

Metastatic Emphysema

A Mechanism for Acquiring Inguinal Herniation

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Since our previous work had indicated that veterans with inguinal herniation demonstrated qualitative and quantitative changes in connective tissue, we tested the hypothesis that a possible mechanism for the defect was chronic exposure to circulating proteases generated in the lung by cigarette smoke. We investigated 59 men (average age: 60 years) with either primary direct or indirect hernias. Most of the patients smoked. Circulating serum elastolytic activity was significantly greater in patients with direct hernias who smoked when compared with controls ($p < 0.001$). In addition, the serum alpha-1-antitrypsin inhibitory capacity was significantly lower in this category than controls ($p < 0.001$). Patients with indirect defects who smoked also had significantly higher elastolytic values but to a lesser degree ($p < 0.01$). Serum antiprotease and protein concentrations were within the normal range in all categories. Our results indicate that an imbalance between blood proteases and antiproteases, resulting from chronic smoking can damage connective tissue in the groin as well as the lung.

WHEREAS THE ANCIENTS considered ruptures to arise from tearing of the peritoneum, all now agree "The fundamental rupture, relaxation or discontinuity . . . in cases of groin hernia occurs in the deeply placed transversus abdominis - transversalis fascia layer."¹ Modern surgical thought regarding causation has become dominated by the saccular hypothesis of the Australian pediatric surgeon, Russell. He stated, "The theory that rejects the view that hernia can ever be 'acquired' in the pathological sense."² . . . and ". . . we may have an open funicular peritoneum with perfectly formed muscles: we may have congenitally weak muscles with a perfectly closed funicular peritoneum: and we may have them separately or together, in infinitely variable gradations."³ The only serious

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attempts to refute Russell's ideas, those of Keith in 1923, and Harrison the previous year, were soon ignored. The former had written, "We are so apt to look on tendons, fascial structures and connective tissues as dead, passive structures. They are certainly alive, and the fact that hernias are so often multiple in middle-aged and old people leads one to suspect that a pathologic change in the connective tissues of the belly wall may render certain individuals particularly liable to hernia."⁴ Harrison, in 1922, stated:

When we consider the dozens and hundreds of men who first show a hernia at 50 or 60, after their active life is over, the hypothesis (saccular) becomes improbable to say the least. However, the main objection to the theory is that, even if true, it gives us no useful guidance. In and of itself the persistence of a more or less elongated narrow processus vaginalis would not predispose to a future hernia if all elements of strength present in the wall of the abdomen were also present in the wall of the process . . . The muscles, however, appeared to be normal . . . The natural conclusion is that the cause of an indirect hernia, as of a direct hernia, is the failure of the transversalis fascia to withstand the intra-abdominal pressure to which it is subjected.⁵

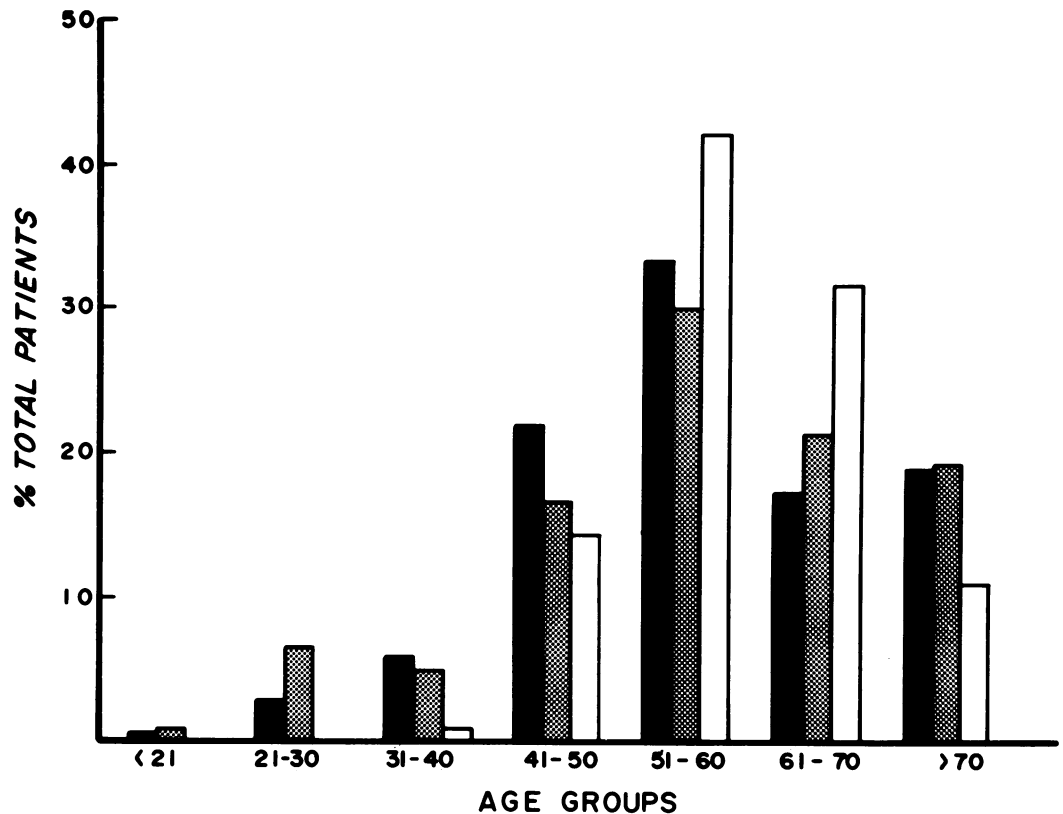
Our own interest in the cause of inguinal herniation was stimulated by a similar question: why do so many veterans, despite normal physical examinations in the military, later develop inguinal herniation. Serendipitously, we noticed, while using a modified preperitoneal approach,⁶ that the rectus sheath some inches above the inguinal defect appeared thin and felt greasy, especially with direct herniation. Samples obtained

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FIG. 1. Age distribution of 2538 patients with inguinal herniation; direct defect (solid bar, $n = 1083$), indirect defect (hatched bar, $n = 1455$) and cancer of the lung (open bar, $n = 475$) among male veterans operated on at the VAMC, Little Rock, 1966–1980.



from patients of similar age and build being operated on for intra-abdominal conditions other than herniation, weighed significantly more per unit area. Bilateral herniation was associated with more severe atrophy than unilateral. Surprisingly, this was not a senile phenomenon since weight of the biopsy specimens did not relate to age or muscle mass.⁷ Hydroxyproline and, therefore, collagen, which comprises 80% of the dry weight of the rectus sheath, was strikingly decreased.⁸ Extraction of the remaining collagen revealed altered precipitability and a reduced hydroxyproline–proline ratio. Intermolecular cross-linking was, unlike experimental lathyrism,⁹ unaffected, but synthesis of hydroxyproline was inhibited and there was variability in the diameter of the collagen fibrils, some of which lay within fibroblasts.¹⁰ Similar electron microscopic findings were present in pericardial and skin biopsy specimens obtained from these patients,¹¹ and have also been described in connective tissue tumors,¹² pulmonary emphysema,¹³ and other conditions.^{14,15}

Thus, in men with groin hernias, fascial degeneration was not restricted to the posterior wall (floor) of the inguinal canal, but a quantitative and qualitative collagen deficiency was identified not only in the rectus sheath some inches from the protrusion, but in distant parts of the body. These patients were considered to be suffering from a true connective tissue disease.¹¹

Since the lesion was more marked in those with direct

herniation which occurred predominantly (and often bilaterally) in middle-aged veterans who also suffer heavily from lung cancer, and emphysema, we wondered whether the changes observed could be caused by circulating proteases generated in the lungs of these smokers. The present study was undertaken to test this hypothesis because

It is most important that surgeons should form a just and true opinion concerning the manner in which hernias arise. If they occur only in those who have hernial sacs already formed during fetal life, then we must either excise the sacs at birth or stand by and do nothing but trust to luck. But if . . . the occurrence of hernia is due to circumstances over which we have control, then the prevention of hernia is a matter worthy of our serious study.⁴

Patient Material

We have followed all patients operated on for inguinal herniation at the Little Rock VA Medical Center from 1966 to 1980. For the purposes of the present study, we have restricted our data to those who presented with primary herniation. These cases have been divided into those with indirect, direct and mixed defects, either unilateral or bilateral. All mixed types (those having both indirect and direct defects) have

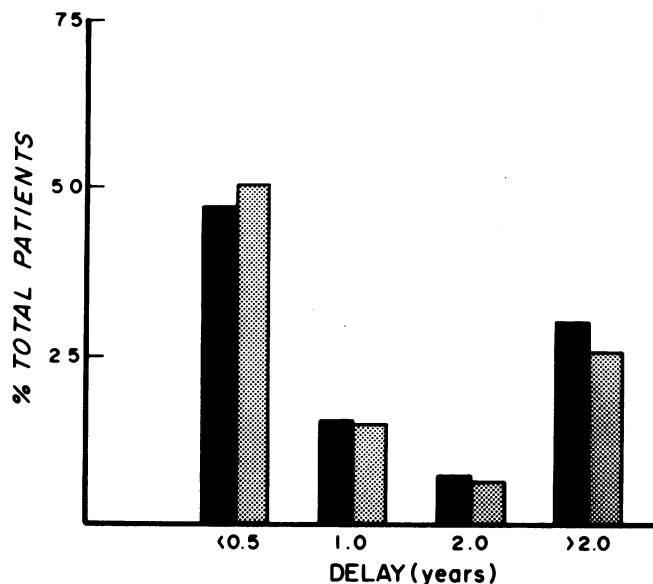


FIG. 2. Comparison of direct (solid) and indirect (hatched) hernia patients in regard to the delay between onset of symptoms and repair.

been classified under their direct component. There was a total of 2,538 patients, 1,455 (57.3%) had indirect defects and 1,075 (42.7%) had direct herniation. The age distribution of these patients is shown in Figure 1. Interestingly, the distribution of direct and indirect defects in this population is remarkably similar, with a peak incidence in the sixth decade. This happens to coincide with the peak incidence of 475 patients with cancer of the lung resected in our hospital during the same period of time. The delays between onset of symptoms and repair for the two types of inguinal herniation are also practically identical (Fig. 2). Right sided herniation was predominant for both indirect (52.4%) and direct (40.9%) defects (Table 1). Bilateral herniation was over four times as common in direct herniation (30.4%) as with indirect defects (7.7%). Most of the 2,538 patients with inguinal herniation admitted to smoking (74.8%; Table 2). The incidence and pattern of smoking activity as determined by a questionnaire, was not different for those with indirect as opposed to direct defects. During the last year, we have investigated more intensively patients who underwent operations for primary inguinal herniation. Those patients with a history of lung disease, alcoholism, connective tissue disorder, or recurrent herniation were excluded from the study. Healthy male volunteers (controls) of similar age were taken from the hospital staff.

Methods

Pulmonary function studies including FVC, FEV₁, FEF (25–75%) and FET (25–75%) were determined with a Model 525 Med-Science® Pulmometer, a wedge

spirometer, and a Hewlett-Packard® X-Y recorder. Arterial blood gas composition (PO₂, PCO₂) and pH were measured using an Instrument Labs® Model 813 blood gas analyzer. The results were compared with predicted normal values and criteria for the diagnosis of chronic obstructive pulmonary disease. Samples of whole blood from each subject were obtained on the morning of surgery. After clotting briefly at room temperature, iced samples were centrifuged and sera were frozen at –50 C. Serum alpha-1-antitrypsin (α₁AT) and alpha-2-macroglobulin (α₂M) concentrations were determined by radial immunodiffusion¹⁶ with standards and internal controls (Melyo Laboratories). Isoelectric focussing on gels of 1% agarose (Isogel, FMC Corporation) and 2% (pH 3.5–5.0) ampholine (Bio-Rad) were used to determine α₁AT phenotyping. Gels were pre-focused at 1200 v for 30 minutes and run at 1200 v for 60 minutes, then 1600 v for 20 minutes. Gels were fixed in 4% trichloroacetic acid, 3% sulfosalicylic and 25% methanol for 20 minutes, dried, soaked for 15 minutes in 50% methanol and, then stained for five to ten minutes in 0.10% Coomassie Blue R-250 (Bio-Rad) in 50% methanol. Serum protein values were obtained by the Biuret assay using bovine serum albumin as a standard. Elastolytic activity was measured by radial diffusion on plates of 10% agarose (Seakem ME, FMC Corporation), 20% K-elastic⁷ with pancreatic elastase (Schwarz-Mann 62U/mg) standards. Values were expressed as μg/ml pancreatic elastase equivalents. Serum trypsin inhibitory capacity was determined in a total volume of 2 ml in the presence of 10⁻³ M benzoyl-arginine-p-nitroanilide. Trypsin activity, standardization of trypsin with soybean trypsin inhibitor and calculation of trypsin inhibitory capacity were performed as described.¹⁸ All assays described above were per-

TABLE 1. Location of Primary Indirect and Direct Inguinal Hernias

Type of Hernia	Location	Number	Per Cent
Indirect	Right	763	52.4
	Left	580	39.9
	Bilateral	112	7.7
		1455	100.0
Direct	Right	383	35.4
	Right mixed*	61	5.6
	Left	274	25.3
	Left mixed*	38	3.5
	Bilateral	226	20.9
	Bilateral mixed†	101	9.3
		1083	100.0

* Indicates patients having both direct and indirect defects on the right or left side.

† Indicates patients having a direct hernia on one side and indirect herniation on the other. Fifty-nine patients had the direct defect on the right, 42 on the left.

TABLE 2. *Smoking History of 2538 Veterans with Primary Inguinal Herniation*

	Total	Per Cent	Indirect	Per Cent	Direct	Per Cent
Nonsmokers	639	25.2	378	26.0	261	24.1
Smokers	1899	74.8	1077	74.0	822	75.9
Totals	2538	100.0	1455	100.0	1083	100.0
Cigarettes						
<1 PPD	258	13.6	154	14.3	104	12.6
1 PPD	887	46.7	478	44.4	409	49.8
>1 PPD	467	24.6	277	25.7	190	23.1
Pipe	183	9.6	102	9.5	81	9.9
Former smokers	104	5.5	66	6.1	38	4.6
	1899	100.0	1077	100.0	822	100.0

PPD: packs per day.

formed in duplicate, some in triplicate. Statistics were analyzed using the nonpaired t-test for the significance of difference between means ($p < 0.01 =$ significant; $p < 0.001 =$ highly significant).

Results

A total of 88 men, 29 controls and 59 with inguinal herniation were assayed for serum elastolytic and antiproteolytic activity (Table 3). These individuals had been screened for α_1 AT phenotype and only MM phenotype men were investigated, less than 10% being discarded because of other phenotypes. The average age of the controls and herniated patients was in the sixth decade, which was consistent with our overall series (Fig. 1). The incidence of direct (32) and indirect (28) defects was approximately equal, as was their ages (mean 58.4 and 61 years). About two-thirds of our controls smoked, there being no age difference with those who did not. Similarly there were more smokers than nonsmokers in our sample of hernia patients.

Overall, the serum elastolytic activity, expressed as $\mu\text{g/ml}$ of pancreatic elastase equivalents for the 59 patients with hernia (103.2) although higher than that of the controls (96.0) was not significantly different. How-

ever, when the data were subdivided into the two types of hernias and into smokers or nonsmokers, significant differences emerged. The most marked change was between nonsmoking controls, 83.3, and smokers with direct hernias, 114.1 ($p < 0.001$). Other significant differences were seen between "direct hernia" smokers, 114.1 and "direct hernia" nonsmokers, 92.3 ($p < 0.001$). Patients with indirect defects also showed a higher elastolytic activity if they smoked, 102.6 compared with their nonsmoking counterparts, 95.2 (ns), and the smokers in the indirect defect group had values significantly higher than nonsmoking controls ($p < 0.005$). It is of interest that within the control group, those who smoked had significantly more elastolytic activity than those who did not ($p < 0.01$).

We did not observe any significant differences in the concentrations of α_1 AT in our various categories. The serum α_2 M levels fluctuated but were within the normal range for men in our age group.

Total serum protein concentrations were within the normal range in all classifications. Table 4 demonstrates that when a sample of "direct hernia" smokers were compared with control nonsmokers, there was a significant difference ($p < 0.001$) in the trypsin inhibitory capacity of the serum even though the concentra-

TABLE 3. *Serum Elastolytic and Antiproteolytic Activity (\pm SD) in Control Volunteers and Patients with Inguinal Herniation*

	Number	Age (Years)	Serum α_1 AT (ml/100 ml)	Serum α_2 M (mg/100 ml)	Elastolytic Activity ($\mu\text{g/ml}$ Pancreatic Elastase Activity)
Controls	29	51.9 \pm 14.5	214.0 \pm 73.6	318.9 \pm 99.1	96.0 \pm 18.9
All hernias	59	59.6 \pm 11.8	221.2 \pm 82.6	212.3 \pm 65.6	103.2 \pm 17.2
Direct hernia	32	58.4 \pm 11.4	233.4 \pm 85.2	204.0 \pm 60.4	106.2 \pm 18.8
Indirect hernia	27	61.0 \pm 12.4	205.4 \pm 78.0	220.6 \pm 70.8	99.3 \pm 14.2
Control: nonsmokers	10	52.8 \pm 14.3	206.7 \pm 43.7	281.0 \pm 81.3	83.3 \pm 12.6
Control: smokers	19	51.4 \pm 15.2	218.5 \pm 86.1	329.0 \pm 103.4	102.8 \pm 18.5
Direct: nonsmokers	14	60.8 \pm 13.6	217.5 \pm 71.3	188.9 \pm 50.2	92.3 \pm 9.7
Direct: smokers	18	57.7 \pm 11.2	244.8 \pm 94.3	213.8 \pm 66.0	114.1 \pm 17.3
Indirect: nonsmokers	12	66.7 \pm 9.2	216.6 \pm 72.8	211.1 \pm 72.5	95.2 \pm 10.7
Indirect: smokers	15	56.6 \pm 12.7	196.1 \pm 86.4	229.3 \pm 71.2	102.6 \pm 16.1

TABLE 4. Serum Trypsin-inhibitory Capacity (TIC) in Patients with Direct Inguinal Herniation Who Smoke Compared with Nonsmoking Controls

	n	TIC \pm SD*	p Value†
Direct hernia smokers	11	0.684 \pm .297	<0.001
Control nonsmokers	6	1.055 \pm .318	—

* Milligram trypsin inhibited per ml of serum.

† Nonpaired t-test.

tions of the two major antiprotease components α_1 AT and α_2 M were similar (Table 3). Pulmonary function data in the various categories demonstrated no significant differences in pH or PCO₂. The mean PO₂ fell below 80 mmHg only in control smokers (70.1) and the direct hernia patients (79.5). Again, in the ventilation data, smokers, both controls and those with direct hernia, showed lower mean FEF values, 1.84 and 1.58, respectively, versus control nonsmokers, 2.17 L/sec. "Direct hernia" smokers had a prolonged mean MMFT, 2.30 sec, versus a control (nonsmoking) value of 1.84. In regard to vital capacity, in each of the two hernia categories as well as the controls, the mean values for the smokers were less than the nonsmokers. Review of the chest roentgenograms showed a small proportion (16%) of previously undiagnosed and apparently asymptomatic chronic obstructive lung disease, and the majority of these cases were discovered in the direct hernia group who smoked.

All of the 2,538 hernia patients had a routine preoperative WBC count. We randomly retrieved these data from 200 smokers and 200 nonsmokers (Table 5). The former had a significantly ($p < 0.001$) higher mean count, 7910 mm³ than the latter, 6730 mm³. There was no difference in WBC counts in the nonsmoking hernia categories. The mean WBC count in those who smoked and had direct defects, 8140 mm³, exceeded that for the "indirect hernia" smokers, 7730 mm³, but the difference was not significant.

Discussion

Twenty years ago, pulmonary emphysema (Latin: swelling) was ascribed to wear and tear of the connective tissue in the lungs from blowing, coughing and bronchiolar obstruction abetted by aging. Similar mechanical forces are still being invoked to explain the incidence of swelling of the groin (inguinal herniation) in the adult. However, our understanding of the mechanisms involved in lung damage produced by smoking was greatly enhanced, in 1963, when Laurell and Eriksson¹⁹ described an association between low serum levels of the protease inhibitor α_1 AT and a rare genetically transmitted form of pulmonary emphysema. This discovery implied that the absence of this globulin allows

endogenous enzymes to destroy alveoli. Support for such a suggestion was provided by the successful induction of emphysema in animals using intratracheal administration or aerosol inhalation of proteolytic enzymes with high elastolytic activity.²⁰ Recently, purified human neutrophil polymorphonuclear leukocytic elastase has been shown to produce this experimental lesion.²¹ Alveolar macrophages increase tenfold²² in the lungs of smokers and also contain elastase, which is released²³ after phagocytosis or exposure to smoke.²⁴ Irritants evoke a neutrophil chemotactic factor from the lung²⁵ and oxidants in cigarette smoke markedly reduce the protease inhibitor efficacy of α_1 AT.²⁶ Thus, the biochemical hypothesis for the destruction of pulmonary connective tissue in emphysema envisages a local disturbance of the normal balance between proteolytic enzymes and their inhibitors favoring the former.

The present study was based on the possibility that the well-known association between inguinal herniation and pulmonary disease was not simply due to coughing, but represented a prolonged metastatic effect in the groin (a locus minoris resistentiae in the male, because of the passage of the testis into the scrotum) of circulating proteases which, although generated in the lung, get carried by pulmonary blood flow into the systemic circulation in a manner analogous to lipases in pancreatitis producing metastatic lipolysis.²⁷ The role of increased intra-abdominal pressure in the development of inguinal herniation in the adult has been discredited^{28,29} since, despite earlier evidence to the contrary,³⁰ chronic obstruction and distension of the large bowel from cancer does not give rise to groin hernias. Aging as the factor responsible for attenuation of the rectus sheath in patients with inguinal herniation was ruled out by our earlier studies since this atrophy was not found to be a senile phenomenon.⁶ Rather, we observed that groin herniation was a disease predominantly of middle age. Since many of these patients had smoked heavily for many years and consequently suffered a high incidence of emphysema and lung cancer,

TABLE 5. White Blood Cell Counts in 400 Men with Inguinal Herniation

Description	Number	WBC $\times 10^3$ /mm ³ (\pm SD)
Nonsmokers	200	6.73 \pm 2.50
Indirect	111	6.74 \pm 1.96
Direct	89	6.72 \pm 3.20
Smokers	200	7.91 \pm 2.02*
Indirect	123	7.73 \pm 1.69*
Direct	77	8.14 \pm 2.35*

* $p < 0.001$ versus nonsmokers.

this led us earlier⁶ to suspect that inguinal herniation in the adult might be yet another disease exacerbated by the cigarette. The present data amply justify our concern. Three-quarters of our patients said they smoked. This proportion would probably have been greater if we had performed carboxyhemoglobin determinations, since smokers frequently deny their habit. This amount of addiction is certainly greater than that observed in the general population and is higher than that seen in veterans hospitalized for diseases other than those known to be related to the consumption of tobacco products. Peak incidence and age distributions of the more than 2,500 hernia cases reviewed were similar to the vital statistics obtained from nearly 500 patients with lung cancer operated on in our hospital over the same 15-year period.

Direct herniation through Hesselbach's triangle, with its penchant for bilaterality, was almost as common as the indirect type in our series. It seems as if the former is increasing in frequency. Perhaps this observation is due to the long-term effects of smoking, since pulmonary function and x-ray data indicated incipient lung damage in a much higher proportion of the direct hernia type, even though those with known lung disease had been excluded from all of the study groups. However, the age incidence and the symptomatic delay before repair were practically identical for both forms of inguinal herniations; thus, the distinction between the two appears mainly anatomic. If a persistent processus vaginalis is present, as obtains in 20% of men who die without groin herniation,³¹ the degeneration of the transversalis fascia results in indirect herniation. In the absence of a preformed sac, a direct defect occurs. Peacock³² has also de-emphasized the different types of inguinal herniation. More severe attenuation is needed to produce the direct as opposed to the indirect form, with its built-in anatomical defect—the peritoneal diverticulum. We found evidence for this in our previous rectus sheath, weight per unit area measurements along with the electron microscopic, biochemical, tissue culture, and radioisotopic studies which demonstrated qualitative as well as quantitative damage to the collagenous matrix.³³ The lesion was worse in direct herniation. More advanced degeneration also helps to explain the bilaterality of direct defects.

The crucial support for the hypothesis of metastatic emphysema as a mechanism for acquiring inguinal hernias in adult life is provided not simply by an observed association between smoking, signs of pulmonary emphysema and a similar age incidence to lung cancer, but the identification of an increased serum elastolytic activity, coupled with a decrease in the inhibitory capacity of α_1 AT (the predominant circulating antiprotease) despite serum concentrations within the normal

range. Again, these observations were particularly striking in the patients with direct defects. It had previously been assumed that in the presence of normal amounts of α_1 AT and a normal phenotype (MM), which all of our study patients were selected for, the body would be protected against circulating proteases, regardless of their source. Nevertheless, increased blood elastase activity has been reported in burn patients.³⁴ There is evidence that elastase after complexing with blood antiproteases is still active, albeit to a considerably reduced degree.³⁵ Furthermore, smoking itself damages the activity of circulating antiproteases, both *in vitro*³⁶ and *in vivo*,³⁷ as we have also demonstrated in our hernia patients. The white blood cell concentration in the blood of smokers who inhale has been shown to be elevated^{38,39} and, again, we were able to confirm this in our series of hernia patients. These cells (leukocytes) contain proteolytic enzymes including elastase. They are directly involved in the inflammatory response of the lungs to smoke and, presumably, could deliver and release enzymes in peripheral tissues as well. Elastase from these cells cleaves elastin and collagen, the latter at sites of terminal cross-links,⁴⁰ and thus could contribute to the destruction of collagenous connective tissue in the groin and elsewhere in a manner analogous to proteolytic injury in the lung.⁴¹ When the body's normal protective mechanism (the concentration and capacity of α_1 AT) is impaired, conditions are ripe for metastatic connective tissue lesions. A manifestation of this was recently demonstrated on a congenital basis in the case of a combined α_1 AT and α_2 M deficiency syndrome.⁴² Interestingly enough, hernias were not reported in this patient, but they were in cases of cutis laxa (congenital elastolysis).⁴³ Obviously, all who smoke do not contract pulmonary emphysema; and similarly, a number of yet unknown factors must contribute to the development of the metastatic lesion in the groin. Whether an individual will develop groin lesion(s) will depend on the interaction of genes, environment, *e.g.*, smoking, and chance but lung damage can produce nonpulmonary pathologic effects, as observed in our present study.

What are the implications of this new concept in regard to treatment? Obviously, as in the management of atherosclerotic disease, smoking should be interdicted not only as a preventive measure but to obviate operative recurrence, which is known to be much higher than generally admitted.⁴⁴ Since herniorrhaphy fails much more frequently with direct defects, where the patient's serum elastolytic levels are highest and attenuation of the groin fascia most severe, prosthetic mesh^{45,46} should be applied more than it has been in the past. This is especially important with large protrusions

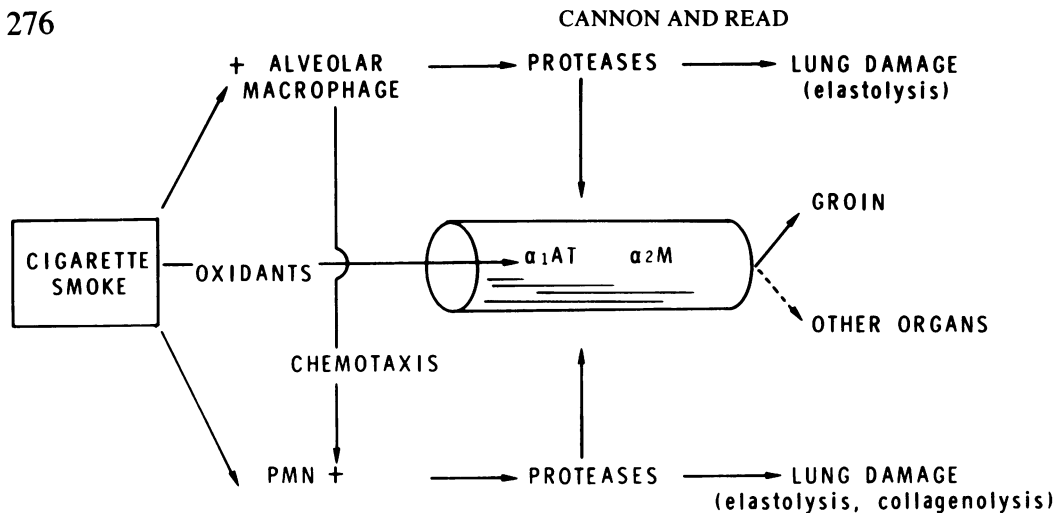


FIG. 3. Proposed pathways of metastatic emphysema.

when, even with a relaxing incision, suture tensions are high.⁴⁷ The surgeon's approach to inguinal herniation should consider more than the anatomic and technical detail. It must now embrace biochemistry, because he is dealing with a local manifestation of a generalized lesion of connective tissue. Just as in pulmonary emphysema, consideration needs to be given to stimulation of blood antiprotease activity by drugs,^{48,49} especially in the many who cannot stop smoking or are found at operation to have particularly poor tissues.

Finally, the present work has implications beyond herniation of the abdominal viscera—important as that is. The demonstration that millions of smokers could be releasing proteolytic enzymes from the lung and damaging their normal defense against such catalysts implies that other organ systems are at risk (Fig. 3). It may be that cancer and the cardiovascular ravages of smoking are initiated by a similar mechanism. The evidence supporting our hypothesis of metastatic emphysema confirms the role of proteases and antiproteases in the development of pulmonary emphysema.

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DISCUSSION

DR. ERLE E. PEACOCK, JR., (New Orleans, Louisiana): I would like to raise four questions about what I consider to be the quantum leap between the data and the conclusions.

My questions are biased because my own work in this field has led me to an opposite conclusion, namely, that development of groin hernia in elderly men is a local phenomenon, involving a specific, difficult-to-measure, enzyme. In spite of such a bias, I would like to raise four questions.

The first question concerns the clinical or biologic significance of the data. The data appear mathematically significant, but, in my experience, removing transversalis fascia in amounts sufficient to allow penetration of intestine requires four or five times greater enzyme levels than reported. So I acknowledge the mathematic significance of the data, but question their biologic significance.

Second, I raise the question of whether any of the substances measured have the ability to digest dense connective tissue. In my experience, only highly specific tissue collagenase or bacterial collagenase will digest collagen at neutral pH.

The third question relates to difficulty in following Dr. Read's general thesis. Through the years Dr. Read has almost convinced us that human groin hernia was caused by a generalized condition featuring reduced net collagen synthesis and deposition. If I understand the present paper, however, increased collagen destruction is the major cause of groin hernia.

Last, simultaneous development of groin hernia and Dupuytren's contracture, common conditions in elderly men, is difficult to explain

by a generalized metabolic abnormality. In many ways the two conditions are metabolically opposite. Groin hernia is characterized by replacement of dense connective tissue with fat; Dupuytren's contracture is characterized by replacement of subcutaneous fat by dense connective tissue.

DR. RONALD W. BUSUTTIL (Los Angeles, California): At UCLA we, too, have been intrigued with the role of elastolytic activity in the development of certain connective tissue disorders. Our studies, which have recently been published, suggested that these enzymes may, indeed, play a role in a more lethal degenerative disease process, namely, abdominal aneurysm formation.

We have now studied 37 patients with abdominal aortic aneurysms or atherosclerotic occlusive disease and have found that there is a marked difference in aortic wall proteolytic enzyme activity between those patients with aneurysmal disease and those with occlusive disease.

(slide) In a group of patients who had abdominal aortic aneurysms, we found a significant level of aortic wall collagenase activity, approximately 33 units per gram of tissue. In contradistinction, patients who had occlusive atherosclerotic aortas had no detectable collagenase activity in the aortic specimens. Similarly, samples of rectus fascia from patients who also had aneurysms did not contain collagenolytic activity.

(slide) Additionally, we have found that collagenase activity was approximately three times greater in patients who had thoracoabdominal, expanding, or ruptured aneurysms, compared with patients who have had elective, stable abdominal aortic aneurysms.