CHRONIC PULMONARY EMPHYSEMA
(An Experimental Study)

III. Experimental Pulmonary Emphysema

H. T. G. Strawbridge, M.D., M.R.C.P.E., F.R.C.P.(C.) *

From the Departments of Pathology, the University of Liverpool, England, and the Winnipeg General Hospital, Winnipeg, Manitoba, Canada

In the past, many different methods of producing pulmonary emphysema experimentally have been employed.

Bayer,[1] in 1870, in an unstated number of rabbits, reported emphysema at the margins of the contralateral lung after periods of half an hour or more of pneumothorax. Kläsi,[2] in 1886, saw marginal emphysema in one rabbit after 9 days. The descriptions indicate that they were dealing with chronic marginal emphysema of the spontaneous variety.

Riegel and Edinger,[3] in 1882, and Sihle,[4] in 1903, using vagal stimulation in dogs and rabbits, produced simple overdistention of the lungs. However, Brown-Séquard,[5] in 1885, stated that even brief vagal stimulation produced emphysema in rabbits.

In 1900, Bullara,[6] in dogs, and Cousteau,[7] in rabbits, claimed, without employing controls, to have produced emphysema by nasal obstruction for periods of 2 weeks to 7 months. Köhler,[8] in 1878, narrowed the trachea by lead wire and reported vesicular and interstitial emphysema in about 20 rabbits after 3 to 4 weeks. Neither controls nor diagnostic criteria were mentioned. In the same year, Hirtz[9] narrowed the trachea by ligature and claimed the production of generalized and marginal emphysema in 2 rabbits after 4 and 9 days. Sudsuki,[10] in 1899, ligated the trachea of 9 rabbits. In 3, surviving between 46 and 84 days, tracheal stenosis was found at necropsy. One showed marked marginal emphysema. In 1925, Nissen and Cokkalis[11] inserted a metal ring into the tracheas of 5 cats and found histologic vesicular emphysema in 3. Nissen[12] later obstructed the tracheas of 3 dogs, 4 rabbits, and 3 cats by packing the mediastinum with wax or plaster of Paris. After 3 to 6 months, local traces of true emphysema were found

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* Present address: Department of Pathology, The Winnipeg General Hospital, Winnipeg, Manitoba, Canada.

in 5, and 3 showed more marked lesions. Nissen employed controls in neither study. Loeb,[13] in 1930, kept 8 of 24 dogs alive for up to 14 months after the insertion of a narrow brass tube into the trachea. He found doubtful dilatation of alveoli but no emphysema.

In 1909, Priese[14] and Schall[15] employed face masks in 7 rabbits and 3 dogs. Daily application for between 3 and 11 months produced no emphysema. In 1917, Friedman and Jackson[16] in three 8-hour experiments, obstructed expiration by an intratracheal T-tube and valve and without giving details, stated that emphysema was present. Similar claims were made by Pfanner,[17] in 1922, in acute experiments with rabbits and dogs. Harris and Chillingworth,[18] in 1919, obstructed expiration by an intratracheal ball valve in 25 dogs, all of which survived 2 to 21 days and were reported to show some degree of emphysema. Their illustrations do not suggest more than a marked degree of distention of the lungs, and Loeb[13] refused to accept these changes as emphysematous. These investigators used an unstated number of controls with "nonfunctional" valves.

Kountz, Alexander and Dowell[19] in 1929, used the method of Harris and Chillingworth in 16 dogs and concluded that emphysema had been produced on the basis of raised intrapleural pressure. No anatomic details were given. In 1945, Sciuto[20] used the same method in dogs. His illustrations are not convincing. Hinshaw,[21] in 1938, used an improved ball valve in various animals for up to 18 months and observed frequent subpleural emphysematous vesicles. In 1940, Paine[22] devised an intratracheal flap valve. Three controls, with nonfunctional valves, showed minimal histologic emphysema after 9 weeks. Of 10 dogs which survived from 5 to 23 weeks with expiratory obstruction, 1 was normal, 3 had minimal alterations while 6 had definite acceptable microscopic emphysema. Of 9 dogs which survived from 4 to 30 weeks with inspiratory obstruction, definite macroscopic and microscopic emphysema was present in 6. Paine assessed his material critically, and his illustrations show convincing chronic emphysema.

In 1927, Nissen[12] enlarged the thorax in 18 dogs by various means. Ten survived for periods of between 2 weeks and 5 months. No emphysema was seen. Paine,[22] in 1940, also enlarged the thorax in 9 dogs by suturing "reefs" in the diaphragm. Two died. Seven survived for periods of 16 to 25 weeks. All but one had naked-eye emphysema, and in all 7, significant microscopic emphysema was present. Paine considered this method superior to valvular obstruction.

Most of the papers concerned with relative increase in the size of the thorax are studies of the fate of the remaining lung after pneumonectomy, rather than deliberate experimental studies of emphysema. Möll-

gaard,[23] in 1909, performed pneumonectomy on three 7-day-old pups which survived for 6 to 14 weeks, and 5 adult cats which survived for 14 days. The remaining lungs were enlarged, but he regarded this as hypertrophy. But his Figure 7 is more convincingly indicative of emphysema than many others in the literature.

Nissen,[12] in 1927, produced convincing chronic compensatory emphysema in cats and dogs after periods of up to 16 weeks following ligation of selected main bronchi and branches of the pulmonary arteries. Adams and Livingstone,[24] in 1932, claimed that the remaining lung tissue in 28 dogs, 2 to 12 months following lobectomy or pneumonectomy, showed various degrees of compensatory emphysema. They gave no details, and their histologic illustration is not convincing. Rienhoff, Reichert, and Heuer,[25] in 1935, in a similar but more detailed and controlled study of 10 dogs for periods of up to 6 months after pneumonectomy, found no emphysema in the remaining lungs. Their Figure 4 is more suggestive of emphysema than many for which positive claims have been made. Kountz, Alexander and Prinzmetal,[26] in 1936, removed up to 80 per cent of the lungs in 19 dogs and implied that emphysema developed in the remaining lung tissue but gave no necropsy details. Longacre and Johansmann,[27] in 1940, compared the long-term effects of pneumonectomy in 2 adult dogs and 3 puppies. After 2 to 4 years no emphysema was found in the "puppies," but they reported true chronic emphysema in both the "adults." However, only their Figure 11A is suggestive of emphysema.

In 1927, Campbell[28] exposed an unstated number of animals, including rabbits and mice, to lowered oxygen tensions for prolonged periods. He noted, incidentally, that "portions of the lungs of most animals were emphysematous." Prinzmetal,[29] in 1934, in a deliberate attempt to produce emphysema, exposed an unstated number of rats to only 8 per cent oxygen for 10 weeks. His illustration is convincing, but no details were given and no controls were employed.

In 1913, Caradonna[30] studied the effect of increased respiratory effort on the alveolar pores of an unstated number of young guinea pigs. One group was kept undisturbed as controls. Two other groups were whipped 4 times daily until they were in a state of collapse. Only occasional pores were seen in the controls between the ages of 5 and 15 months. In the whipped animals, pores became visible at 3 months and increased in number until, at 1 year, the lungs were frankly emphysematous. Kelman,[31] in 1919, used rabbits. Seven were exposed to intermittent tracheal inflation, 3 were killed by anaphylactic shock, and 18 were inoculated intratracheally by *Hemophilis influenzae* cultures or culture filtrates. She claimed that marginal emphysema was present in all these animals.

No precise criteria were given, and no controls were employed. Rasmussen and Adams,[32] in 1942, overinflated the lungs of 7 dogs for periods of 15 minutes twice weekly. The dogs survived from 1 week to 11 months. Vesicular emphysema was noted in one animal only. They did not claim that this was the result of the experimental procedure.

The literature suggests that many claims to the production of emphysema experimentally are unacceptable because of lack of controls, failure to state precise criteria for the diagnosis of emphysema, or the failure of illustrations to substantiate claims made in the text. The most careful study was that of Paine[22] in 1940. He assessed his results very critically and supplemented his anatomic studies by measurements of the intrapleural pressure by the method of Christie and McIntosh.[33]

Quite apart from the validity of the experimental work, nearly all the methods have been designed to produce abnormal distention of all or part of the lungs or to increase the amount of functional stress placed upon the lungs. The claims of the experimental workers lend support to the mechanical theories of pathogenesis of emphysema and show that different remote mechanisms may alter the conditions of respiration and produce emphysema. The methods employed do not shed any light on the intimate mechanism of pathogenesis and, indeed, few of the authors have commented on this aspect of the problem. Paine[22] regarded the development of emphysema as the result of physical stress on the alveolar walls. In passing, he mentioned the possibility of nutritive disturbances, due to capillary occlusion in the course of distention.

The Present Study

The present study resulted from observations on human lungs in thick sections in which it is obvious that the capillary bed is a major constituent of the alveolar wall. It seemed possible that the appearances of chronic emphysema might be produced if the capillary bed could be destroyed. Study of the literature[34] showed that there is ample evidence for regarding chronic emphysema as an atrophy of lung tissue. Further, it has been suggested that ischemia is at least an ancillary factor in the production of emphysematous atrophy.

If chronic emphysema can be regarded as an ischemic atrophy, it should be possible to produce emphysema by interfering with the blood flow through the pulmonary capillaries without the presence of mechanical overdistention of the lungs.

To test this hypothesis, repeated intravenous injections of a particulate substance were used in an attempt to cause enough vascular obstruction to produce tissue ischemia.

Material and Methods

Histologic Technique

The methods described in the previous section[35] were again employed. However, at least one block was taken from each of the major lobes of each pair of lungs. Additional blocks were taken as necessary. Thick sections cut at 100 μ were used routinely for the study of the emphysematous lesions.

Experimental Method

The method thought most likely to produce an adequate degree of vascular obstruction was the oft-repeated intravenous injection of a particulate substance of such a size as to produce blockage of the capillaries and precapillaries. It was necessary that the substance be nontoxic systemically, nonirritant locally and insoluble in body fluids.

Caledon blue R.C. seemed a likely substance. This is an anthraquinone dyestuff, 3',3' dichloro-indanthrone, which is insoluble in water and organic solvents. It was possible to obtain samples which had a majority particle size between 10 and 25 μ. The dye was supplied as an aqueous paste containing 10 to 12 per cent total solids as Caledon blue. Trials showed that a suitable dilution for intravenous use was an approximate 3 per cent of total solids. The diluent was 0.85 per cent saline with 0.05 per cent of a dispersing agent, Dispersol T, added.

Preliminary trials in mice showed that the material was nontoxic. Tissue reaction was minimal. It became obvious that, due to aggregation of the particles, it would not be possible to block at will vessels of a definite caliber by exact selection of particle size. This was no disadvantage, for it was not possible to get batches of Caledon blue of exactly the same particle size. In rabbits, as in mice, there was no immediate tissue reaction to the Caledon blue, but after a day or two there was a slight histiocytic response at the site of lodgment. Even this might be absent. Otherwise Caledon blue produced no tissue response. This was true even in rabbits which received repeated injections of the dye for periods of a year or more. At no stage was any granulomatous reaction or fibrosis produced.

In rabbits, the majority of the particles lodged in the precapillaries and to a lesser extent in the capillaries themselves. Even after a single injection, the blockage was the result of aggregates of particles rather than of individual particles. With repeated injections the aggregation became more marked, with the result that the vessel became grossly dilated around the large mass of dye. After prolonged injections, aggregates occurred in terminal arterioles but not larger vessels. The histologic appearances suggested a very marked degree of vascular obstruction in the lungs, but neither thrombosis nor infarction were produced. Not all of the particles were retained in the lungs, and Caledon blue became lodged in the vessels and taken up by the reticuloendothelial tissue of other organs.

Details of Experiments

First Experimental Series (22 rabbits). A suitable initial dose was found to be 2.5 ml. of the diluted Caledon blue, containing approximately 3 per cent of Caledon blue.

This was injected slowly into an ear vein over a period of 1 to 2 minutes. On a first injection, about 1 in 5 rabbits died following tachypnea and convulsions. In about half the rabbits, tachypnea commenced during or immediately after the injection but lasted only 2 to 3 minutes, after which the animals remained well. After 2 or 3 injections at weekly intervals, the dose was increased to 3 ml., and this was maintained until the end of the experiments. After the rabbits had been injected weekly for about 2 months, it was realized that aging might interfere with the assessment of the results. Consequently, further rabbits added to the series were selected

as appearing to be less than one year old. The weekly injections were continued until the survivors had been receiving them for over a year. The survivors were sacrificed by stunning, one to two weeks after their last injection.

During the collection of a control series, it became evident that spontaneous emphysema developed in rabbits. Details of this have been given in the preceding section.[35] The most important fact to emerge was that some degree of generalized emphysema developed in just over 50 per cent of rabbits over the age of 2½ years.

While it was thought that over half of the animals in the first experimental series were under two years old at the end of the experiment, it was impossible to be sure of this, and it was felt that the controlling was inadequate.

Second Experimental Series (25 "pairs" of rabbits). The experiment was repeated using rabbits of known ages. Most of these were 8 or 9 months old at the start, the extreme ages being 7 and 12 months. The controls were the paired litter mates of the animals which received the Caledon blue. Encouraged by the results in one of the animals in the first series which had received injections thrice weekly, the rabbits in the second series received injections twice weekly after the second week. The dosage was maintained at 2.5 ml. of diluted Caledon blue (approximately 3 per cent total solids) since there was a higher death rate in the second series as compared with the first. The injections were continued twice weekly until the survivors had received Caledon blue for 24 weeks. These were sacrificed by stunning 1 to 2 weeks after the last injection so that no rabbit was more than 18 months old at the conclusion of the experiment.

The litter mate controls were treated identically, so far as possible, to the experimental animals. Each received a biweekly injection of 2.5 ml. of 0.85 per cent saline with 0.05 of the dispersing agent added, but without the Caledon blue, at the same time the experimental animals were injected. The controls were sacrificed by stunning when their experimental litter mates died or were killed. The control lungs were processed in strict parallel to the experimental lungs at all stages.

In this series 25 pairs of rabbits survived for between one and 24 weeks. (One of the "pairs" consisted of 3 litter mates, of which 2 were given Caledon blue and the third retained as a control.)

Assessments of Results

In view of the experience of spontaneous emphysema in rabbits described in the previous section,[35] the results were assessed solely upon a comparison of the incidence of microscopic generalized emphysema in the injected animals and the controls.

Emphysema in marginal lobules was ignored, as the lobules are of inflammatory origin. Vesiculation is usually a marginal accentuation of generalized emphysema and did occur more frequently in the injected animals. As some cases of vesiculation may be the result of local inflammatory changes, it was ignored in the assessment. Vesiculation was, however, a very useful naked-eye guide as to the success of any individual experiment (Fig. 1).

Microscopic Appearances. The generalized and marginal emphysema found in rabbits injected with Caledon blue was identical in every respect to spontaneous rabbit emphysema[35] and to the classical descriptions of chronic emphysema in humans[34] (Fig. 2). The lesion was complicated, however, by the presence of masses of Caledon blue in the vessels. This did not modify the histologic appearance of the emphysema. There was destruction of the alveolar walls by fenestration (Fig. 3), which, at the margins, progressed until there was complete destruction and disappearance of the alveolar septums and fusion of neighboring alveolar sacs and ducts (Fig. 4). The changes in the elastic fibers were the same as in spontaneous emphysema.

Assessment of the Degree of Generalized Emphysema. An arbitrary system of plus grading was adopted. This was based on the extent and severity of the destruction of lung tissue by fenestration. Alveolar pores occur in all rabbit lungs and, as the emphysematous process consists of the development of abnormal numbers of fenes-

TABLE I

DETAILS OF FIRST EXPERIMENTAL SERIES

Rabbit no.	Body wt. at death (kg.)	Duration of Caledon blue injections (wk.)	Total Caledon blue *	Macroscopic			Microscopic				Degree of generalized interstitial pneumonia
								Degree & type of emphysema			
				Normal	Marginal lobule	Vesiculation	Nonemphysematous	Marginal lobule	Vesiculation	Generalized	
R. St./											
13	2.41	1	5.5	+	−	−	+	o	o	o	+++
4	2.41	3	8.5	+	−	−	+	o	o	o	+
6	3.95	5-1/7	15.0	+	−	−	−	o	o	+	+++
9	2.13	5-1/7	15.0	+	−	−	+	o	o	o	+++
17	2.23	6-5/7	17.5	−	−	+	−	o	+++	o	o
20	2.64	11-5/7	30.0	−	+	+	−	+++	+++	o	+++
26	2.43	14-2/7	39.0	−	+	+	−	+	++	+	o
24	2.03	15-5/7	42.0	−	−	+	−	o	++	++	+++
16	2.33	17-6/7	48.0	−	−	+	−	o	+	+	+
28 †	2.34	31-1/7	169.5	−	−	+	−	o	+	+++	+
25	2.68	37	87.0	−	+	+	−	++	+++	++	++
18	2.87	42	92.0	−	−	+	−	o	+	+	+++
11	2.73	43	91.5	−	−	+	−	o	+++	+	+++
7	3.73	47	103.0	−	+	−	−	++	o	++	+
21	2.80	49	107.5	−	−	+	−	o	+	+	++
22	2.36	49	108.0	+	−	−	−	o	o	+++	+
23	2.74	49	108.0	+	−	−	−	o	o	+	+
10	2.84	52	110.5	−	−	+	−	o	++	++	++
14	3.12	52	111.5	−	+	+	−	++	++	+++	++
15	3.11	52	114.0	−	−	+	−	o	+	+++	+
8	2.74	55	122.0	+	−	−	−	o	o	+	+
5	3.26	56	126.0	+	−	−	−	o	o	+++	+
Total incidence of lesions					5	13		5	13	17	20

Total number in series: 22

* Ml. of approximately 3% suspension.

† R.St./28: Received injections thrice weekly.

TABLE II

DETAILS OF SECOND EXPERIMENTAL SERIES AND CONTROLS

Pair no.	Rabbit no.*	Age at start (mo.)	Body wt. at death (kg.)	Duration of Caledon blue injections (wk.)	Total Caledon blue †	Macroscopic			Microscopic				Degree of generalized interstitial pneumonia
										Degree & type of emphysema			
						Normal	Marginal lobule	Vesiculation	Nonemphysematous	Marginal lobule	Vesiculation	Generalized	
	R. St./												
1	64	9	2.53	1	5.0	+	—	—	+	o	o	o	++
	65	9	2.11		o	—	+	—	+	o	o	o	+
2	90	9	2.06	1	4.5	+	—	—	+	o	o	o	+++
	91	9	2.72		o	—	+	—	+	o	o	o	o
3	94	10	2.25	1	o	+	—	—	—	o	+	o	++
	95	10	2.26		4.5	+	—	—	+	o	o	o	o
4	80	12	1.93	2-2/7	9.5	+	—	—	+	o	o	o	+++
	81	12	1.75		o	—	+	—	—	++	o	++	++
5	86	9	2.02	3	15.0	+	—	—	+	o	o	o	+++
	87	9	2.36		o	+	—	—	+	o	o	o	o
6	56	9	2.56	4-2/7	22.5	—	—	+	—	o	++	o	+++
	57	9	2.89		o	+	—	—	+	o	o	o	+
7	110	10	2.66	5-3/7	26.5	—	+	+	—	++	+	+++	++
	111	10	2.29		o	—	—	+	—	o	+	+	++
8	44	10	3.01	6	31.5	+	—	—	+	o	o	o	++
	45	10	3.04		o	+	—	—	+	o	o	o	o
9	46	11	1.59	6	31.5	+	—	—	—	o	o	+	++
	47	11	1.62		o	+	—	—	+	o	o	o	+
10	78	12	2.65	7	35.5	—	—	+	—	o	++	o	+++
	79	12	2.57		o	—	+	—	+	o	o	o	++
11	104	7	2.06	8	40.0	—	—	+	—	o	+	o	++
	105	7	2.32		o	+	—	—	+	o	o	o	++
12	48	10	2.33	10	50.0	+	—	—	+	o	o	o	+
	49	10	2.01		o	+	—	—	+	o	o	o	+
13	76	8	1.92	15	72.0	—	+	+	—	++	++	+++	o
	77	8	2.05		o	—	—	+	—	o	+	o	++
14	102	7	2.88	17-4/7	83.5	+	—	—	—	o	o	++	++

	103	7	3.32		0	+	−	−	+	0	0	0	+
15	106	9	3.04	20	90.5	+	−	−	−	0	0	+++	+
	107	9	2.89		0	+	−	−	+	0	0	0	+++
16	108	7	2.16	20	90.0	+	−	−	−	0	0	+	++
	109	7	2.16		0	+	−	−	+	0	0	0	+
17	52	12	2.80	23-4/7	104.0	−	+	+	−	+++	++	+++	0
	53	12	2.84		0	−	+	−	−	+	0	0	+
18	54	12	2.70	24	116.5	+	−	−	−	0	0	++	0
	55	12	2.82		0	+	−	−	+	0	0	0	+
19	62	9	2.82	24	116.5	−	+	+	−	+++	+++	+++	+
	63	9	2.53		0	−	+	−	−	+	0	+	+
20	70	9	2.08	24	113.5	−	−	+	−	0	+	+++	0
	72	9	2.32	24	114.5	+	−	−	−	0	+	0	0
	71	9	2.00		0	+	−	−	+	0	0	0	+
21	82	11	2.13	24	115.5	+	−	−	+	0	0	0	0
	83	11	2.15		0	+	−	−	+	0	0	0	+++
22	88	9	2.33	24	115.5	+	−	−	−	0	+	++	+
	89	9	2.75		0	−	+	−	−	++	0	0	+
23	92	7	2.87	24	115.5	−	−	+	−	0	+	++	+
	93	7	3.04		0	+	−	−	+	0	0	0	0
24	96	8	2.41	24	115.5	+	−	−	+	0	0	0	0
	97	8	2.67		0	+	−	−	+	0	0	0	++
25	100	7	2.73	24	116.0	−	−	+	−	0	+	0	+
	101	7	2.91		0	+	−	−	+	0	0	0	0
Total incidence of lesions:				After Caledon blue (i.v.)			4	10		4	13	12	19
				Controls			7	2		4	2	3	19

Total number in series: Experimental = 26
Control = 25

*Odd numbers: controls

†Ml. of approximately 3% suspension. Discrepancies between the duration of injections and the total dosage of Caledon blue were the result of unavoidable interruptions of the weekly or bi-weekly injections.

trations which enlarge and fuse with destruction of the alveolar walls, it is obvious that there is no hard and fast dividing line between "emphysematous" and "normal." However, in the normal lung, while the number of pores is variable, large pores are rare and there is little or no tendency to fusion.

Classed as grade o were lungs in which the alveolar pores were within normal limits as judged from the experience in 155 rabbits previously reported.[35] Lungs where there was not only a greater amount of fenestration than in the arbitrary normal but where there was also obviously enlargement and fusion of the pores were classified as grade + (Figs. 5 and 6). This grade was also applied to lungs where, though individual foci showed a degree of fenestration characteristic of the more severe grades, the lesions had a rather patchy distribution throughout the lungs. Grades ++ and +++ were the more severe cases where the fenestration was gross and obvious in all parts of the lungs (Figs. 7 to 11).

Experimental Results

Details of the incidence of all types of emphysema, duration of injections and amounts of Caledon blue injected are given in Tables I and II.

First Experimental Series

Table III shows the incidence of the various grades of generalized emphysema in this series. Although no strict controls are available, the incidence of generalized emphysema found in the 155 "normal" rabbits previously described[35] is included for comparison. These received no Caledon blue and were divided into 3 age groups: viz., young (5 to 11 weeks old), miscellaneous adults (probably 9 to 18 months old), and old (over 2½ years old). These figures show that the incidence of the

Table III

Incidence of generalized emphysema in first experimental series

Degree of generalized emphysema	After i.v. Caledon blue	Young	Misc. adults	Old
+++	5	0	1	3
++	4	0	2	4
+	8	0	6	4
0	5	20	105	10
Total no. in group	22	20	114	21

various grades of generalized emphysema in the rabbits which received Caledon blue is very much higher than that in the untreated young and miscellaneous adults. However, the incidence in the experimental series is not significantly greater than that in the old rabbits. In view of this, no definite conclusion can be drawn, as the ages of the experimental animals are uncertain. Nevertheless, the results are suggestive.

Second Experimental Series

Table IV shows the incidence of the various grades of generalized emphysema in the experimental animals of this series and in their litter mate controls. There is a greatly increased incidence of generalized emphysema in the animals which received intravenous Caledon blue.

TABLE IV

INCIDENCE OF GENERALIZED EMPHYSEMA IN SECOND EXPERIMENTAL SERIES

Degree of generalized emphysema	After i.v. Caledon blue	Controls (litter mates)
+++	6	0
++	4	1
+	2	2
0	14	22
Total no. in group	26	25

The results were analyzed by the exact factorial method of Fisher[36] in the following manner: (1) All grades of emphysema were pooled in the injected and control groups respectively, and the incidence of emphysema compared with that of the 0 grade in the two groups. This gave $P = 0.008$. (2) The ++ and +++ grades of emphysema were pooled in the injected and the control groups respectively, and the incidence compared with that of the pooled grades 0 and + in the two groups. This gave $P = 0.003$. Thus the increased incidence of emphysema in the group receiving injections is clearly significant, and it therefore can be concluded that the intravenous Caledon blue has, in fact, produced experimental emphysema.

Influence of Duration of Caledon Blue Injections

Table V shows that the incidence of generalized emphysema increases as the duration of the injections, and hence the amount of Caledon blue, increases. This supports the view that the Caledon blue has produced the emphysema found in the injected animals.

Mode of Action of Caledon Blue

The experiments were performed on the theoretical basis that chronic emphysema should be regarded as an atrophy of lung tissue and that interference with blood supply might produce such an atrophy. Insofar as emphysema has been produced by the introduction of a particulate substance into the pulmonary vessels, the experimental results appear

to substantiate the hypothesis. However, there are other ways in which the Caledon blue might have acted.

There is no indication that fibrosis is produced, and this definitely is not the mechanism involved. Infarction does not occur, and there is no evidence that the emphysema is of the compensatory type. The Caledon

TABLE V

DURATION OF CALEDON BLUE INJECTIONS AND DEGREE OF GENERALIZED EMPHYSEMA

Degree of generalized emphysema	Duration of Caledon blue injections (wk.)						
	First experimental series				Second experimental series		
	1–3	4–11	12–23	24–56	1–3	4–11	12–24
+++	0	0	0	5	0	1	5
++	0	0	1	3	0	0	4
+	0	1	2	5	0	1	1
0	2	3	0	0	5	5	4
Total no. in group	2	4	3	13	5	7	14

blue produces only a slight histiocytic response, which bears no relation to the anatomic distribution of the emphysema, and there is nothing to suggest that the emphysema is the direct result of inflammation or the mere mechanical presence of the Caledon blue particles. It is possible that the particles act as irritants and reflexly alter the mechanics of respiration. However, the only evidence in support of this is the fact that, especially during the first few injections, about half of the animals exhibited a transient tachypnea. This lasted for only 2 or 3 minutes; then the respirations became normal and remained so. This transitory tachypnea was not a constant feature and was rare after an animal had been established on routine injections. Between injections, the animals were clinically normal, and ausculation of the chest never gave any hint of bronchial spasm or increased bronchial secretions. Binger and colleagues,[37,38] in 1924 and 1927, made a careful study of the mechanisms involved in the production of transitory tachypnea in experimental pulmonary embolism in dogs. They concluded that reflex irritation was not the mechanism involved and that the tachypnea was directly related to the amount of vascular obstruction produced.

The suggestion remains, therefore, that Caledon blue acts by causing the obstruction of large numbers of small blood vessels in the lungs, thereby producing an ischemic atrophy of lung tissue—chronic pulmonary emphysema.

GENERAL DISCUSSION

If it can be accepted that Caledon blue R.C., in the absence of distention, produced the experimental emphysema by causing tissue is-

chemia, this affords strong support for the view that chronic emphysema should be regarded as an ischemic atrophy of lung tissue. As was shown in the historical review,[34] this idea is an old one but has received relatively little attention.

The present experiments do not provide an explanation of how tissue ischemia is produced in human cases, but it appears that there are two main ways in which this might occur:

(1) Increased intra-alveolar pressure, produced by any one of the recognized remote mechanisms such as bronchial obstruction or coughing, could directly compress the capillaries which lie unsupported in the delicate alveolar septums and are exposed, on either side, to the intra-alveolar pressure. The upper limit of normal pulmonary arterial pressure is given as 30 mm. of Hg by Cournand,[39] while the upper limit of normal pulmonary "capillary" pressure is stated to be 15 mm. of Hg by Dexter and associates.[40] Estimates of intrathoracic pressure during coughing considerably exceed these levels and may reach as high as + 250 mm. of Hg according to Sharpey-Shafer.[41] Such figures suggest that direct capillary occlusion could arise in diseased states known to be associated with the development of chronic emphysema. In addition to direct occlusion of capillaries by this means, it seems likely that linear stretching or distortion of the vessels, in the course of distention, could also contribute to the production of ischemia.

(2) Pulmonary or bronchial inflammation could interfere with the blood supply of the affected parts of the lungs either by producing endarteritis, as was suggested by Korol,[42,43] or by direct destruction of minute blood vessels. Christie[44] and Whitfield,[45] among others, have pointed out that clinically the severity of the emphysema cannot always be correlated with the severity of the bronchitis or cough. It is possible that ischemia of inflammatory origin, even in the absence of distensive forces, may explain such cases. In this connection it should be remembered that the anatomic studies of Orsós,[46,47] Letulle,[48] Antoniazzi,[49,50] and Bezançon and Delarue[51] led them to believe that inflammatory changes were an integral part of the emphysematous process.

It is felt, as was tentatively suggested by Rindfleisch[52] in 1871, that adoption of the ischemic theory of the intimate pathogenesis of chronic emphysema would help to reconcile the numerous mechanical theories of remote pathogenesis with each other and also with the apparently conflicting nutritional views. Consideration of the known remote pathogenetic factors shows that the views expressed above can be applied equally well to both hypertrophic and compensatory emphysema. In the case of the latter, it might well be, as was suggested by Korol[42] in 1938, that inflammatory vascular changes are more important than mechanical

effects *per se*. As was pointed out in the historical review,[34] there is no systematically documented evidence to prove the existence of "pure" senile emphysema as opposed to emphysema in the lungs of the elderly due to remote causes operative in all age groups. But if such an emphysema exists, it is possible that senile changes in the vascular tree might be important in its genesis.

Other types of chronic emphysema, including the focal emphysema described in the simple pneumoconiosis of coal miners and workers by Heppleston[53,54] have been excluded from consideration. However, it is suggested that ischemia resulting from vascular occlusion in the course of the pneumoconiotic fibrosis might better explain the localization of the focal emphysema around the respiratory bronchioles than disturbance of air flow at this level.

In conclusion, it is felt that this outlook provides a means of reconciling many apparently conflicting views on the etiology and pathogenesis of chronic vesicular emphysema and is in keeping with the basic histologic identity of the lesions in all forms of the disease. Further, a case can be made for ceasing to regard emphysema as a disease in its own right. Pathologically, chronic emphysema should be considered as a nonspecific atrophy of lung tissue which can be produced by many remote factors, all of which, however, operate by means of the intimate mechanism of tissue ischemia. Viewed in this light, chronic emphysema is no more an entity than nephrosclerosis or myocardial fibrosis.

Summary

Experimental chronic pulmonary emphysema has been produced in rabbits by the repeated intravenous injection of an inert particulate dyestuff, Caledon blue R.C. The experimental lesions are identical to those of spontaneous pulmonary emphysema in rabbits and to human chronic emphysema.

It is considered that the Caledon blue R.C. acted by obstructing large numbers of pulmonary blood vessels, thereby causing ischemia. If this is accepted, the experiments afford direct support for the view which considers that chronic emphysema is an ischemic atrophy of lung tissue.

The mechanisms which might be operative in human emphysema are discussed and it is suggested that the ischemic theory of intimate pathogenesis provides a means of reconciling the many varied views on the nature and pathogenesis of chronic pulmonary emphysema.

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[*Illustrations follow*]

Legends for Figures

All microscopic-sections have been cut at 100 μ. Sections were stained with hemalum and eosin.

Fig. 1. Vesiculation in experimental emphysema. Scale in mm.

Fig. 2. Fenestration in human chronic vesicular emphysema. × 60.

Fig. 3. Fenestration in emphysematous alveolar septum in experimental emphysema. The large black masses are aggregates of Caledon blue R.C. in vessels. × 480.

Fig. 4. Vesiculation in experimental emphysema, showing loss of alveolar septums, fenestration in septums between alveolar ducts, and Caledon blue R.C. aggregates in the vessels. × 30.

Fig. 5. Fenestration in experimental generalized emphysema grade +. × 60.

Fig. 6. Normal litter mate control for comparison with Figure 5. × 60.

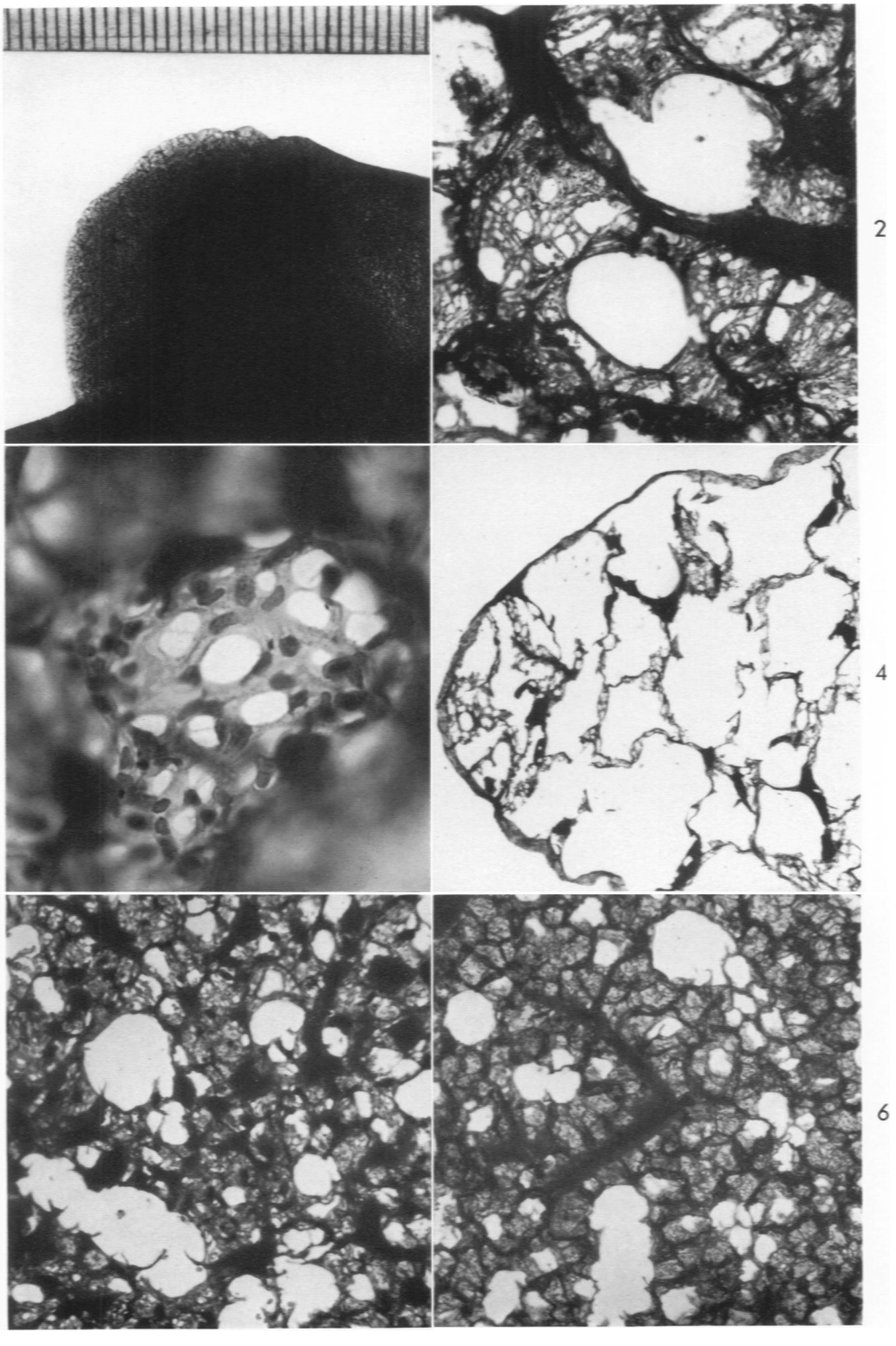
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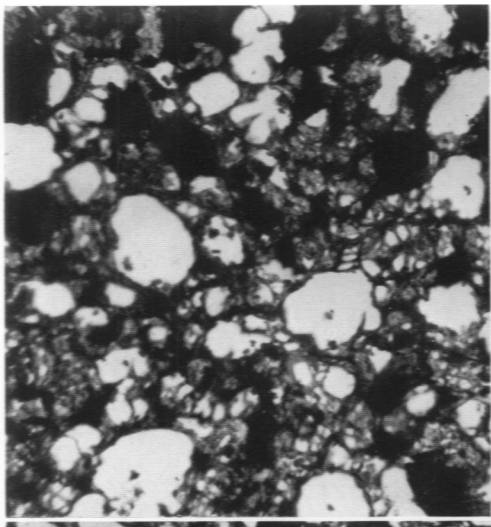
FIG. 7. One of the least fenestrated areas in experimental generalized emphysema grade +++. × 60.

FIG. 8. Normal litter mate control for comparison with Figure 7.

FIG. 9. One of the most fenestrated areas in experimental generalized emphysema grade +++. × 60.

FIG. 10. Normal litter mate control for comparison with Figure 9. × 60.

FIG. 11. Spontaneous generalized emphysema grade +++ in an old rabbit. for comparison with the experimental lesion. × 60.



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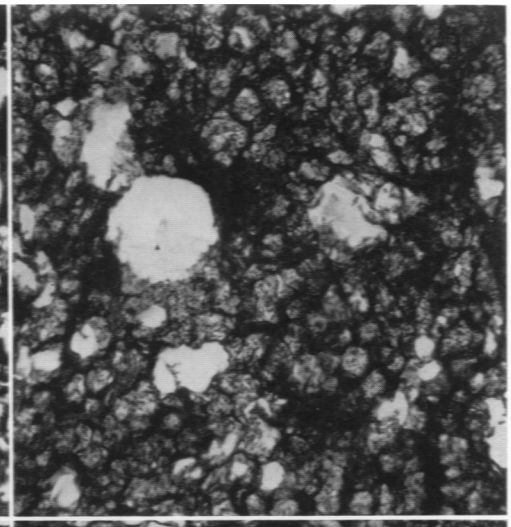

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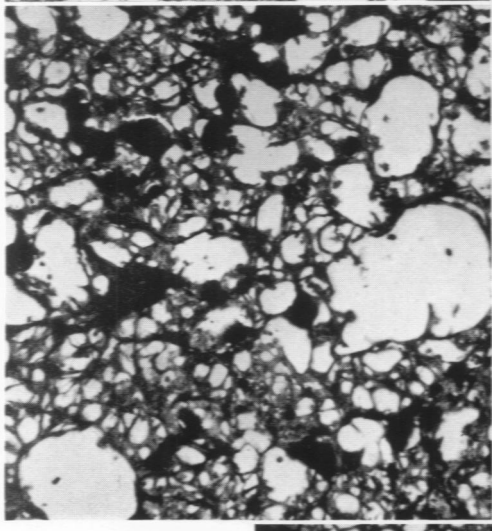

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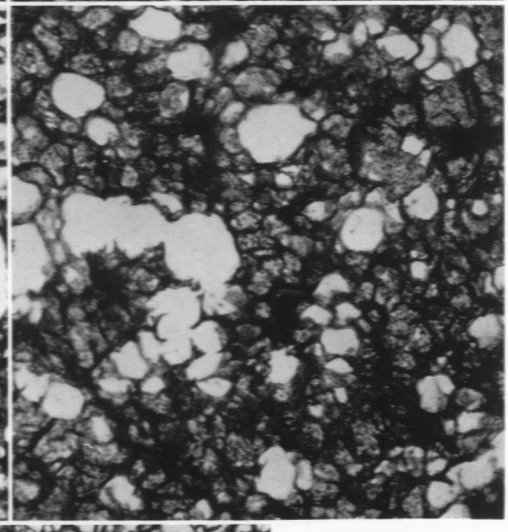

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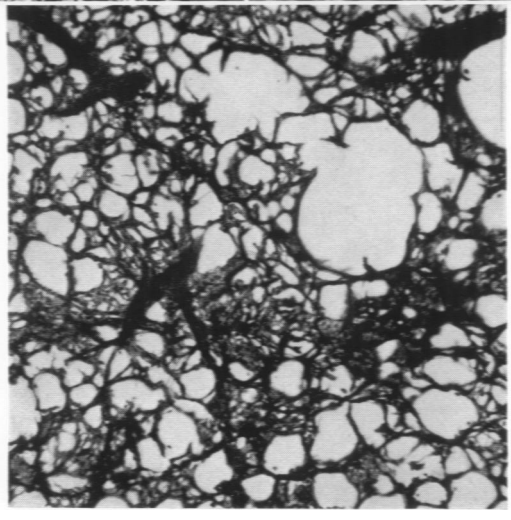

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