that can be obtained; and the rabbit was chosen because the complicating element of broncho-constriction does not occur in this animal's response to phosgene.

**Experimental**

Rabbits, normal adult male and female New Zealand white albinos weighing between 2.8 and 5.1 kg. (average 3.9 kg.), to make up a total of ten successive and successful runs, were used. Urethane anesthesia (1.3 g./kg. IP), after pentobarbital sodium induction (7.5-20.0 mg./kg. IP), was employed. A midline incision was made in the anterior region of the neck to expose the trachea, which was cannulated; the right carotid vascular bundle was now approached, and from behind it the right cervical sympathetic was carefully dissected. This cervical sympathetic nerve was next stripped clean of its surface connective tissue, by means of fine forceps under the binocular microscope, and draped over platinum electrodes, electrodes and nerve then being submerged in oil. The electrodes led to a pre-amplifier which was connected to a cathode ray oscilloscope. A camera, equipped with self-developing film, was fitted on to the oscilloscope screen and photographs of the sympathetic activity were taken at suitable intervals. A copper wire screen was lowered over the animal preparation when ready to record. Once the setting up of the nerve-electrodes-oscilloscope train had been achieved, a constant rate and volume pump was connected to the tracheal tube and adjusted at a rate and volume just sufficient to inhibit the animal's own respiratory movements: this added control, essential to the reproducibility of the results, was not introduced until later in the series of experiments.

Exposure began after a normalization period of half-an-hour to one hour. The phosgene gas was metered out of a cylinder at a constant rate and added to air also flowing at a constant rate into a reservoir, whence, by negative pressure, aliquots of the dynamic mixture were drawn into the breathing pump, and thence, by positive pressure, into the animal's lungs. Thus, the amount of gas received by the animal, the precise concentration of the gas, and the duration of the exposure to the gas, could be regulated. Exposures varied from 50 ppm for 14 minutes to 200 ppm for 25 minutes.

The crucial measurement of the experiment was that of the changes in the total electrical activity of the cervical sympathetic nerve before and after the animal had been gassed. This datum was obtained by photographing the activity that appeared on the oscilloscope screen before, during, and at suitable intervals after gassing had taken place. These recordings were later compared among themselves for overall differences in general activity levels.

As a check on the viability of the preparation before gassing, breathing of a progressively higher concentration of exhaled carbon dioxide and progressively lower concentration of oxygen, and the stimulating effect of this induced hypercapnia and moderate oxygen deprivation on the recorded total nervous activity of the cervical sympathetic (hereafter referred to as the rebreathing test) was used in all of our stabilized preparations a few minutes before exposure.

Those animals which survived four hours after exposure were sacrificed at that time; the lungs of all animals were fixed in situ with 10 per cent formol and dissected out immediately for pathologic observation.

Three animals were also exposed to the inhalation of SO₂, a pulmonary irritant gas that does not produce neuroparalytic acute pulmonary edema. The same experimental setup and procedure were used as for the phosgene experiments.

**Results**

The exposure to overwhelming concentrations of phosgene in the rabbit is followed by an immediate abrupt marked drop in total recorded electrical activity of the cervical sympathetic nerve (Fig. 1A and 1B; Fig. 2A and 2B). This change in...
FIGURE 1: Recordings from cervical sympathetic nerve of rabbit demonstrating decrease in activity between control (A) and following exposure to phosgene (B). Each tracing represents 1 second. Calibration 50 microvolts. Experiment No. 9 (Controlled respiration).

total sympathetic recorded activity usually appears during exposure, never later than 20 minutes after its termination, and is always observed in the controlled breathing preparations and in about half of the preparations not so controlled (Table 1).

In all experiments, the rebreathing test was used before gassing, thus assuring the viability of the preparation and a sufficient level of baseline sympathetic activity for recording purposes.

In one-third of the preparations, a transient rallying of the total sympathetic activity was observed to occur between one-quarter hour and one hour after the initial drop. Of short and variable duration (one-
quarter to one-half hour), this increase never brought the total sympathetic activity back to control levels and was soon followed by a new drop which took the sympathetic activity back to its original low level. The level of activity then usually remained more or less stable until the end of the experiment.

On several occasions, great increase in urinary bladder and intestinal peristaltic activity was observed in the gassed animal, coincident with the recorded drop in total electrical activity of the nerve.

In every case, gross observation of the lungs at the end of the experiment revealed congestive changes of the patchy hyperemia type, usually limited in extent.

After exposure to phosgene the rebreathing test did not produce the increase in sympathetic activity recorded prior to gassing. An example of the slight response occasionally obtainable in our preparations after phosgene poisoning is shown in Fig. 2C (50 minutes after exposure) and Fig. 2D (rebreathing test immediately thereafter).

Assay of total sympathetic activity was also performed in three animals, using SO$_2$ as the pulmonary irritant, employing the same technique and setup as described for phosgene. As the data summarized in Table 1 reveal, SO$_2$ gassing leads to a great increase in sympathetic activity in the rabbit.

**Discussion**

1. **General Considerations Regarding Methods and Results**

Employing essentially the same technique as Adrian et al.$^{14}$ in 1932, we have assayed directly the total electrical activity of the right cervical sympathetic before and after exposures to overwhelming concentrations of phosgene in the rabbit, and have found that it drops suddenly and markedly immediately after gassing. The axiom that the sympathetic nervous system acts in a diffuse rather than an organ-specific fashion has not required revision since it was proposed.

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Anesthesia</th>
<th>Exposures</th>
<th>Respiration</th>
<th>Sympathetic Activity</th>
<th>Rally</th>
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<tr>
<td>E</td>
<td>S</td>
<td>W</td>
<td>G &amp; C</td>
<td>D</td>
<td>Change</td>
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<tr>
<td>1 M</td>
<td>3.8</td>
<td>20.0</td>
<td>1.25</td>
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<td>2 M</td>
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<td>15.0</td>
<td>1.25</td>
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<td>20 min.</td>
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<td>3 M</td>
<td>3.5</td>
<td>7.5</td>
<td>1.30</td>
<td>Phosgene</td>
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<tr>
<td>4 M</td>
<td>4.8</td>
<td>15.0</td>
<td>1.30</td>
<td>Phosgene</td>
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<td>5 M</td>
<td>3.2</td>
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<td>Phosgene</td>
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<td>7 F</td>
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<td>10 M</td>
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<td>11 M</td>
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<td>1.70</td>
<td>SO$_2$</td>
<td>10 min.</td>
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<tr>
<td>13 M</td>
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<td>11.0</td>
<td>1.30</td>
<td>SO$_2$</td>
<td>25 min.</td>
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**Observation:** SO$_2$ animals begin to struggle against the respiration pump as soon as exposure to the gas begins.

E=experimenter number; S=sex; W=weight in kg.; P=pentobarbital sodium in mg./kg. IP; U=urethane in g./kg. IP; G=gas; C=concentration of gas in ppm; D=duration of exposure to gas concentration.
by Cannon early this century. It is upon a practical corollary of this principle that we derive the rationale of our measurement. We assume that the abrupt sharp drop in electrical activity of the right cervical sympathetic that follows phosgene gassing in our animals reflects a similar and coincident fall in sympathetic tone everywhere else in the organism, including the lung. Earlier investigators have documented fully several other manifestations of decreased sympathetic tone consequent to phosgene poisoning and chronologically parallel to our own observation of a sharp decrease in cervical sympathetic activity: Patt et al. reported bradycardia and systemic arterial hypotension; Coman et al. mentioned the increased motor activity of the bladder and gastrointestinal tract which we have also seen; Gibbon et al. reported pulmonary arterial hypotension.

Concerning the tracings themselves, our records of cervical sympathetic outflow agree closely in general nature with those reported in the literature. When assayed together, these small, dys-synchronously firing fibers project upon the oscilloscope screen a steady continuum of electrical activity showing by low amplitude and a variable character.

A further confirmation of the validity of our data lies in the trustworthiness of our rebreathing test, where the key observation was that of an immediately recognizable increase in the nerve’s total electrical activity. Not surprisingly, when one considers the massive sympathetic depression present, the sympathetic activation response to rebreathing was either greatly reduced or unobtainable after phosgene poisoning.

The transient phenomenon which we observed in one-third of our phosgene animals and called sympathetic rally is indistinguishable neurophysiologically from the electrical activation response to rebreathing. This identity, together with the fact that the phenomenon occurs at the moment when the alveolar edema is known to start forming, seems to indicate that the rally is the effect again of anoxic and hypercapnic stimulation of the central nervous system. The fact that this phenomenon, when present at all, is transient and of slight magnitude, points in the direction again of marked sympathetic unresponsiveness, but does not by itself provide any clue as to whether the sympathetic depression is primarily peripheral or central in origin.

Whether sacrificed deliberately at four hours or dying earlier as a result of the exposures, all animals exhibited at necropsy the patchy hyperemic type of pulmonary congestion that constitutes our anatomic criterion for neuroparalytic acute pulmonary edema. The fact that the patchy hyperemia was still in the first stages of its development, judging from the limited extent and distribution of the hyperemic areas, is important to note also, since it agrees with the view that the lung changes are secondary to the neural, rather than the other way around. In the particular case of phosgene poisoning, the finding of such a before-and-after relation between a sympathetic nervous failure and a vascular dynamic disturbance in the lungs occurring immediately afterwards, is tantamount to saying that a cause-and-effect relation exists between the two: for as Coman et al. demonstrated definitively in 1947, there are no capillary-alveolar membrane lesions in phosgene poisoned lungs; the bronchiolar changes cannot explain the parenchymal findings; and the lesions elsewhere are nonspecific and unimportant.

The fact that SO₂, a pulmonary irritant gas that does not produce neuroparalytic acute pulmonary edema, causes a marked increase in sympathetic activity, is another indirect confirmation of the significance of our findings concerning phosgene.

Meyers and other investigators have shown that the activity of smooth muscle tubes or sacs, including blood vessels, is primarily an intrinsic quality of these organs, and that such smooth muscle structures react in terms of activity in a manner exactly opposite that of the sympathetic influence normally modulating their tone, when that influence is removed. In the particular case
of the lung, the overall effect of an increase in sympathetic tone is one of smooth muscle inhibition. This we derive from the observation that in such classic states of sympathetic stimulation as exercise and moderate hypoxia the physiologic increase in pulmonary blood flow is associated with an increase in pulmonary arterial pressure, but a decrease in pulmonary resistance, which means vasodilation, an axiom demonstrated experimentally by Daly and Daly in 1959. It comes as no surprise, then, that elimination of the lung's sympathetic tone, such as that observed by us, results in a generalized pulmonary vasoconstriction: this pulmonary shutdown has been identified by Wyllierd and Meyers in guinea pigs, through protection studies with dioxylined and rutin. A different species was used for these toxicologic studies, but rabbits and guinea pigs are similar in their response to phosgene.

We can also affirm that the pulmonary sympathetic neuropaIysis identified in our experiments is not a direct sympatholytic effect of the gas, since we can discard a ganglionic blockade-like action by the presence in phosgene poisoning of bowel and bladder hyperactivity, and a terminal effector endings blockade-like action by the greatly decreased sympathetic activity which we measured directly in postganglionic fibers. It therefore follows that the process is reflex in nature.

Inasmuch as we have proved a sympathetic neuropaIysis to be operative in phosgene pulmonary shutdown, our data likewise affirm the validity of our general classification of acute pulmonary edema and its two dichotomous sets of closely related criteria, since the mechanism demonstrated is the basic assumption underlying that pragmatic systematization. In this connection it must be mentioned that pulmonary vasoconstriction, the primary vascular dysfunction present in our experimental model of neuropaIytic acute pulmonary edema, can be identified in the other pulmonary shutdown entities mentioned in the introduction. This identification has been formal in the case of vagal section and silo filler's disease, where it was done pharmacologically, and of so-called high altitude pneumonia, where cardiac catheterization was used. The well known beneficial effect that pulmonary musculotropic vasodilators e.g. aminophylline, isoproxylterenol, norepinephrine, exert in the treatment of bulbar poliomyelitis acute pulmonary edema, chronic paroxysmal nocturnal dyspnea, hyaline membrane disease and explosive recompression, constitutes a less formal identification of a presumed pulmonary vasoconstriction in the latter entities—highly suggestive but lacking controlled experimental confirmation.

2. Theoretical Considerations on the Vascular Dynamics of the Lung

Daly and associates have developed over several decades and by means of highly ingenious and careful experiments the theory that the lung vasculature is under reflex nervous control. Their recent data on the reflex effect that anoxia exerts on the pulmonary arterial pressure, increasing it or decreasing it depending on whether the lung is perfused through the pulmonary arterial system alone (increase) or the bronchial and pulmonary arterial systems together (decrease), establish experimentally several key principles about the vascular dynamics of the lung that have a bearing on our results. These are: the vascular dynamics of the lung are controlled by the sympathetic nervous system; the nature of this sympathetic control is reflex; sympathetic stimulation produces a pressor response on the pre-capillary side of the lung vasculature; sympathetic stimulation produces a depressor, i.e., vasodilator response on the post-capillary side of the lung vasculature.

Our results are in full agreement with Daly's theory of lung vascular dynamics. We have, in fact, demonstrated exactly the opposite effect as his under exactly the opposite circumstances of sympathetic activity. Where Daly established a pulmonary
vasodilation by the reflex stimulation of the sympathetic nervous system, we have succeeded in showing a pulmonary vasoconstriction by the reflex abolition of sympathetic activity.

Our thesis also supports, again by converse reasoning, the hypothesis that the post-capillary segment of the lung vasculature is the main effector of the reflex sympathetic mechanism which controls pulmonary vascular dynamics. Daly’s finding that this venous segment of the pulmonary vascular bed is the one involved in the sympathetic vasodilation response establishes a physiologic role for it which is in complete agreement with the anatomic facts of the situation, i.e., with the organic vasomotor preponderance of the venous side over the arterial side of the pulmonary circulation, from the point of view of the amount and distribution of vascular smooth muscle present and of its innervation. This same vasomotor preponderance allows us to propose that the pulmonary vasoconstriction identified in acute pulmonary edema due to phosgene and in general in all other pulmonary shutdown entities, is essentially a venoconstriction.

While there remains no reasonable doubt that a sensorimotor reflex is involved in the control of the pulmonary circulation, much is still unknown concerning the anatomic pathway of this negative feedback neural circuit. At the moment we can only state with certainty that its afferent arc courses with the vagus, that its central link lies in the bulbar reticular formation, and that its efferent arc courses with the upper thoracic sympathetics.

Summary

Conditions of acute pulmonary edema are classified into two great groups, according to certain empirically useful anatomic, physiologic, pharmacologic, clinical and radiologic criteria. The hyperactive-sympathetic group is characterized by diffuse lung hyperemia, pulmonary hypertension, amelioration by sympatholytic agents, systemic hypertension and uniformly dense lung fields; it includes epinephrine toxicity and brainstem irritation. The hypoactive-sympathetic or neuroparalytic group is characterized by patchy lung hyperemia, pulmonary normo- or hypotension, non-amelioration by sympatholytic agents, systemic normo- or hypotension and generalized reticulogranular images in the lung fields; it includes vagal section, so-called high altitude pneumonia, hyaline membrane disease, explosive recompression, probably paroxysmal nocturnal dyspnea, and phosgene poisoning.

The basic assumption of this classification, specifically in relation to the neuroparalytic group, is tested by direct assay of total electrical activity of the right cervical sympathetic nerve in the rabbit before and after a lethal dose of phosgene. An immediate abrupt marked drop in systemic sympathetic outflow which precedes the lung changes occurs upon phosgene poisoning in the rabbit.

Other data are marshalled to establish that the sympathetic neuroparalysis of phosgene poisoning is reflex in nature and associated with vasoconstriction of the lung vascular bed, such pulmonary shutdown being essentially a post-capillary phenomenon.

The autonomic sensorimotor negative feedback reflex thus identified as controlling the vascular dynamics of the lung is presented as coursing afferently with the vagus, synapsing at the bulbar reticular formation, and coursing efferently with the upper thoracic sympathetics.

Resumen

De acuerdo con ciertos criterios empiricamente útiles, fisiológicos, farmacológicos, clínicos y radiológicos, se han clasificado las condiciones del edema pulmonar agudo en dos grandes grupos. El grupo hiperactivo-simpático se caracteriza por la hiperemia difusa pulmonar, la hipertensión pulmonar, la mejoría por los agentes simpaticolíticos, la hipertensión general y los campos pulmonares uniformemente densos; incluyen toxicidad de la adrenalina e irritación de las ramas cerebrales.

El tipo hipoactivo-simpático o grupo neuroparalítico se caracteriza por hiperemia en manchas, normo e hipotensión pulmonar, falta de
mejoría con los agentes simpaticolíticos, hipotensión general o normal e imágenes generalizadas reticulo-granulares en los campos pulmonares; incluyen lo observado en la sección del vago, la neumonía de las altitudes, enfermedades de la membrana hialina, recompresión explosiva, probablemente la diarrea nocturna paroxística y el envenenamiento por el fosgeno.

La presunción básica en esta clasificación, específicamente en relación con el grupo neuro-paralítico, es probada por ensayo directo de la actividad eléctrica del ganglio simpático cervical derecho en el conejo antes y después de la intoxicación por el fosgeno. Una caída brusca inmediata en el flujo eferente simpático general que precede a los cambios pulmonares del pulmón ocurre al envenenar al conejo con fosgeno. Otros datos son controlados para establecer que la neuroparálisis simpática de la intoxicación por el fosgeno es de naturaleza refleja y asociada con la vasoconstricción del lecho vascular pulmonar, siendo tal clausura esencialmente un fenómeno post-capilar.

El reflejo autónomo sensorio-motor negativo de rebote así identificado, como se controla el dinamismo vascular, se presenta como siguiendo un curso eferente con el vago, con simapisia en la formación bulbar reticular y cursando eferentemente con los simpáticos torácicos superiores.

Referencias


MEDIASTINAL PARATHYROID ADENOMA

After an unsuccessful exploration for suspected parathyroid adenoma, a decision has to be made as to whether the neck is to be re-explored or a mediastinoscopy is to be performed. In these circumstances, any help obtainable from the radiologist is of great importance. Anterior pneumomediastinoscopy is sufficiently safe to warrant its use in this situation. While a negative result does not constitute evidence for the absence of a tumor, the actual demonstration of a mass, as in this case, is of considerable help. It should be noted that inferior thyroid arteriography recommended as one of the procedures for the diagnosis of parathyroid adenoma was unsuccessful in this instance, though operative arteriography was not performed.


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