SUMMARY OF PROJECT:

Acute bovine interstitial pulmonary emphysema can be produced experimentally by oral tryptophan administration to cattle (see reprint). The disease is characterized by shallow, rapid respiration, expiratory dyspnea, lethargy and loss of appetite. The animals usually die within 2-6 days after an oral dose of tryptophan. On necropsy, the lungs are extended, dark pink with pronounced interstitial pulmonary emphysema and edema. Severe edema occurs early in the development of the disease. This experimentally-induced disease is similar to a naturally occurring disease in cattle but sheep and goats are apparently not susceptible to the disease. Since sheep and goats are also ruminants they may serve as excellent control animals for comparative studies on tryptophan metabolism and on pulmonary physiology and biochemistry.

Our work has shown that only an oral dose of tryptophan causes pulmonary lesions in cattle. Young calves or other cattle lacking normal rumen fermentation are not affected by oral doses of tryptophan. These findings indicate that a product of tryptophan fermentation in the rumen leads to the development of pulmonary lesions and that tryptophan itself is probably not the direct causative agent. Only the naturally occurring L-tryptophan (not D-tryptophan) is effective in producing pulmonary lesions.

A major objective of these experiments is to identify the specific pathways and metabolites of tryptophan metabolism which lead to the development of pulmonary lesions in cattle. A method suitable for quantitative determination and radioisotope counting of many end-products of tryptophan metabolism was developed (copy enclosed). This method is being used to measure the relative pathways of tryptophan metabolism in cattle after a dose of tryptophan. Later experiments will be designed

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to compare tryptophan metabolism in cattle to the metabolism in sheep and goats and to monitor the effect of various metabolic inhibitors and drugs on these pathways.

In an attempt to inhibit specific pathways of tryptophan metabolism and prevent the development of pulmonary lesions, some antibiotics and metabolic inhibitors are being tested. Chlortetracycline and zinc - bacitracin prevent the development of pulmonary lesions when given along with a dose of tryptophan. Other narrow spectrum antibiotics will be tested. Antagonists of pyridoxal phosphate inhibit many pathways of tryptophan metabolism. Two of these compounds, aminooxyacetic acid and 4-deoxypyridoxine have been used. Deoxypyridoxine prevented the development of pulmonary emphysema but it probably acted by inhibiting total microbial fermentation in the rumen. These studies will be extended to include other antagonists of pyridoxal phosphate and inhibitors of tryptophan hydroxylation reactions.

At the present time we are initiating limited studies on the changes in pulmonary physiology that occur during the development of pulmonary disease in cattle.

Other work has shown that liver tryptophan pyrrolase is not inducible in ruminants as it is in similarly treated rats (copy enclosed). At the present time we feel that the lack of tryptophan pyrrolase adaptation in cattle is not directly related to the development of pulmonary disease in cattle. The lower levels of tryptophan pyrrolase in ruminants may be related to quantitative differences in the relative pathways of tryptophan metabolism and could conceivably be indirectly related to the development of pulmonary disease in cattle.

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OBJECTIVES:

The objectives of this research are:

1. To determine the specific causative agents responsible for the development of tryptophan-induced interstitial pulmonary emphysema in cattle.

2. To establish the mechanism of action of the causative agents.

3. To characterize the specific biochemical and physiological lesions associated with the development of pulmonary disease.

4. To develop effective methods of treatment and of reversing the biochemical and physiological symptoms of pulmonary emphsema in cattle.

PROCEDURE:

In order to attack this project in a comprehensive manner, there are several major areas which should be investigated.

1. Tryptophan Metabolism

It is likely that a tryptophan metabolite produced in the rumen initiates a response that leads to the development of pulmonary lesions. We propose to quantitate the relative pathways of tryptophan metabolism in the body tissues and rumen fluid of cattle by measuring the accumulation of radioactive tracers in the end-products of tryptophan metabolism at intervals after an oral dose. These data will be compared to similar data collected from sheep which are not susceptible to this disease. These studies will include in vitro fermentation experiments and the administration of specific metabolic antagonists and inhibitors to cattle as a means of altering the relative pathways of metabolism. Special attention will be given to blocking specific pathways of metabolism in cattle and determining whether pulmonary lesions develop in these animals. When feasible, specific metabolic intermediates such as nicotinic acid, 5-hydroxytryptamine, indole, or other compounds will be given to cattle in an attempt to produce pulmonary lesions.

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2. Rumen Microbiology

It is possible that one or more species of bacteria produce some toxin in response to excess tryptophan in the rumen. Data on the effect of tryptophan on rumen microbial metabolism may provide information on whether the causative agent is a metabolite of tryptophan or other toxic substance chemically unrelated to tryptophan. Specific narrow spectrum antibiotics will be used to determine whether a particular group of microorganisms is involved. If a particular species of microorganisms is implicated by these studies, their metabolism in the presence of tryptophan would be studied in detail.

3. Pulmonary Physiology

Severe pulmonary edema is one of the early signs of interstitial pulmonary emphsema in cattle. We propose to characterize the early changes in pulmonary physiology which accompany the development of pulmonary lesions. Observations on pulmonary blood circulation, respiratory gas exchange, pulmonary blood pressures, and other physiological parameters will be made. Changes observed during the development of pulmonary emphysema will be compared to changes elicited by various pharmacological agents. The presence of substances known to affect capillary permeability in the lung and to elicit other physiological and pharmacological responses in lung tissue will be investigated and the effect of some of these compounds on normal animals will be studied. These compounds include tryptophan metabolites serotonin and tryptamine as well as histamine, lung kinins, and other substances. These studies might indicate whether or not the causative agents result in an anaphylactic shock reaction in the lung. In any event, they will be useful in establishing the sequence of events during the development of this severe respiratory disease.

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4. Pulmonary Biochemistry

It is important to establish whether pulmonary lesions result from a direct metabolic block in lung tissue or as a result of a general physiologic response involving circulatory and nervous systems. Metabolism of lung tissue will be studied at various times after dosing animals with tryptophan. Observations will include oxygen consumption, carbon dioxide production, glycolysis and TCA cycle activity, and protein and amino acid metabolism in the tissue. Changes in pulmonary surfactants will be noted during the development of pulmonary lesions. Some thought is being given to the development of a perfused lung system which would facilitate both biochemical and physiological studies. These studies will be designed to characterize the sequence of biochemical changes that occurr and to determine their significance in the development of pulmonary disease.

JUSTIFICATION:

Cattle are the primary experimental animals for this project and the disease seems fairly species specific. The relationship to human pulmonary disease is not known precisely but it might be similar to asthma or the farmer's lung syndrome. The relationship to human alveolar pulmonary emphysema may be clarified during the course of the studies.

This model system offers a unique opportunity to identify a specific causative agent and study the precise sequence of events which lead to the development of severe pulmonary disease. The biochemical, physiological, and pharmacological observations to be made should yield a substantial amount of basic information on the nature of pulmonary disease which might be applicable to other species.

CURRENT SUPPORT:

1. Washington State University Research Committee

2. National Institutes of Health

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