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Porcine atrophic rhinitis: a model for studying nasal physiology and pathophysiology

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SUMMARY

Porcine infectious atrophic rhinitis is a disease of swine which ought to be of considerable interest to rhinologists. We have reviewed some aspects of human atrophic rhinitis, and some aspects of etiology incidence, pathology and physiology of porcine infectious atrophic rhinitis. Swine with this nasal problem fail rather dramatically, to gain as much weight as unaffected animals. We have speculated on several reasons for this including altered nasal physiology and trigeminal reflexes and reduced olfaction. Photographs of infected pigs are included.

SIGNIFICANCE OF ATROPHIC RHINITIS

Porcine atrophic rhinitis is a topic which ought to be of considerable interest to the comparative rhinologist. Parallels between animal and human function and disease should enable us to better delineate a specific etiology and a specific therapy of a particular disorder or malfunction whatever the organ. It is unfortunately quite difficult to draw exact parallels between the human nose and the nose of most other mammals for two reasons. First, the human nose anatomically is quite unique. It is also physiologically unique in that the human nose is microsmatic. Which is a trait which it shares with bats and whales (Ingersoll 1904). Noses of most other animals have a heightened sense of smell, due to more abundant nasal glands which serve to dissolve odorants. Nasal diseases like atrophic rhinitis appear to occur much less frequently in other mammals than man.

Atrophic rhinitis is as its name implies, an inflammatory disorder with a degeneration of nasal mucosa. Since the mechanism of repair after an inflammatory episode is scar and fibrosis, the normal glandular structure of the nose tends to atrophy and disappear. This leaves mucosa draped over fibrosis, laid onto the supporting bony and cartilagenous structures of the nose. The disastrous physiological consequences of this degeneration may be quite profound indeed, although the complaint may be desceptively simple; the patient says

he cannot breathe. The nasal passages are in fact overly patent. His problem is that his nose is unable to develop enough resistance between the anterior nares and the posterior choanae.

Ogura (1977) has recently restated the tremendously important role played by the nose in breathing. Cottle (1966) has cited the importance of the nose in diseases of the entire body and has made considerable contributions to the fundamental understanding of nasal physiology.

It is not the purpose of this paper to report an answer to the questions of the understanding of nasal mechanism in systemic diseases but simply to acquaint rhinologists with an interesting nasal malady found in swine, i.e. infectious porcine atrophic rhinitis, and to analyse long term effects of this disease in relation to some of the principles elucidated by Cottle. We will not be presenting our own data but rather a collation of assorted fairly recent reports. It is our hope that this paper will serve as a stimulus to further research.

HUMAN ATROPHIC RHINITIS

Human atrophic rhinitis is certainly not a new disease. The ancient Greek physicians were concerned enough about it to describe treatment for it. Atrophic rhinitis is to be distinguished from ozena as it occurs in humans. The late Henry Williams (1973) felt that the incidence of ozena in North America had decreased markedly over the prior thirty years. This decrease may be related to a broader use of antibiotics for nasal conditions. Ozena was characterized by degenerative changes in the Schneiderian epithelium with a vasculitis involving arteries as well as veins. Instead of the simple fibrosis of submucosa there was noted to be a dense lymphocytic and plasmacytic infiltration and also deposits of hyaline material. The patient with ozena had a characteristic foul odor. *Klebsiella* was often related to this disorder.

In atrophic rhinitis there is an increase in nasal patency, due to glandular mucosal atrophy and more submucosal fibrosis. There is often a history of nasal abuse, as for example, cigarette smoking and past over use of nasal topical and even systemic medication. In the dry portions of the western United States, the nose seems to be required to produce more humidity and perhaps as a consequence of that, the glandular structures tend more to atrophy earlier leading to a greater frequency in the occurrence of atrophic rhinitis. On inspection of the nose, there is often a large dry greenish crust and if this crust is removed there is a tendency to epistaxis, and there may also be a partial perforation. Mucosal leukocytes are not increased in atrophic rhinitis.

PORCINE ATROPHIC RHINITIS

Atrophic rhinitis of swine was reported in Germany as early as 1830 (Switzer, 1955), but not until 1944 was it reported in the United States (Doyle et al., 1944).

It occurs with high incidence in most of the major pig raising areas of the world. The incidence of the disease is reported to range as low as 5% and as high as 76% (Earl et al., 1962). A survey conducted in Nebraska between 1962 and 1969 reported an incidence of 25% in 1,600 pigs examined at slaughter (Earl et al., 1962). A survey conducted in Iowa in 1974 and again in 1975 found that 44% (1974) and 51% (1975) of market weight swine examined had some degree of turbinate atrophy at slaughter (Farrington et al., 1977). It is not a fatal disease unless complicated. Its primary importance evolves around the economic loss resulting from the retarded rate of growth and that ensues in swine suffering from atrophic rhinitis even after active disease has apparently subsided (Earl et al., 1962). It is estimated that the disease retards the growth rate up to 10% (Hasebe, 1971). The reduction in weight gain highly correlates with the degree of atrophic rhinitis, the growth retardation is most pronounced in those animals that demonstrate the greatest degree of atrophic (Earl et al., 1962). The estimated total loss due to atrophic rhinitis alone is estimated to be $ 90,000,000 annually. Over the years, a complexity of causes for atrophic rhinitis have been suggested including nutritional factors such as calcium/phosphorus imbalance, ammonia and a variety of bacteria and viruses. A convincing amount of evidence now exists which indicates that *Bordetella bronchiseptica* plays a major role if not the only role in the etiology of the disease (Cross et al., 1962) although *Pasturella multocida* has not been completely ruled out. Koch's postulates have been clearly filled in a study recently reported (Brassinne et al., 1976) in which 19 gnotobiotic piglets (originally germ free pigs inoculated with nonpathogenic bacteria to establish normal GI function), four to six days old, were inoculated intranasally on three consecutive days with a pure culture of *B bronchiseptica.* Necrospy ten to thirteen days after inoculation revealed atrophic rhinitis lesions in all and pneumonia in thirteen of the piglets. *B bronchiseptica* was isolated from the ethmoid turbinates, the trachea and pneumonic lesions in all infected piglets. A number of strains of *B bronchiseptica* have been isolated from swine and other animals. The pathogenicity of the different strains so far as their ability to produce atrophic rhinitis in swine varies markedly. Strains of low virulence may infect a nasal passage but do not cause atrophic rhinitis. The mode of transmission is via a nasal contact between infected sows and their offsprings, via aerosol infection of young pigs, nasal contact with infected litter mates and from other species carrying virulent forms of the bacteria, the most probable being the domestic cat (Earl et al., 1962). Ammonia acting as a mucosal irritant may enhance the pathogenicity of the bacteria (Broderson et al., 1976). Significant atrophy of the turbinate occurs only in pigs that experience rhinitis at a young age, generally less than ten days, and in those that experience active infection for greater than three to five weeks. Infection after three weeks of age may result in rhinitis, but not atrophy of the turbinates. Early clinical

symptoms are sneezing accompanied by varying degrees of dyspenea and serous or mucinous discharge which may progress to a catarrhal or purulent discharge. Occasionally the nasal discharge may contain flecks of blood and rarely profuse hemorrhage. Pneumonia may or may not be present. In uncomplicated infections the animals generally do not have a significant elevation in body temperature and their appetites remain good as does their general condition. After a period of time the clinical signs of infection subside with the only observable remaining lesions being atrophy of the nasal turbinates. After the fifth or sixth week of age in animals with severe atrophic rhinitis, facial deformities are occasionally observed (Figure 1). This is usually presented as a shortening and deviation of the upper face. The nose may be turned up in the case of some symmetrical intranasal lesions, or deviated to the side with the most severe lesions. The deviations may be severe enough to produce thick transverse folding of the skin on the dorsal aspect of the nose.

Infections are generally chronic in nature usually taking from six to twelve months for the bacteria to be cleared from the nasal passages. Clinically apparent rhinitis usually subsides long before the bacteria are cleared from the nasal passage. Once the bacteria have been cleared the animals are resistant to re-

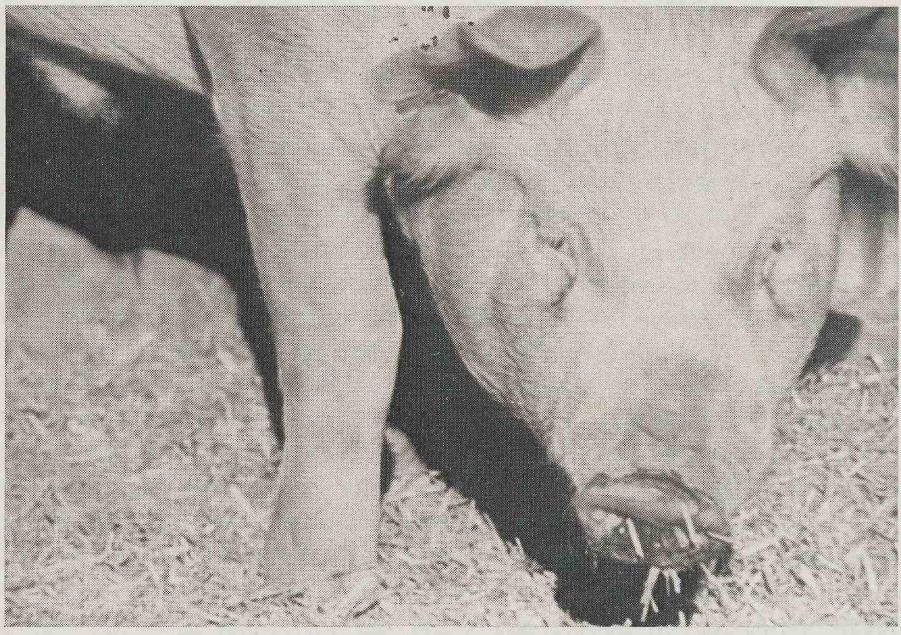

Figure 1. Pig with atrophic rhinits. Note discoloration beneath the eyes. This is due to tearing caused by nasolacrimal duct obstruction. Also note the deviation and deformity of the snout.
Courtesy of Burns-Biotec.

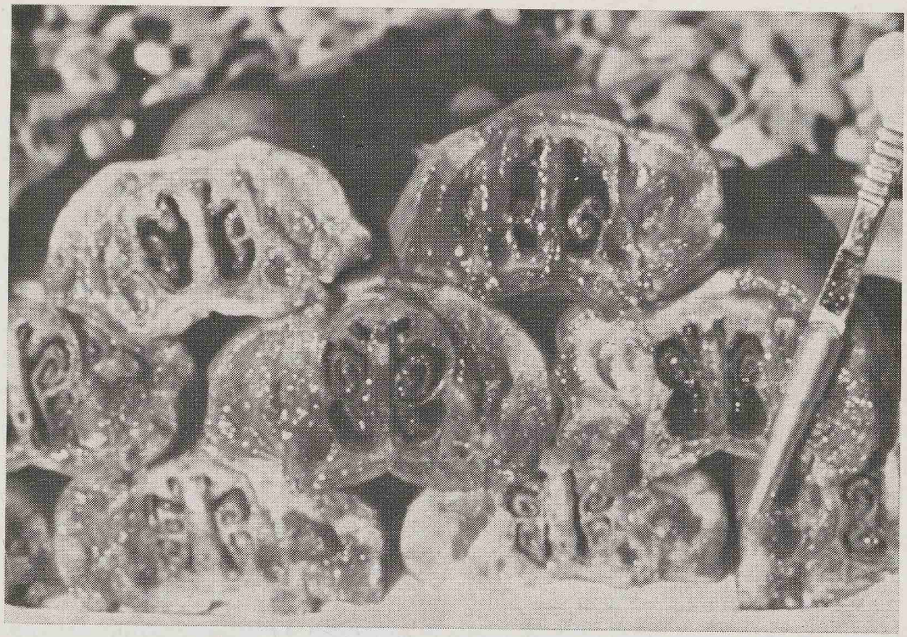

Figure 2. Snorts from pigs at slaughter. Those in the bottom row are the most normal, while the two in the top row show the greatest degree of porcine infections atrophic rhinitis. Note the loss of mucosa and supporting structure, more pronounced dorsally.
Courtesy of Dr. W. P. Switzer, Iowa State University

infection (Earl et al., 1962). Sulfonamides have been used extensively in an attempt to control the disease, however, many drug resistant strains of *B bronchiseptica* have developed.

Recently, a bacterin has been developed which appears to be effective in controlling the disease. In a clinical trial in which one group of 200 pigs was vaccinated at seven and twenty-eight days of age, 1% developed atrophic rhinitis and reached a projected weight of 220 lbs. in 170 days. The unvaccinated control group of 138 swine had a 20% incidence of atrophic rhinitis and required an average of 194.5 days to reach 220 lbs.

Atrophy of the turbinate bones is a consistent necropsy finding (Figure 2). There are many gradations of atrophy with no clear division between normal and pathological. Lesions are most severe anterior to the nasal frontal suture and when mild, they may be present only on the anterior portion of the ventral turbinate but as the disease becomes severe, gross changes, primarily atrophy, become evident in the dorsal turbinate and progress back into the nasal cavity until even the ethmoids are affected. In long standing cases, atrophy is accompanied by irregular hypertrophy of portions of the turbinates and facial bones. The nasal mucosa may vary from no gross changes to being thick and edematous

with a covering of thin seromucous exudate or a thick mucopurulent exudate or it may be pale and dry with no exudation.

Inflammation of the nasal mucosa is a consistent finding at least in the early stages of the disease. The degree of inflammation present in the nasal mucosa varies considerably and the severity of it appears to have no correlation with the severity of the osseus lesions. The mucous membranes on the anterior dorsal aspect of the ventral turbinate are most consistently involved. Metaplasia and hyperplasia of the mucosal epithelium is usually observed. It changes from pseudostratified ciliated columnar to cuboidal stratified with loss of cilia. The goblet cells disappear and are replaced by irregular polyhedral cells. Occasionally, in long standing cases, squamous metaplasia and focal ulceration is present. The lamina propria becomes diffusely and progressively infiltrated primarily with mononuclear leukocytes. Polymorphonuclear leukocytes are sparse, especially in the later stages of infection. Leukocytes are generally not found in the osseous layers of the turbinates.

The periosteum is thin and consists of a layer of elongated fibroblast-like cells. The number of osteocytes is greatly reduced. The osseous core of the turbinates may be completely absent, resulting in opposition of periosteal surfaces (Fetter et al., 1975). The number of osteoclasts is generally not changes from normal. Ultrastructural changes in pigs experimentally infected with *B bronchiseptica* at three and five days of age have been reported (Fetter et al., 1975). Changes were most severe in the osteoblasts of the nasal turbinates, progressing from early degenerative changes of cytoplasmic organelles and cell membranes to lysis of affected osteoblasts. The layer of osteoid normally interposed between the osteoblasts and the bone surface was reduced or absent. The surface of the bone beneath degenerative osteoblasts frequently was frayed or roughened in appearance, similar to that observed beneath the brush border of osteoclasts. Bacterial organisms occasionally were observed around degenerating oseoblasts and near the mineralized matrix of bone. Bacteria were observed in the cytoplasm of some degenerating osteoblasts. The portion of the osteoblasts in the immediate vicinity of the bacterial organism was translucent, devoid of cytoplasmic organelles while the organelles surrounding the translucent area showed progressively degenerative changes.

Degenerative changes were less severe in the osteocytes and absent in the osteoclasts except for occasionally observed degenerative changes in the brush border.

Experimental data clearly demonstrate that *B bronchiseptica* rhinitis when induced in baby pigs less than five days of age will result in the development of atrophic rhinitis. The reduced size of the turbinates appears to be the result of agensis of bone tissue resulting from the destruction of osteoblasts, apparently by the bacteria, and to the reabsorption of bone unrelated to osteoclastic

activity. It has been suggested that the degenerative osteoblasts may contribute to the overall reabsorption of bone (Fetter et al., 1975). There are several proposed mechanisms for such activity based on observations that osteoblasts and osteocytes contain hydrolytic enzymes similar to osteoclasts (Doty et al., 1968). Other evidence suggests that endotoxins may be partially responsible for the observed pathology. Extracts of *B bronchiseptica* inhibit or uncouple the energized process of bovine and porcine heart mitochondria and energy dependant uptake of calcium and phosphorus is markedly inhibited in the mitochondria (Harris et al., 1971). This would inhibit the calcification of osteoid tissue. An immune-mediated response has also been suggested as a possible mechanism for the bone reabsorption (Fetter et al., 1975).

CORRELATION

The slow degenerative change and the retarded rate of growth in animals with atrophic nasal turbinates is made even more significant by the observation that anesthesia can be maintained in pigs simply inserting a nozzle of anesthetic gas to their nostrils without regard to their mouths, suggesting a propensity for nasal breathing.

It is our contention, although we have as yet no firm data to support the hypothesis, that the reason swine fail to gain their expected weight is simply that their noses have been deformed by disease and inflammation. The diseased nose does not process air properly, thereby causing abnormal nasopulmonary reflexes and reduced sense of olfaction. It is suggested that retarded growth rate is not exclusively due to ongoing infection, nor due to diet or other external environmental influences but instead is due to a profound alteration in the internal nasal environment. If Cottle's concepts are applied to this state of disordered nasal physiology, it may be readily supposed that altered air currents, improperly humidified, have hampered the adjustments of these animals, causing them to gain considerably less weight than expected. From a physiological point of view, the pig decided what the wants to eat by means of his nose. In fact, pigs have keen sense of olfaction they are used to determine the location of that famous French delicacy, truffles. If it is deprived of the ability to dissolve odorants by atrophy of its nose it is quite natural to expect that the pig will eat less and thus gain less weight and therefore, require a longer time to reach a marketable body size.

An overly patent nasal airways will provide an altered stimulus to the nasal mucosa and the trigeminal nerve. The implications of trigeminal stimulation have been well known to comparative physiologists for a long period of time, yet there remains much to be learned in this area. A classical example of this is the "diving reflex" found in seals, and perhaps present in a *form fruste* in man. The reason that pigs with atrophic rhinitis may fail to gain weight may

be due to abnormal trigeminal stimulation of an overly patent nasal airway. Another reason that pigs with atrophic rhinitis fail to gain weight is that air that reaches the lung of the pig has not been properly "treated", i.e., humidified, cleansed and warmed. A greater chronic effort on the part of the pig to process his air might be at least in part responsible for a decreased weight gain. It is possible only to speculate as to how much difficulty this adds. We hope that these insights provide a stimulus for further research in other laboratories.

ZUSAMMENFASSUNG

Die infektiöse Stinknase des Schweines ist eine Schweinekrankheit welche für den Nasenarzt von grossem Interesse sein sollte. Wir haben die verschiedenen Gesichtspunkte der Ätiologie, die Verbreitung, die Pathologie und Physiologie der atrophischen Stinknase des Schweines nachgeprüft. Schweine mit diesem Nasenproblem haben grosse Schwierigkeiten in ihrer Gewichtszunahme im Vergleich mit gesunden Tieren. Wir haben die verschiedenen Ursachen dafür, einschliesslich der geänderten Physiologie der Nase und der Trigeminusreflexe und der herabgetzten Geruchsinnes. Lichtbilder von infizierten Schweinen sind beigeschlossen.

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