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*Original articles*

# Metabolic factors contributing to herniation*

## A review

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**Summary:** Modern herniology began during the golden century of anatomy (1750-1850), the underlying assumption being that the tissues lining the various abdominal defects were normal and would stay so. Even though Harrison [1922], Keith [1923] and Andrews [1924] questioned this dictum, it was not until 1964 that the possibility of connective tissue abnormalities was suggested. Thirty years ago, I noticed attenuation of the rectus sheath, and therefore, transversalis fascia in veterans undergoing preperitoneal repair. Evidence was accumulated suggesting leakage of proteases from the lungs of these heavy smokers as the mechanism (metastatic emphysema). A similar phenomenon was cited to explain the development of aortic aneurysm in this population. The evidence to support these concepts is reviewed and the mechanism has been extended to incisional herniation. Recently, studies primarily in non-smokers have shown that the genetic expression of collagen type I and III synthesis can be influenced by mutation. These data indicate that more than one factor can cause a systemic metabolic disease of collagen leading to abdominal herniation.

**Key words:** Herniation – Metabolic diseases – Collagen

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Modern herniology began during the golden age of anatomy (1750-1850), the underlying assumption being that the tissues lining the various abdominal defects were normal and would stay so. Causation was attributed to a mechanical disparity between visceral pressure and the resistance of the musculature. Cooper [1804] not only described the transversalis fascia and its role in preventing groin herniation, but listed factors which increase intra-abdominal pressure - cough, obesity, constipation, pregnancy, ascites and unusual exertion, i.e. heavy lifting. Strength of the abdominal wall was considered to be diminished by congenital deficiency, debility or aging. Rupture of the peritoneum or abdominal musculature (Galen) was disproved as a significant factor by dissection and the fact that trauma, unless massive, did not result in herniation.

Even though it was well known [Cloquet 1819] that, at autopsy, persistence of a patent processus vaginalis did not equate with herniation, surgical thought regarding etiology became dominated by Russell's saccular theory [1906] "which rejects the view that her-

nia can ever be "acquired" in the pathological sense... the presence of a developmental diverticulum is a necessary antecedent in every case" 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". Harrison [1922] was the first to question this dictum - "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 should 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 processus... 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."

The following year, Sir Arthur Keith [1924] dealt another blow to the saccular concept stating "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 me to suspect that a pathological change in the connective tissues of the belly wall may render certain individuals particularly liable to hernia." And further "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." Andrews [1924] followed, suggesting that atrophy of the conjoined tendon played a role. In 1964, Wirtschafter and Bentley pointed to connective tissue abnormalities as a possible cause of herniation in humans. They cited an increased incidence of hernia in patients with lathyrism coupled with its experimental induction in animals using lathyrogens. Nevertheless, little attention was paid to these pioneers. Zimmerman and Anson [1967] in their textbook, continued to state that inguinal herniation developed as a result of a congenital anatomical predisposition. Indirect herniae were ascribed to the presence of a preformed sac; direct herniation was explained by the absence of the lowermost fibers of the internal oblique muscle, leaving the transversalis fascial floor of the inguinal canal unsupported.

## Personal observations

My interest in the role of metabolic factors in hernial causation was stimulated by a finding made in the late 1960's [Read 1968] during the development of a modified McEvedy posterior preperitoneal approach to the repair of groin herniae. The rectus sheath some centimeters above the defects appeared thinner than normal [Read 1970] and felt greasy. Samples of constant size weighed significantly less than those taken from matched controls operated upon for other conditions. Patients with direct or bilateral herniae showed more attenuation than those with indirect defects [Wagh and Read 1971]. Atrophy was unrelated to age or muscle mass [Wagh and Read 1972] Hydroxyproline content and therefore collagen, which comprises 80% of the rectus sheath, was strikingly decreased. Collagen showed altered salt precipitability and impaired hydroxylation with decreased amounts of mature insoluble (polymeric) collagen [Wagh, et al. 1974]. Cultured fibroplasts proliferated less and had reduced uptake of radioactive proline. Collagen fibrils on electron microscopy showed irregular periodicity, variable diameters, with some intracellular positioning. Similar findings were present in pericardial and skin biopsies [Sun 1974]. Since, as McVay [1954] emphasized, the anterior rectus sheath is continuous with the transversalis fascia (as demonstrated historically by the success of relaxing incisions in the former to reduce suture tension after herniorrhaphy) the data reflect changes in the floor of the inguinal canal unaffected by scarring, secondary to the protrusion itself.

## Hypothesis

Thus, veterans were presenting in late middle-age with a surprisingly high incidence of primary inguinal herniation, almost half having direct or bilateral defects. They showed evidence of widespread damage to connective tissue, different to that seen in lathyrism because crosslinking of collagen was unaffected. Almost all smoked heavily, having become addicted to nicotine when, during World War II, cigarettes were sent up with the rations. Many had already suffered the consequences - emphysema, lung cancer, accelerated atherosclerosis, etc. Since the collagen changes in their skin biopsies (similar to those in the groin) resembled those seen in the skin and lungs of patients with pulmonary emphysema, with or without deficiency of alpha-1-antitrypsin, [Read 1984] it seemed likely that smoke was not only damaging their lungs, but by a systemic effect, the abdominal wall. This thereby allowed herniation through a locus minoris resistentiae, the inguinal canal. The conclusion was that long term excessive exposure to tobacco smoke was a risk factor for groin herniation. To ascertain the mechanism involved, we first considered what was known about how smoking damages the lung.

## Pulmonary emphysema

Prior to 1962, clinicians speculated that destruction of alveoli in this condition resulted from mechanical factors (cough and forced expiration against

resistance) similar to those once ascribed for herniae. However, Laurell and Eriksson's [1963] report of predisposition to this disease secondary to an inherited deficiency of alpha-1-antitrypsin, coupled with its experimental production by Gross, using tracheal installation of proteolytic enzymes, [Gross 1965] led to the now accepted protease-antiprotease imbalance theory. Smoking stimulates a neutrophil-macrophage response. Their five-to-tenfold concentration in the lungs, with activation and release of zymogen elastase, is the prime mover. Further, oxidant combustion products of tobacco damage antiprotease defenses [Wewers 1987].

## Metastatic emphysema

To explain the systemic effects of smoking and in particular the effect on connective tissue, we envisaged that the chronic inflammatory response in the lungs was spilling over into the systemic circulation. Uninhibited proteolytic activity and large numbers of activated neutrophils and macrophages, along with products of tobacco combustion, were causing collagenolysis and inhibiting repair [Cannon and Read 1981]. The process would be analogous to metastatic damage to the lung and skin seen in acute pancreatitis or the secondary pulmonary effects of visceral or extremity ischemia [Lee and Howard 1979].

## Supporting data

Our patients with inguinal herniation, 18% of whom had associated pulmonary emphysema, had leukocytosis with elevated circulating elastolytic activity and a reduced antiproteolytic inhibitory capacity. Neutrophils showed enlarged zymogen granules and were primed for proteolysis. The changes were more marked in direct herniation and those with bilateral defects. [Cannon, et al. 1984] Thus the data suggested that the presence of a preformed indirect sac allowed indirect herniation with less attenuation of the transversalis fascia than seen with direct protrusions. The age distribution of 2,500 hernia cases admitted to our surgical service resembled that of 500 patients treated for lung cancer, and another 3,000 cases with cardiovascular diseases related to chronic smoking. The changes in collagen that we observed in our patients resemble those previously described in the skin of smokers (wrinkles) [Kadunce 1991] Peacock, while maintaining that the connective tissue changes in adults with groin herniation are restricted to the groin, did allow that the pathology was also present on the clinically normal side [Peacock 1978]. In 1988, the use of tobacco was reported to be significantly more common in patients presenting with hernia, especially women [Bielecki 1988]. The year before, Weitz and his colleagues [Weitz 1987] provided independent support for the metastatic emphysema hypothesis when they unequivocally recovered the "fingerprints" of free active neutrophil elastase (increased fivefold) from the plasma of cigarette smokers by measuring a specific fibrinopeptide cleavage product of fibrinogen identified by radioimmune assay. They concluded, "Our findings raise the possibility that other systemic complications of cigarette smoking (for example, atherosclerotic disease) may be the result of uncontrolled neutrophil elastase activity."

## Proteolysis in patients with aneurysm

Yet another abdominal protrusion, aortic aneurysm, was once blamed on mechanical factors, turbulence, hypertension and aging, abetted by atherosclerosis. Nevertheless, smoking was shown to be a risk factor in 1968 [Hammond 1969]. Auerbach [1980] later, found non-smokers to be outnumbered eight to one, while Cronenwett [1985] determined that the presence of obstructive pulmonary disease was the best predictor of rupture. In 1980, Swanson et al. for the first time invoked a metabolic factor, endogenous collagenase, in the pathogenesis of ruptured aneurysm. Busuttil et al. [1989] the same year, reported that elastase caused aneurysm with its 70-80% loss of elastin, but prevented occlusive disease. They suggested the enzyme originated in neutrophils or monocytes. Two years later, we [Cannon and Read 1982] reported that smokers with aortic aneurysm, but not Leriche syndrome, demonstrated leukocytosis with elevated serum and leukocyte elastase activity (later to be confirmed, even after excision of the aneurysm) [Cohen 1990] and reduced antiproteolytic capacity. Smoking was then shown to increase aortic elastase content experimentally [Cohen 1989]. Since these findings were similar to those previously described by us in patients with hernia, we investigated the possibility of an association between the two conditions. We found inguinal herniation to be twice as common in patients with aneurysm compared to those having Leriche syndrome. In addition, the former had more severe fascial attenuation with earlier and larger, mainly direct, recurrent or bilateral hernial defects [Lee 1979]. A similar relationship was later shown [Stevick 1988] and repeatedly confirmed [Hall 1995, Holland 1996] to hold with incisional herniation after resection of an aneurysm, but not for occlusion with aortofemoral prosthetic interposition. In 1984, Brown et al. [1985] reported increased serum monocyte circulating elastase activity persisting long after the aneurysm was excised, proving again that these proteases do not originate in the aortic wall. Rizzo et al. [1989] described inflammatory cell infiltrates permeating the wall of aneurysms.

Cigarette smoking has also been correlated with the formation, expansion and rupture of saccular aneurysms arising in the intracerebral arteries, previously thought to be congenital [Misra 1988]. The fact that pancreatic trypsins and elastase have also been identified in the blood of smokers and may contribute to the development of abdominal aortic aneurysm emphasizes the damage inflicted by consumption of tobacco on the protective antiprotease mechanisms [Dubick 1988].

Thus, in smokers, aneurysm, like herniation, has to be considered the result of a systemic protease-antiprotease imbalance. This conclusion is supported by a reported eightfold increase in the incidence of cerebral aneurysm in patients with alpha-1-antitrypsin deficiency correlated with a similar change in plasma elastase [Baker 1995].

## Congenital and genetic influences

Smoking does not always lead to death from lung cancer or a heart attack. Similarly, not all smokers develop aneurysms or herniae. Further, these latter may arise in patients who have never used tobacco. Thus, many herniae occur soon after birth, especially if premature. Such congenital defects have been ascribed to a delay in normal development, i.e. closure of the processus vaginalis. However, herniation may be multiple, familial or part of various connective tissue disorders, including osteogenesis imperfecta, Marfan's or Ehlers-Danlos syndromes, congenital elastolysis (cutis laxae) or more commonly, hip dislocation of childhood. Some of these conditions are known to arise from genetic mutations. In 1992, Deak et al. demonstrated abnormal synthesis (collagen gene expression) in cultured skin fibroblasts taken from two patients with multiple aneurysms, suggesting sporadic mutation. However, a number of individuals with single aneurysm showed no such change despite a positive family history. The following year this group studied nine men, 17 to 67 years of age, with either indirect or direct inguinal herniation. Few smoked, some had a familial history, and a third demonstrated joint hypermobility. Isotopically labeled skin fibroblasts secreted twice as much type III collagen (one of the two common among the 29 different forms) as controls. The altered ratio with predominant type I collagen led to a decrease in insoluble (polymeric) fibrils, confirming our original observations. The collagen type proportion also regulates fibrillogenesis, fibril diameter and bundle architecture. They commented, "An increase in type III collagen, (a metabolic abnormality of production) may predispose certain individuals to the development of inguinal herniation and recurrence after corrective surgery" [Friedman 1993]. Genitourinary prolapse in women was shown [Baker 1990] in 1990 to be similarly associated with hypermobility, suggesting an underlying connective tissue disorder. In 1996, collagen deficiency with increased cross-linking and decreased solubility associated with collagenolysis was identified [Jackson 1996] in this condition. The role of smoking in herniogenesis was emphasized in 1998 by Scott, who found that the use of tobacco was twice as common in 130 patients operated upon for recurrence, compared to those treated for primary herniation. At the same meeting, Pans and Pierard using biomechanics [1997] and immunohistochemistry [Pans 1998] confirmed the changes in collagen, which we had previously described. They concluded, "The collagen framework of the transversalis fascia was modified, mainly in the direct hernia group, associated with increased vascularity and cellularity. Similar changes were observed on the non-herniated sides, suggesting that a connective tissue pathology plays a role in the genesis of groin hernias."

## Conclusion

In infancy, herniation is known to relate to prematurity or known connective tissue disorders. In adults, cigarette smoking has now been shown repeatedly to damage connective tissue, causing attenuation of the transversalis fascia, thus leading to inguinal and incisional herniation (metastatic emphysema). Genetic mutation can also interfere with collagen type I and III synthesis, thereby playing a role in herniogenesis. Thus, 75 years later, Keith's suggestion that a pathological change in connective tissue could cause herniation has been confirmed by a number of investigators.

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## Appendix

Since the review was accepted for publication, further evidence supporting the concept that smoking systematically impedes collagen production was published by Jorgensen, et al. from Copenhagen, Denmark, [(1998) Less collagen production in smokers. Surgery, 123: 450]. In this elegant study, the authors blindy assessed, using a subcutaneous wound-healing model, the effects of cigarette smoking (average of 20 for 10 days) on wound healing in 37 volunteers (19 smokers and 18 non-smoking controls). They, average age 28 years, were carefully matched for baseline characteristics. Non-smokers synthesized 1.8 times more hydroxyproline in the granulation tissue than their counterparts, who smoked ($p<0.01$). Other proteins were unaffected. Impairment of collagen production correlated negatively with tobacco consumption before ($p<0.01$) and during the investigation ($p<0.005$). The importance of this work is that relatively young individuals were studied so that the long term consequences of tobacco use were obviated. Further, the scientifically controlled study was prospective and it indicated a specific effect of cigarette smoking on wound healing, in particular, collagen synthesis.