BOVINE NASAL GRANULOMA (ATOPIC RHINITIS) IN VICTORIA
EXPERIMENTAL REPRODUCTION BY THE PRODUCTION OF IMMEDIATE TYPE HYPERSENSITIVITY IN THE NASAL MUCOSA


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SUMMARY: The Australian type of bovine nasal granuloma (bovine atopic rhinitis) was reproduced clinically, grossly and histopathologically in 7 of 9 experimental cattle by subjecting them to repeated acute episodes of immediate-type hypersensitivity on their nasal mucosa over periods of several months.

Introduction

There is evidence that the Australasian type of bovine nasal granuloma is an atopic disease similar to hay fever in humans (Pemberton and White 1974a, b, 1976; Pemberton et al 1974).

This paper reports the successful experimental reproduction of nasal granuloma in cattle by the production of repeated hypersensitivity reactions in the nasal mucosa and provides further evidence that nasal granuloma has an allergic basis.

Materials and Methods

Cattle

Thirteen cattle of mixed breed, age and sex as summarised in Table 1, were used for these investigations. Animals 1, 10 and 11 were obtained from the Hamilton area of Western Victoria, while the remaining animals were obtained from Gippsland. All animals were clinically normal at the beginning of the experiment and were run at pasture at the Regional Veterinary Laboratory, Hamilton.

Experimental Design

Experimental animals were allotted at random to the following groups (see Table 1).

* Sensitised, challenged group — Seven animals (numbers 1, 2, 3, 4, 5, 6, 7) were sensitised to commercial hen egg albumen* (ovalbumen) and subjected to repeated unilateral nasal and conjunctival challenge by the method given below.

* Unsensitised, challenged group — Two animals (8, 9), without prior sensitisation, were subjected to unilateral nasal and conjunctival challenge with ovalbumen by the method given below.

* Unsensitised, unchallenged control group — Four control animals (10, 11, 12, 13) were run in the same paddock as the treated animals but were not sensitised and were not challenged with ovalbumen.

Sensitisation Procedure

Sensitisation for production of an homocytotropic antibody (HCA) response was carried out in animals 1 to 7 inclusive, using a modification of the methods described by Wells and Eyre (1970) and Hammer et al (1971). A mixture of 10 ml 5% ovalbumen and 10 ml incomplete adjuvant was divided into 4 equal doses and injected into separate subcutaneous sites on the same day.

Each animal undergoing sensitisation received injections on three occasions as shown in Table 1.

Challenge Procedure

Except for animal 1, all animals being challenged had powdered ovalbumen applied to the nasal and conjunctival mucosae at least 3 times per day, on an average of every second day, between day 21 and the day of slaughter. Conjunctival challenge was less frequent in the latter stages of the experiment because of the extremely severe and unpleasant reaction that it provoked. The ovalbumen was administered using a plastic puffer pack and each challenging dose contained approximately 25 mg ovalbumen. At all times challenge was restricted to the left nasal cavity and left conjunctiva so that both experimental (left side) and control (right side) tissues were maintained in the one animal.

Animal 1 was challenged in a slightly different manner. Aerosol challenges with aqueous solutions of ovalbumen which, varied in strength from 0.1% to 5.0%, were carried out 2 to 3 times per day between day 21 and day 35. No response was detected following this method of challenge so after day 35, and for the remainder of the experiment, powdered ovalbumen was applied as above. In addition, in an attempt to prolong challenge, a soft gauze impregnated with approximately 100 mg ovalbumen was gently placed in the left nasal cavity. This gauze treatment was applied on 10 occasions between day 63 and day 80. The gauze remained in place for periods ranging from a few minutes to several hours, until the animal was able to expel it by sneezing.

Clinical Observations

Throughout the course of the experiment both control and experimental animals were regularly observed for clinical signs. Smears of nasal and ocular discharge were stained with Leishman's stain (Gurr 1969) and examined for the presence of eosinophils.

Characterisation of the Antibody Response

Direct skin tests were performed in all animals to demonstrate the development of immediate-type hypersensitivity to ovalbumen. Injections of 0.2 ml 0.5% ovalbumen were given intradermally (ID) and resulting...
## TABLE 1

**Summary of Experimental Cattle, Experimental Design and Comparison of the Severity of Rhinitis and Nodulation in Treated and Control Cattle**

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Animal Identification</th>
<th>Breed</th>
<th>Age at Start of Expt (months)</th>
<th>Sex</th>
<th>Sensitising Injections (Days Given)</th>
<th>Challenge with Ovalbumin</th>
<th>Day Detected</th>
<th>First Day Marked Severity</th>
<th>Severity at Slaughter</th>
<th>Day Detected</th>
<th>Severity at Slaughter</th>
<th>HCA Title just prior to slaughter</th>
<th>Day Slaughtered</th>
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<td>C</td>
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<td>23 52</td>
<td>+</td>
<td>35</td>
<td>70</td>
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<td>++++</td>
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<td>47</td>
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<td>++++</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>628</td>
<td></td>
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</table>

* M = male  
  C = castrate male  
  F = female  
  **Severity of Rhinitis and nodulation:***  
  - not present  
  + very mild  
  ++ mild  
  +++ moderate  
  ++++ marked

---

## TABLE 2

**Maximum HCA Titre, Severity of Rhinitis and Severity of Nodulation**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Maximum HCA Titre Detected</th>
<th>Severity of Rhinitis at Slaughter</th>
<th>Severity of Nodulation at Slaughter</th>
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<tr>
<td>1</td>
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<td>++++</td>
<td>++++</td>
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</tr>
<tr>
<td>8</td>
<td>1</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

* Severity of Rhinitis and Nodulation:  
  - not present  
  + very mild  
  ++ mild  
  +++ moderate  
  ++++ marked

1 This animal was slaughtered relatively early in the experiment before there was time for more severe nodulation to develop.
weals were measured 15 minutes later. Biopsies of the test sites in animals 1, 2 and 3 were taken approximately 20 hours later.

Animal 2 calved on day 271 of the experiment and skin tests were performed in the calf immediately after birth and three days later.

Homologous passive cutaneous anaphylaxis (HPCA) tests—These tests (Hammer et al 1971) were performed to confirm that a HCA response had been provoked in the experimental animals and to quantify the serum concentration of HCA at various stages of the experiment.

The hair was clipped from the side or ventral abdomen of three 1 to 5-month-old white skinned calves and the skin was marked with a pen into squares approximately 6 cm x 6 cm. Whole and serially diluted serum samples were injected ID, in 0.2 ml aliquots, into separate skin sites. Seventy two hours later 20 ml 2.5% Even's blue and 8 ml 5% ovalbumen were injected intravenously. Positive reactions, indicated by the development within 10 minutes of circular, raised, blue areas greater than 5 mm diameter at the sites of injection of serum, were recorded approximately 15 minutes later. The titre of HCA was considered to be the reciprocal of the highest dilution of serum that produced a positive reaction.

Histopathological Techniques

The experimental animals were destroyed on the days shown in Table 1 and were subjected to detailed pathological examination. In addition to the whole of the nasal septum and both ventral turbinates, a comprehensive range of tissues was studied including pharynx, trachea, lung conjunctiva, oral mucosa, digestive tract, liver, spleen, heart and kidney.

Mucosal tissues were fixed in Bouin’s fixative and other tissues were fixed in 10% formal saline. Tissues were embedded in paraffin wax and stained routinely with haematoxylin and eosin and Giemsa.

Results

Clinical Response

Sensitised, challenged group — The first observed response to challenge was detected in the sensitised animals between days 30 and 47 and was manifested by the development within a few minutes of mild unilateral congestion of the nasal and conjunctival mucosas and mild serous nasal and ocular discharge. Smears of nasal secretions, taken at this time, contained moderate numbers of eosinophils.

In animal 1, the clinical response increased markedly in severity after several days of the ovalbumen-impregnated gauze treatment. In the remaining animals, which were not subjected to the gauze treatment, the clinical responses to challenge increased gradually in severity from approximately day 30 until slaughter. An exception was animal 6 in which the response failed to progress beyond mild rhinitis.

Marked clinical responses developed between days 70 and 123 in all animals except number 6. At this stage, the response to a single small intra-nasal dose of powdered ovalbumen, occurred within 2-5 minutes. The initial reaction was wrinkling of the skin lateral to the nares followed by a profuse seromucinous nasal discharge with repeated licking of the nostrils and violent sneezing. Swelling of the nasal mucosa was often sufficiently marked to cause severe respiratory distress and animals breathed through their mouths. Strands of fibrin formed in the anterior nasal cavity and the nasal discharge often contained clear, straw-coloured fluid which tended to clot. All animals attempted to rub their left nostril on any object in the vicinity and all, at some stage, suffered minor haemorrhage from the left nostril after challenge. If the animals had not been challenged in the previous 48 hours, nasal smears taken during the acute response contained moderate numbers of eosinophils. Fifteen to 30 minutes after challenge the character of the nasal discharge altered the mucoid and by about 6 hours after challenge the discharge had dried up. By this time a greenish-yellow, purulent discharge was evident in the nose and smears revealed that this was composed almost entirely of eosinophils and eosinophil granules.

A similar response could be elicited in the left conjunctiva after challenge. There was profuse lachrymation with severe congestion and oedema of the conjunctiva. Fine strands of fibrin formed over the conjunctiva and later there was a greenish-purulent discharge rich in eosinophils. These changes were more severe in animals 2, 5 and 7.

Nodules were first detectable in the nasal mucosa of individual cattle between day 100 and day 210 as given in Table 1. The left nasal mucosa was thicker and spongier than normal and small elevations were palpable and visible on the left ventral nasal mucosa. The nodules became more numerous and enlarged progressively. At the time of slaughter, the nodules were grossly indistinguishable from those of field cases of nasal granuloma. The right nasal mucosa, in contrast, was palpably and visibly normal.

Unsensitised, challenged group — Mild rhinitis and conjunctivitis were first detected in animal 9 on day 47 and animal 8 on day 66. The severity of the clinical response to challenge increased only slightly during the experiment and was much less severe than that described above in the sensitised animals. Immediately prior to slaughter, a single challenging dose of ovalbumen produced mild seromucinous nasal discharge in animal 8 while animal 9 responded with mild seromucinous nasal discharge, nasal pruritis and sneezing.

Unsensitised, unchallenged control group — There were no clinically detectable changes in the nasal...
or conjunctival mucosae of the control animals at any stage of the experiment.

**Characterisation of the Antibody Response**

**Direct skin tests** — Skin sensitising antibodies were not detected in the control animals at any stage of the experiment, but were present in all sensitised animals by day 14 and in the unsensitised challenged animals by day 56. A positive reaction, indicated by an urticular weal at the site of injection, occurred within 5-10 minutes and reached a maximum by 30 minutes. The diameter of weals in the sensitised animals increased as the experiment progressed and ranged from 1.5 cm at day 14 to 7-20 cm by the end of the experiment. Biopsies of the test sites, approximately 20 hours post injection, revealed marked oedema and marked infiltration of eosinophils and neutrophils.

Skin sensitising antibodies were not detected in the calf of animal 2 prior to sucking. However, when tested again at 3 days of age an urticarial weal 3 cm in diameter developed within 5 minutes.

**Homologous passive cutaneous anaphylaxis tests** — In the sensitised animals HCA was generally first detected between day 15 and day 40. Titres ranged from 1 to 20 at this time and increased to a maximum of 640 just prior to slaughter. The results of a typical HPCA test are shown in Figure 1. Animals 3 and 6 were exceptions to this general trend in that they failed to develop detectable levels of HCA until much later in the experiment, on days 231 and 364 respectively. In animal 3, the titre of HCA rose to 80 whereas in animal 6 the titre failed to rise above 20. In the unsensitised challenged animals, HCA was not detected until day 630. Titres at this time were 1 and 20 for animals 12 and 13 respectively.

Homocytotropic antibodies to ovalbumen were not detected in the control animals.

Serum taken from the calf of animal 2 prior to sucking was negative. However, positive reactions were produced with serum obtained 3 days after birth and initial sucking and the titre of HCA in the serum of the calf at this time closely approximated that of its dam.

Table 2 demonstrates the close correlation between maximum titre of HCA detected and the severity of both rhinitis and nodular lesions in the nasal mucosa.

**Gross Pathology**

**Sensitised, challenged group** — There were no gross pathological changes in animal 6. In all other animals of this group, the gross appearance of the right nasal mucosa, that had been protected from antigenic challenge, was normal. In contrast the nasal mucosa of the left side, which had been subjected to repeated challenge, showed lesions grossly indistinguishable from those of nasal granuloma (Figures 2 and 3).

The nasal mucosa of the left side was markedly thickened and numerous nodules, 1-4 mm diameter, were present. Nodules were smooth and rounded, and varied in shape from papilliform to polypoid. Their distribution was, in most animals, restricted to the posterior vestibule and anterior respiratory portion and more nodules tended to be present on the floor and longitudinal ridge of the nasal septum than other areas. In animal 2, however, nodules were also scattered...
over the mucosa of the pharynx, larynx and trachea.

The conjunctiva and nictitating membrane of the left eye was thicker than normal in all animals. In animals 2, 5 and 7 the conjunctiva was markedly thickened, nodular and ulcerated. The structures of the right eye appeared normal except in animals 2, 5 and 7 where changes similar to, but less severe than, those described in the left eye were present.

*Unsensitised, challenged group* — There were no significant gross pathological findings in animal 8. In animal 9, several nodules, similar to those described above, were present ventrally in the left vestibule and on the first few centimeters of the anterior part of the left nasal turbinate.

*Unsensitised, unchallenged control group* — There was no significant gross pathology in any of the control animals.

**Histopathology**

*Sensitised, challenged group* — The histological appearance of the unchallenged right nasal mucosa, posterior to the vestibule, was normal and similar to that described previously in clinically normal Jerseys (Pemberton and White 1974a). Mild epithelial hyperplasia and mild eosinophil infiltration were present in the vestibule and this was probably caused by transfer of ovalbumen from the challenged side to the control side by the tongue.

The histological appearance of the lesions in the challenged nasal mucosa of all animals, except animal 6, was identical to that described previously for field cases of nasal granuloma (Pemberton and White 1974b). The reaction was characterised by hypertrophy and hyperplasia of nasal and glandular epithelium with squamous metaplasia of nasal gland ducts. There was a marked increase in the number of subepithelial mast cells, marked oedema and marked eosinophil infiltration of the superficial lamina propria, nasal epithelium and metaplastic duct epithelium. Mononuclear cells, particularly plasma cells, were present in very large numbers and there was fibrosis and vascular proliferation in the superficial lamina propria.

In animal 6, the histological appearance of the left nasal mucosa was similar to that described below in the unsensitised challenged group.

The conjunctivae of all animals in the group showed changes similar to those described in field cases of nasal granuloma (Pemberton and White 1974b). There were varying degrees of epithelial hypertrophy and squamous metaplasia, increased numbers of subepithelial mast cells, oedema and infiltration of the superficial lamina propria with eosinophils, plasma cells and lymphocytes. Changes in the left, challenged, conjunctiva were invariably more marked than those in the right unchallenged, conjunctiva. In animals 2, 5 and 7 there was marked squamous metaplasia of the conjunctival epithelium, elongation of epithelial rete pegs, marked eosinophil and mononuclear cell infiltration and development of nodules similar to those in the nasal mucosa.

Oral lesions were minimal and confined to areas where epithelial integrity had been disrupted, for example, by grass seeds and erupting teeth. In these areas, there was epithelial hyperplasia and marked eosinophil infiltration. Delayed healing of oral ulcers, as described previously for field cases of nasal granuloma (Pemberton and White 1974b), was not observed.

The nodules in the pharynx, larynx and trachea of animal 2 were morphologically similar to those in the nasal mucosa.

Pulmonary, liver and intestinal changes similar to those described previously (Pemberton 1975) were present in all animals in the group but were least marked in animal 6. The pulmonary changes were characterised by hypertrophy and hyperplasia of smooth muscle walls of arterioles and bronchioles, hypertrophy and
hyperplasia of bronchial epithelium, eosinophil, lymphocyte and plasma cell infiltration of peri-
bronchial tissue and focal lymphoid aggregation. The liver lesions included eosinophilic degenera-
tion of individual, and groups, of hepatocytes, focal accumulations of mononuclear cells, peri-
portal fibrosis and small areas of haemorrhage in the parenchyma towards the tip of the ventral 
lobe. In the intestine, particularly the ileum and 
proximal colon, there was moderate to marked 
hypertrophy and hyperplasia of smooth muscle 
of the walls of blood vessels and the intestines. 

Unsensitised, challenged group — The histo-
logical appearance of the right, unchallenged, 
nasal mucosa was normal.

Histopathological changes in the left, chal-
enged, nasal mucosa were similar to, but milder 
than, those described above in the sensitised 
challenged group. The nasal and glandular epi-
thelium was moderately hyperplastic, the popula-
tion of subepithelial mast cells was moderately 
increased and there was moderate to marked 
oedema and eosinophil infiltration of the super-
facial nasal mucosa. These changes extended 
from the anterior vestibule to the middle of the 
respiratory portion, but were more severe on the 
afterior floor of the nasal mucosa. The reaction 
was more marked in animal 9 and several nodules 
typical of nasal granuloma were present on the 
ventral lining of the vestibule and anterior part 
of the nasal turbinates.

Mild allergic conjunctivitis was present in the 
left eye of both animals.

Allergic oral ulceration was not observed.

Pulmonary, liver and intestinal lesions, similar 
to those described in the sensitised animals, were 
observed in both unsensitised animals.

Unsensitised, unchallenged control group — There 
were no significant histopathological changes in 
either nasal mucosa or conjunctiva of any of the 
control animals.

Pulmonary, liver and intestinal changes were 
not observed in animals 19 and 11. However, 
mild changes, similar to those described above, 
were observed in animals 12 and 13.

Discussion

Gross and histopathological lesions indistin-
guishable from those of field cases of nasal 
granuloma (Pemberton and White 1974b) were 
reproduced in the left nasal mucosa in 6 of 7 
sensitised animals, and one of two unsensitised 
animals, by subjecting them to repeated acute 
episodes of immediate-type hypersensitivity on 
the left nasal mucosa. Minimal changes developed 
in the unchallenged, right, nasal mucosa of these 
animals and no changes occurred in the nasal 
mucosae of the 4 untreated control animals.

The results of the skin tests, clinical observa-
tions and pathological findings indicated that the 
experimental disease was the direct result of 
immediate-type hypersensitivity reactions on the 
nasal mucosa.

The results of the direct skin tests and the 
HPCA tests confirmed that production of HCA 
had been provoked in both the sensitised and 
unsensitised animals, and demonstrated the 
development of increasing titres of these antibodies 
throughout the experiment. The development of 
higher titres of HCA to ovalbumen in the sen-
sitised rather than the unsensitised animals was 
expected since the former group was subjected 
to prolonged, artificial, exposure to antigen. The 
reason for the failure of animals 3 and 6 to 
develop high titres is not known, but may be 
related to inherent genetic differences in ability 
to produce HCA.

The immediate nature of the clinical response 
in the challenged nasal mucosa and conjunctiva, 
and the presence of large numbers of eosinophils 
in the secretions, indicates that the rhinitis was 
probably produced by a reaction involving com-
bination of allergen and HCA on or near the 
mast cell surface with release of pharmacologic 
mediators from mast cell granules (Humphrey 
and White 1970; Becker 1971). The absence 
of a clinical response, and the presence of only 
very mild lesions in the unchallenged right nasal 
mucosa, provided a control and supplied further 
proof of the specificity of the reaction. Further 
supportive evidence was provided by the strong 
association between the development of a high 
titre of HCA and marked clinical and patho-
logical changes.

Work with the calf born to animal 2 on day 
271 of the experiment showed that HCA does 
not cross the bovine placenta but can be trans-
ferred from dam to calf via colostrum, thus con-
firming the findings of Hammer et al (1971).

Pulmonary, hepatic and intestinal lesions 
similar to those recorded in this paper have 
been described in cattle with nasal granuloma, 
in clinically normal Jerseys and to a lesser extent 
and severity in other breeds (Pemberton 1975). 
The findings presented here support the previous 
suggestion that these generalised changes are 
hypersensitivity lesions possibly caused by cir-
culating pharmacologic mediators and/or aller-
genic substances released from primary sites of 
allergic reaction such as the nasal mucosa in 
nasal granuloma and the intestine in intestinal 
parasitism.

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Although the sensitisation of animals to ovalbumen in these experiments was artificial, it demonstrates the basic mechanism of field cases of nasal granuloma, but it leaves unsolved the question of which allergens are involved in the field and how cattle become sensitised. The results of skin sensitivity tests carried out on 50 cows with nasal granuloma using 35 different allergen extracts, and the identification of a range of environmental allergens that may be involved in the aetiology of nasal granuloma has been reported previously (Pemberton and White 1976). The allergens considered likely to be most important included mite, the pollens of dock, capeweed, clover, paspalum, sorrel, rye-grass, pepper tree and wattle and the spores of penicillium, cladosporium, botrytis and rye grass rust.

There is strong evidence to suggest that in Victoria there is a familial predisposition to develop nasal granuloma in the Jersey breed and Victorian Jerseys are probably an atopic strain of cattle (Pemberton and White 1974b). Evidence from the experimentally produced disease described in this paper suggests that the degree of sensitisation increases gradually with repeated exposure to allergen and this probably related to a progressive increase in both the population of mast cells in the nasal mucosa and the production of HCA. Sensitisation in the field probably occurs at an early age and, as in humans, once sensitised an animal probably remains so for many years (Sherman 1971). In man, clinical signs of hay fever usually develop between 3 and 5 years after initial exposure to pollen (Sherman 1971). The development of nasal granuloma is more rapid with cases having been observed in calves as young as 6 months of age (Pemberton and White 1974b).

In conclusion, it appears likely that nasal granuloma is the bovine analogue of hay fever in humans and would more appropriately be termed bovine atopic rhinitis. The development of more marked pathological changes in cattle compared with man is probably related to the unfortunate circumstances in which atopic cattle must exist. Whereas atopic people are generally able to avoid very heavy allergenic challenge, atopic cattle spend a lifetime grazing pastures containing heavy concentrations of allergens.

References


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ABSTRACT

KETAMINE AND POST-HAEMORRHAGE SURVIVAL

Longnecker and Sturgill administered 1 of 4 anaesthetic agents — halothane, fluroxene, phenobarbitone and ketamine — to separate groups of rats. The animals were then subjected to a controlled haemorrhage protocol in order to determine the effect of the anaesthetic agent on the survival post-haemorrhage. It was found that the survival rate in the group anaesthetised with ketamine was significantly higher than in the other 3 groups. The long term survival rate was significantly lower in the group anaesthetised with fluroxene. Histopathology was performed, and it was found that splenic ischaemia occurred in fewer animals, and to a lesser degree, in the ketamine group as compared to the other three groups. The key factor in the higher survival rate seems to be the ability of ketamine to either alter the oxygen supply or demand of the tissue; this is apart from its ability to cause an alteration in the blood flow to the body organs, and so minimise the development of ischaemia.


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