Experimental analysis in dogs of the relationship between pulmonary emphysema, alveolitis, and hyperinflation

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This report concerns an endeavour to produce pulmonary emphysema experimentally. Some preliminary features of this programme have been described elsewhere (Azcuy, Anderson, Batchelder, and Foraker, 1961; Anderson, Azcuy, Batchelder, and Foraker, 1963). Inferences drawn from a continuing study of emphysema in man (Anderson and Foraker, 1961 and 1962; Anderson *et al.*, 1963; Azcuy, Anderson, and Foraker, 1962) provided the basis for the current experimental investigation in dogs. Our concepts on pathogenesis may be paraphrased briefly as follows.

The primary event in emphysema is considered to be inflammation of distal parts of the lungs. The designation 'distal' is applicable to non-respiratory bronchioles, respiratory bronchioles, alveolar ducts, and contiguous alveoli. Inflammation in these areas, *i.e.*, bronchiolar-alveolitis, apparently occurs repeatedly in varying degrees during the life of modern man. The constant exposure of the lungs to the irritating influences of the external environment and their position in the vascular circuit are probably largely responsible for such a propensity. The alveolar phase of this process is especially noteworthy. Indeed, it is difficult to conceive of bronchiolitis without some degree of adjacent alveolitis. Alveoli seemingly suffer greater primary damage from peripheral inflammation than bronchioles.

The nature of the parenchymal or alveolar alteration is a function of the intensity of the initial inflammatory reaction. Thus, mild alveolitis is likely to lead to an inconspicuous interstitial alveolar fibrosis. In contrast, severe pneumonic involvement may produce fibrous entrapment and consolidation of entire distal lung foci. Departitioning, the histological hallmark of emphysema, occurs in relation to intermediate degrees of

inflammation. Once such inflammatory dissolution of air-suspended alveoli has occurred, there is practically no chance of continuity being re-established.

The lung ordinarily abides in a state of constantly varying tensions. Moreover, healthy alveolar membranes are extremely resistant to these normal, as well as abnormal, mechanical forces. On the other hand, normal stresses are sufficient to cause separation of parenchyma which has been damaged by inflammation. Exaggerated tissue tensions and dehiscence of degenerate alveolar walls may result (1) from pressure within parenchymal spaces by entrapped air, and (2) by traction from without, due to contracture of fibrotic foci. Air trapping is felt to be the more important of these two mechanisms.

Although there may be multiple causes of air trapping in emphysema, a major source is considered to be a partial collapse of the semi-rigid non-respiratory bronchioles. This is essentially a secondary effect, brought about by dissolution of some of the radially attached alveoli.

Briefly, then, we think that emphysema is largely a result of inflammation coupled with normal and secondarily abnormal mechanical forces.

In order to test this working hypothesis, parenchymal inflammation and air trapping have been induced separately and in combination in dogs, and their effects on the lungs have been systematically analysed. These two factors together resulted in a lung defect highly reminiscent of human emphysema.

SUBJECTS AND METHODS

A total of 31 adult greyhounds were the subjects of this investigation. All recently had been retired from

racing but were otherwise presumably healthy specimens. Fourteen of these served as controls and were designated group I. Pulmonary hyperinflation and, hence, increased tissue tensions were induced by surgically implanting an intratracheal Venturi valve alone into 12 of the dogs. These were designated group II. The valve was designed to cause 50 to 60% more obstruction to expiration than to inspiration (Eiseman, Petty, and Silen, 1959). The remaining five dogs, group III, were subjected to the effects of the Venturi valve plus chemical bronchopulmonary inflammation. Inflammation was produced by the intratracheal instillation of 30 to 50 ml. of a 1% solution of nitric acid every three months through a catheter after the valve had been well established. This provided a convenient method of exposing lung tissue to the irritative action of nitrogen dioxide which is released under such circumstances (Moran and Hellstrom, 1958).

Open lung biopsies were performed on the experimental subjects (groups II and III) at roughly three-monthly intervals until their death. Five of the hyperinflation subjects (group II) were still alive at the time of this analysis, so that only biopsy tissue was studied from these animals. Necropsy and biopsy samples were available from the remaining seven hyperinflation (group II) and all five of the hyperinflation plus inflammation (group III) subjects. Most of these dogs died spontaneously, but a few were sacrificed by the intravenous injection of sodium barbiturate. All control animals were killed in this fashion. The mean duration of life of the group II animals was 7.6 months (range 3 to 11 months). Group III animals had a mean life span of 7 months (range 4 to 10 months).

All post-mortem lung specimens were fixed expanded by running 10% formalin into the trachea *in situ* or into the removed whole lung specimen. Tissue samples were then selected systematically from abnormal and normal (or least abnormal) areas of the lungs. A large number of blocks were chosen in order to minimize sampling error. In the final analysis, there were 153 necropsy samples from group I, 142 from group II, and 84 from group III. In addition there were 52 and 38 biopsy samples respectively from the experimental groups II and III. Three μ thick tissue sections were stained with haematoxylin and eosin, Snook's reticulin, Verhoeff's elastica, and by the periodic acid-Schiff method (Lillie, 1954).

Each tissue section (from the control and two experimental groups) was given a randomized code number and assessed 'blindly' according to a prepared form. The case identity and the lung region from which a given sample was selected were not known to the examiner of the slides at any time. One of us (A. A.) studied every slide. In addition, every fourth and all emphysematous samples were examined by a second individual (A. E. A.), and the interpretations were compared in order to enhance the uniformity of results. The degrees of emphysema and alveolar inflammation were rated numerically as 0, 1+, 2+, and 3+, corresponding to designations of absent, mild, moderate, and severe, respectively. It was found that good agreement could be obtained by different observers with these procedures.

The data so obtained were statistically analysed (Walker and Lev, 1953). Since the number of experimental subjects was relatively small at this phase of the investigation, it was deemed appropriate to compare mean changes per tissue sample rather than per subject.

These general methods were developed previously in one of the earlier studies of human emphysema (Azcuy *et al.*, 1962).

RESULTS

INCIDENCE OF EMPHYSEMA

Control samples Surprisingly, tissue from the controls (group I), all of which was obtained at necropsy, exhibited a mean of 0.59 unit of emphysema per sample (Table I). This set of dogs could perhaps have been predisposed to lung damage through the exertion of their racing experiences, but this was considered unlikely. In any event, parenchymal disruption and expansion was quite prominent in degree at times (Figs. 2 and 3). Such changes were highly reminiscent of emphysema in man and of abnormalities occurring in our experimental subjects (Figs. 4 to 6). Henceforth they will be designated emphysema, although it should be borne in mind that this represents our interpretation of circumstances. Because of the observations of naturally occurring 'emphysema' in dogs, it

TABLE I
NECROPSY SAMPLES FROM GREYHOUNDS WITH EXPERIMENTAL EMPHYSEMA

Group	No. of Subjects	No. of Tissue Samples	Mean Observation Interval (mth.)	Emphysema per Sample*	Groups Compared	t	P
I Controls	14	153	—	0.59	I vs. III	3.1306	0.01 > P > 0.001
II Hyperinflation (tracheal valve)	7	142	7.6 (range 3-11)	0.63	II vs. I	0.4926	P > 0.50
III Hyperinflation (valve) plus inflammation (nitric acid) ..	5	84	7.0 (range 4-10)	0.94	III vs. II	2.7507	0.01 > P > 0.001

* Mean of individual sample ratings of 0, 1+, 2+ and 3+

FIG. 1. *Normal canine lung shown at the two magnifications employed for all the photomicrographs used in this report: (a) Haematoxylin and eosin $\times 32$; (b) Haematoxylin and eosin $\times 128$.*

FIG. 2. *Sample of naturally occurring emphysema from a control dog. Compare with Fig. 1. There is extreme parenchymal departure and dilatation, which is highly reminiscent of the human variety of the disease. Haematoxylin and eosin $\times 32$.*

FIG. 3. Some aspects of naturally occurring emphysema from a control dog: (a) shows emphysema, interstitial 'alveolitis', and a centrally located non-respiratory bronchiole cut at cross section. There has been disruption of the surrounding parenchymal support of this small air passage, resulting in partial collapse and infolding of the internal surface. Haematoxylin and eosin $\times 32$. (b) Higher magnification of interstitial inflammatory reaction of the lung sample seen in (a). It appears essentially as a hypercellularity with thickening of the alveolar walls. Areas of disruption can be seen along the upper region. Haematoxylin and eosin $\times 128$. (c) Connective tissue staining of comparable section of lung from same subject. This shows the interstitial inflammation to be associated with a well-developed, interstitial fibrosis. The capillary bed has been considerably reduced. Reticulin $\times 128$.

FIG. 4. Lung samples with emphysema from experimental subjects exposed to hyperinflation and inflammation. Such changes were substantially greater than in either the control subjects or animals exposed to hyperinflation alone (see Table I). Compare with Figs. 1 and 2. (a) Mild emphysema. Haematoxylin and eosin $\times 32$. (b) Extreme emphysema. Haematoxylin and eosin $\times 32$.

became necessary to note the relative degrees of emphysema in the experimental groups.

Necropsy and biopsy samples from experimental subjects Initially, samples of lung obtained by biopsy from the two sets of experimental subjects (groups II and III) were combined respectively with those obtained at necropsy for comparison with the controls (Table II). Animals with 'pure' overdistention from the valve (group II) were found to have a mean of 0.94 unit of emphysema per sample in contrast to 0.59 unit for the controls (group I) in this phase of the analysis. The hyperinflation plus inflammation samples (group III) showed an even greater mean involvement, i.e., 1.22 units per sample. It was felt, however, that certain considerations rendered inapt strict interpretations of the differences between heterogenous necropsy and biopsy samples.

FIG. 5. (opposite) A sample of lung from a dog subjected to hyper-inflation plus inflammation demonstrating some effects of inflammation: (a) There is considerable emphysema and interstitial reaction. The interstitial response is most pronounced centrally. The bronchiole at the upper left is in a partial state of collapse (note corrugated effect of lumen), apparently due to the loss of surrounding parenchymal support. Haematoxylin and eosin $\times 32$. (b) Higher magnification of portion of bronchiole from Fig. 5a. The radially oriented alveoli are undergoing active dissolution. Haematoxylin and eosin $\times 128$. (c) Higher magnification of central interstitial reaction in Fig. 5a. The alveolar septa appear to have escaped the inflammatory dissolution, which has occurred elsewhere in this sample, and are largely fibrous. Less fibrous septa at upper left seem stretched and attenuated. Haematoxylin and eosin $\times 128$. (d) Same general field as shown in Fig. 5c prepared with connective tissue stain. There is well developed fibrosis and capillary replacement. Note similarity to Fig. 3c. Reticulin $\times 128$.

(b)

(d)

(a)

(c)

(a)

(b)

(c)

FIG. 6. Lung samples from three experimental subjects exposed to hyperinflation plus inflammation. Differing responses to inflammation are demonstrated. (a) Inflammation varies in severity from complete consolidation at lower right of field to negligible involvement at upper left. The intermediate degree of inflammation located centrally is predominantly interstitial. This is also the area of most prominent disruption and expansion, i.e., emphysema. This parenchymal dilatation does not appear to be compensatory due to traction from without. Rather, it seems to be largely the result of communications having developed between adjacent air spaces and to intraluminal dilatation. Haematoxylin and eosin $\times 32$. (b) There is thickening of the central alveolar septa in association with interstitial 'alveolitis'. Less involved septa above seem attenuated and under stretch but are intact. Haematoxylin and eosin $\times 128$. (c) Thickening of alveolar septa in association with interstitial inflammation. The degenerate septa appear to have ruptured and pulled away from the adjacent interlobular septum in a similar way to the separation from bronchioles that has occurred in Figs. 3 and 5. Haematoxylin and eosin $\times 128$.

TABLE II
COMBINED NECROPSY AND BIOPSY SAMPLES

Group	No. of Subjects	No. of Tissue Samples	Mean Observation Interval (mth.)	Emphysema per Sample*	t	P
II Hyperinflation (tracheal valve) ..	12	194	5.8 (range 1-11)	0.94	2.6667	0.01 > P > 0.001
III Hyperinflation (valve) plus inflammation (nitric acid)	5	122	7.4 (range 4-10)	1.22		

* Mean of individual sample ratings of 0, 1+, 2+, and 3+

TABLE III
COMPARISON OF EMPHYSEMA IN NECROPSY* AND BIOPSY SAMPLES

Group	No. of Subjects	No. of Tissue Samples	Mean Observation Interval (mth.)	Emphysema per Sample†	t	P
Necropsy samples (groups II and III) ..	11	226	7.4 (range 3-11)	0.74	11.26	0.001 > P
Biopsy samples (groups II and III)	16	90	4.6 (range 1-9)	1.81		

* Exclusive of control samples. † Mean of individual sample ratings of 0, 1+, 2+, and 3+

It became apparent during the course of the study that biopsied tissue samples demonstrated emphysema much more consistently than those obtained from necropsies, regardless of their experimental grouping (Table III). Thus, in all the experimental subjects (combined groups II and III) there was a mean of 0.74 unit of emphysema per necropsy sample as compared with 1.81 units per biopsy sample. Two possible explanations were considered for this apparent discrepancy. First, superficial lung areas may have been predisposed to emphysema in dogs, as is the lung of man, so that pulmonary tissue taken from living subjects would, out of technical expediency, have shown more emphysema. In the second place, abnormalities in biopsies could have reflected artefact produced by handling and fixation of these small pieces of tissue.

Necropsy samples from experimental subjects
Because of probable sampling of artefactual errors entailed in the use of biopsies, it was next thought appropriate to compare only necropsy tissue (Table I). Here, the extent of emphysema in the samples with hyperinflation (group II) did not

show appreciable variations from the controls. The former showed a mean of 0.63 unit of emphysema and the latter 0.59 unit. On the other hand, there was 0.94 unit of emphysema in samples that had been exposed to hyperinflation plus inflammation (group III). This was substantially greater than in either the hyperinflation specimens or the controls.

RELATIONSHIP OF EMPHYSEMA TO DURATION OF METHODS
If the procedures which were used in this study did have the capacity to produce emphysema, as seemed apparent in the necropsy samples from group III (Table I), a cumulative effect with the passage of time might be anticipated. The severity of emphysema was correlated with the duration of methods in order to explore this possibility (Table IV). There were increments of emphysema in the hyperinflation samples (group II) with longer periods of exposure, but this was not apparent at an acceptable probability level. A higher correlation between severity and time occurred with hyperinflation plus inflammation (group III), however, even though the mean

TABLE IV
RELATION OF SEVERITY OF EXPERIMENTAL EMPHYSEMA WITH DURATION OF METHODS IN NECROPSY SAMPLES

Group	No. of Subjects	No. of Tissue Samples	Mean Observation Interval (mth.)	Emphysema per Sample*	Correlation Coefficient	P
II Hyperinflation (tracheal valve) ..	7	142	7.6	0.63	0.0445	P > 0.10
III Hyperinflation (valve) plus inflammation (nitric acid)	5	84	7.0	0.94	0.2164	0.05 > P > 0.02

* Mean of individual sample ratings of 0, 1+, 2+, and 3+

interval was somewhat less than in samples from subjects with hyperinflation alone.

LOCAL TISSUE RELATIONSHIPS BETWEEN EMPHYSEMA AND ALVEOLITIS In analysing the association between emphysema and inflammation locally in the lungs, only necropsy samples were used, since inflammation in biopsy samples was partially artefactual due to manipulation of the small pieces of tissue at thoracotomy.

Increments of emphysema were closely related with greater degrees of interstitial alveolar inflammation in all three groups of necropsy samples (Table V). In the controls (group I), this varied from a mean of 0.67 unit of inflammation with no emphysema to 2.45 units per sample with severe emphysema. Inflammation varied from 0.74 unit

TABLE V
RELATION BETWEEN SEPARATE NECROPSY SAMPLE RATINGS OF INTERSTITIAL ALVEOLAR INFLAMMATION AND EMPHYSEMA

Degree of Alveolitis	Degree of Emphysema				Mean Emphysema
	0	1+	2+	3+	
I Control samples (0.001 > P*)					
0	28	6	0	0	0.18
1+	49	35	3	0	0.47
2+	2	18	9	1	1.30
3+	0	0	1	1	2.50
Mean alveolitis ..	0.67	1.20	1.85	2.45	
II Hyperinflation samples (0.001 > P*)					
0	23	1	0	0	0.04
1+	41	42	3	0	0.56
2+	5	15	11	0	1.19
3+	0	0	0	1	3.00
Mean alveolitis ..	0.74	1.24	1.79	3.00	
III Hyperinflation plus inflammation samples (0.001 > P*)					
0	13	0	0	0	0
1+	17	30	5	0	0.77
2+	0	3	10	3	2.00
3+	0	1	0	2	2.33
Mean alveolitis ..	0.57	1.15	1.67	2.40	

* Based on χ^2 analysis

per sample with no emphysema to 3 units with severe emphysema in the hyperinflation subjects (group II). In dogs exposed to hyperinflation plus inflammation, alveolitis varied from a mean of 0.57 unit per sample with no emphysema to 2.40 units with severe emphysema. It is of interest that milder degrees of inflammation were frequently unassociated with emphysema but that emphysematous foci were rarely free of discernible inflammation. It is also noteworthy that in the higher grades of emphysema, the relative extent of inflammation lessened somewhat.

A study of individual areas of abnormality revealed progressive phases of an inflammatory

sequence. This was qualitatively similar in all three groups. The earliest alteration was an interstitial infiltration of alveolar septa with polymorphonuclear and mononuclear cells. This appeared simply as a hypercellularity at times (Figs. 3b, 6b, and 6c). Where inflammation was more prevalent there was also an intraluminal exudate (Fig. 6a). Interstitial inflammation was associated with fragmentation of the elastic fibres and variable necrosis of the septa. Some septa were completely disrupted by interstitial necrosis, resulting in communications between adjacent distal air spaces (Figs. 3b, 5b, and 6c). Bronchioles in such areas frequently showed diminished parenchymal support and appeared collapsed, though contracture may have contributed to this effect (Figs. 3a and 5a). Later, surviving alveolar membranes showed interstitial fibrosis and loss of capillaries (Figs. 3c, 5c, and 5d). They were often thicker than normal. Maximum areas of inflammation occasionally proceeded to large parenchymal openings analogous to those seen when damage was predominantly interstitial. More often, however, they produced grossly scarred foci (Fig. 6a). Adjacent to scarred areas, the alveolar membranes usually appeared stretched and attenuated (Figs. 5c and 6b).

COMMENTS

Many attempts have been made to produce emphysema experimentally since the first description of the affection by Laennec nearly a century and a half ago (1819). In general, they have been unsuccessful and poorly controlled. The essential aspects of these endeavours are considered in two recent comprehensive papers (Eiseman *et al.*, 1959; Strawbridge, 1960b). They have all attempted to simulate some mechanism considered by the investigators to be important in the pathogenesis of the disorder in man.

The important theories regarding the pathogenesis of human emphysema have been reviewed in a historical account by Strawbridge (1960a). Abnormal mechanical tensions (distension from within distal air spaces by trapped air and from without by external traction), inflammation, ischaemic atrophy (from vascular occlusion), fatty degeneration, desquamation of alveolar epithelium, and constitutional deficiencies have all been implicated. The mechanical, inflammatory and ischaemic theories have had the most advocates individually.

A number of authorities have propounded a specific process, but it is now widely suspected that emphysema is the product of multiple factors. Since parenchymal disruption and expansion can

occur in relation to a variety of known entities, e.g., tuberculosis, sarcoidosis, and silicosis, it is quite likely that multiple occult mechanisms can produce similar changes. A single mechanism may be dominant, but various factors probably contribute to the end result in a given case. Therefore, we have suggested that emphysema is the result of an interplay between inflammation and mechanical factors (Anderson and Foraker, 1961 and 1962; Azcuy *et al.*, 1962). Even this represents an oversimplification. Nevertheless, it is consistent with changes which we have found to be most prevalent, and it provides a rational foundation to which other agents might contribute.

The evidences for and against air trapping (considered by us to be the major source of increased mechanical forces) and parenchymal inflammation as factors of importance in the pathogenesis of emphysema will be briefly reviewed in the light of previous evidence and the present experimental study. Other data bearing on ischaemic atrophy will also receive comment.

THE ROLE OF AIR TRAPPING Despite valid objections, mechanical pressure from trapped air (due to airways obstruction) has seemed to have the most advocates individually as a disruptive mechanism in emphysema, particularly in recent years. This is probably the result of dynamic concepts of physiologically oriented workers. Although intra-alveolar mechanical forces are undoubtedly increased, a crucial factor is the capacity of normal pulmonary tissue to withstand these forces. Morphological observations in two types of 'pure' obstructive lung disease, *i.e.*, congenital lobar emphysema (Leopold and Gough, 1957) and fatal bronchial asthma (Gough, 1961), seem more relevant than physiological considerations in this respect. Essentially, studies in both these conditions have shown that normal alveolar septa can undergo extreme overdistention without rupture. Previous experimental attempts by others to produce emphysema by obstructing the expiratory flow of air from the lungs of animals have resulted in the same conclusion (Eiseman *et al.*, 1959). Overdistention has resulted, but there has been little disruption of lung tissue. Our studies in dogs have confirmed this.

In an earlier report (Azcuy *et al.*, 1961), we found that dogs exposed to sustained pulmonary overdistension alone (Venturi valve) developed a prominent barrel deformity of the chest. Pascal's principle relating to the equal transmission of pressures of enclosed fluids was invoked in explaining the defect. In the present morphological

analysis, however, parenchymal departitioning was no greater in this group than in the controls, even after a mean interval of 7.6 months (range up to 11 months). Apparently an additional or separate factor was needed to initiate the entire structural picture of emphysema.

If this reasoning were not correct, and if the cause of emphysema actually did lie in air passage narrowing, we would expect the morphological basis for the obstruction to be a primary change. This has not been the case. Rather, it has appeared that narrowing of small air passages in emphysema is largely secondary to a loss of supporting, radially attached alveoli (Anderson and Foraker, 1962). The significant lesion of emphysema is probably a destructive one of the alveolar septa. The nature of this destructive process is a subject for further analysis. Its most likely basis is, we consider, inflammatory.

THE IMPACT OF INFLAMMATION Expressions of inflammation are intimately associated with those of emphysema in man. Clinically, these may consist of cough, sputum, and acute chest illnesses. Morphologically, the grosser phases of inflammation are often apparent in necropsy specimens as bronchopneumonia, pleuritis, and residual fibrosis. Close attention to the fine structure of alveolar septa in our laboratory has revealed subtle, but widespread, comparable alterations (Anderson and Foraker, 1960 and 1961; Azcuy *et al.*, 1962). These included interstitial alveolitis, thickening of the septa, necrosis, rupture of elastica, and interstitial fibrosis. These features have been noted in varying degrees by others (Sudsuki 1899; Orsós, 1907).

Despite the well-known prevalence of inflammation with the inevitable sequels of necrosis and fibrosis in emphysema, its full recognition as a pathogenetic mechanism has been tardy. Sudsuki (1899) proposed that emphysema was caused primarily by mechanical factors but assumed that inflammation of lung tissue could enhance its development. Letulle (1928) considered inflammatory weakening of the lungs as important as mechanical factors; however, his concepts did not invoke lasting support. A few contemporary workers have also stressed the significance of inflammation in emphysema. Reid (1954) proposed that it could result from peripheral lung damage in association with bronchitis. Leopold and Gough (1957) considered that inflammation was most intimately associated with the centrilobular variant of the disease. It is our opinion that panlobular, as well as centrilobular, emphysema also commonly occurs in relation to inflammatory damage.

Regardless of the lobular distribution or of co-existing bronchitis, a crucial lesion of emphysema in man appears to be an alveolitis, the genesis of which has been presented elsewhere (Anderson and Foraker, 1961) and briefly reviewed in the introduction of this report. The alveolar defects in the canine lungs which we exposed to inflammation were similar from a morphological standpoint to alveolitis described in human emphysema. Moreover, as in man (Azcuy *et al.*, 1962), an increasing severity of experimental alveolitis was generally associated with increments of emphysema. There was also an enhancing effect with time.

Certain discrepancies in the occurrence of interstitial alveolar inflammation and emphysema deserve comment. Alveolitis sometimes was noted in the absence of emphysema in our experimental subjects. This indicates that lesser degrees of damage did not necessarily cause rupture of the septa. Inflammation often seemed to progress simply to an interstitial alveolar fibrosis. On the other hand, emphysema in dogs was almost always associated with some extent of alveolitis. These circumstances tend to designate precedence to alveolitis, with interstitial fibrosis and parenchymal departitioning as consequences.

In contrast with the comparative prominence of interstitial inflammation in the more intact lung areas, experimental samples with higher grades of emphysema showed relatively less alveolitis. There are two possible explanations for this apparent paradox. First, areas of greater destruction contained less parenchyma in which interstitial inflammation might be observed. Secondly, some of these 'burnt-out' lesions appeared interstitially fibrous, suggesting a more active inflammatory process at some previous time.

It may be argued that the addition of the tracheal valve and its coincidental overdilation were artificial and complicated the picture in our study. This was done in order to simulate the mechanical forces known to be prevalent in human emphysema. They presumably develop secondarily in man, but are considered to enhance emphysema formation, once in effect. The failure of dogs with the valve alone to develop an excessive degree of emphysema indicates that abnormal mechanical tensions alone have poor or only secondary capacity to cause disruption of normal parenchyma, as already mentioned. Their effect is probably only potentiating and may not be necessary at all. We intend to explore this possibility further by exposing animals to the effects of inflammation alone.

ISCHAEMIC ATROPHY Ischaemic atrophy has also been indicated as a source of tissue damage in human emphysema (Strawbridge, 1960a and b). The co-existence of occlusive vascular changes with the disorder at both the level of capillaries and in small muscular arteries has provided the main support for this concept, as noted in a recent review (Liebow, 1959). On the other hand, it has also been stressed that extreme thickening of the small muscular arteries of the lungs can occur with ageing alone in the absence of emphysema (McKeown, 1952). The extreme pallor of many 'normal' ageing lungs may be cited in this connection. McKeown (1952), in an effort to reconcile these seeming incongruities, reasoned that emphysema merely accentuates the normal structural changes of advancing years in the pulmonary circulation. This idea provides a logical explanation for the intimate relationships that have been shown to exist in man between pulmonary arteriosclerosis and ageing on the one hand and emphysema on the other. Opinions, however, are by no means unanimous, and some workers still attribute an important role to arteriosclerosis.

Strawbridge (1960b), endeavouring to establish the role of ischaemic atrophy in the pathogenesis of emphysema, performed an experimental study in rabbits. He produced occlusion of the small pulmonary arteries by intravenous injection of particulate dye-stuff. He noted an increased prevalence of emphysema in this group, as compared with the controls, and thought that this was the result of ischaemia. It is of interest, however, that he reported a high incidence of associated interstitial pneumonitis in his subjects.

Utilizing a similar theme, but employing a different approach, Edwards (1961) observed an emphysematous defect in horses after injecting their bronchial arteries with chlorpromazine. In addition to parenchymal expansion and departitioning, his subjects showed necrotizing endarteritis, alveolitis, and bronchiolitis. Ischaemic necrosis may have caused the emphysema, as was suggested. It is also reasonable to suspect that one of the concurrent variations of inflammation that occurred may have been at fault, as was suggested. Inflammation induced by other avenues might well have a similar effect.

PATHOGENESIS OF EXPERIMENTAL EMPHYSEMA Emphysema has been characterized anatomically as an overexpansion of the distal air spaces of the lung, accompanied by destructive changes of the alveolar walls (American Thoracic Society, 1962). We have been able to produce a structural defect

in dogs which conformed to this definition. We now can review the circumstances leading to the development of this lesion.

Normal alveolar septa in dogs demonstrated a remarkable capacity to withstand chronic overdistension (from an intratracheal valve). A separate factor was needed before emphysema occurred. Alveolitis, resulting from exposure to nitrogen dioxide, seemingly provided this critical feature. The parenchymal departitioning attendant to such inflammation apparently was accomplished through direct destruction and reduction of the innate resistance of alveoli to mechanical forces.

In most body tissues, scarring is the natural sequel to inflammatory destruction. Slight alveolitis also produced scarring interstitially in the lungs of our experimental subjects. Owing to peculiarities of lung structure, however, the lung response to greater degrees of inflammation was modified and was roughly comparable to that of damaged fabric. Thus, individual alveolar walls were normally under constant stretch and surrounded by air, so that inflammatory dissolution was likely to be permanent. With recurrent destruction and separation, large defects and widespread communications between adjacent distal air spaces developed. When alveolar partitions were not completely destroyed, thickening with disruption of elastica and obliteration of capillaries frequently occurred. Fewer fibrous membranes became stretched and attenuated.

INFERENCES For the past several years, we have been engaged in a study of the pathogenesis of pulmonary emphysema. In previous communications, attempts were made to describe the evolution of structural changes which presented in man. When dogs were subjected to influences simulating those observed in the disease in man, emphysematous defects ensued. This tends to confirm the potentialities of those influences. In short, emphysema may be largely an expression of an interplay between inflammatory and mechanical factors (normal and secondarily abnormal) in peripheral parts of the lung.

It should be stressed that inflammation is a non-specific response to a wide variety of irritants. Nitrogen dioxide from the nitric acid used in this study merely provided a convenient method of inducing inflammatory changes. Although such agents are present in the environment of civilized man (Haagen-Smit, 1961), another factor (or factors) may well be more important in the development of the inflammatory parenchymal destruction that characterizes human emphysema.

One prevalent irritant, tobacco smoke, is currently being studied in our laboratory under conditions similar to those already utilized for nitric acid.

SUMMARY

An investigation of experimental emphysema in greyhounds has been conducted in an attempt to shed light on the pathogenetic role of mechanical and inflammatory factors. There were three groups of animals: (1) controls, (2) subjects with sustained pulmonary hyperinflation (intratracheal Venturi valve), and (3) subjects with hyperinflation and parenchymal inflammation (Venturi valve plus dilute solution of nitric acid).

Lung samples from the controls unexpectedly demonstrated significant degrees of naturally occurring 'emphysema'. In comparison, samples comparably chosen from dogs with 'pure' hyperinflation for sustained periods did not show greater amounts of emphysema than the controls. On the other hand, there was considerably more emphysema in samples from dogs with hyperinflation plus inflammation. There was also a cumulative effect with time in this last group.

These circumstances were comparable to changes previously described in man and we think they support the concept that emphysema can and does result from an interplay between peripheral lung damage and secondary mechanical processes.

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