Section of Comparative Medicine

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Epizootic Adenomatosis of the Lungs of Sheep: Its Relation to Verminous Pneumonia and Jaagsiekte

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FOR some years we have had in Iceland a disease raging among sheep, causing an average loss of 50 to 60 per cent. in affected flocks in the course of one or two years.

Origin of the disease.—The disease originated on one farm and spread excentrically from there. On this farm was a ram of Karakul breed which had been imported from abroad, and the two sheep which shared a compartment with the ram during the winter of 1934 were the first of the home stock to be affected after the ram had disappeared in sick condition to the mountains, never to come back.

In the autumn of 1934 great losses, which have been going on ever since, began in the stock on this farm. Meanwhile the disease has been spreading from one farm to another in the neighbourhood, the spread of infection being facilitated by the large collections in autumn, when sheep from a great number of farms meet in the big common folds.

Clinical symptoms.—The disease is chronic and the initial symptoms are slight and unnoticeable, so that several sheep may be affected in a flock without showing any obvious change. Perhaps the first symptom to attract the trained observer's attention is an occasional cough in a hitherto healthy sheep. Eventually there may be an attack of spasmodic coughing after exertion. In the initial stage the sheep will show no symptoms when at rest, but after being driven for some distance it may get out of breath, and this dyspnœa may continue for one or two hours after the other sheep have been breathing normally.

Auscultation will reveal moist râles somewhere in the lungs, particularly in the lower region. According to our experience the most reliable signs are the moist râles, which in an advanced case can be heard many yards away, and the great increase in bronchial secretion, which is best demonstrated by inclining the head of the animal to the ground and watching the white, frothy, thin fluid, which drops or streams out of the nostrils. This is considered to be the pathognomonic symptom of adenomatosis, as we have never found it in a sheep which was not affected with this condition.

After the appearance of these symptoms the disease may go on for weeks and months, and we know of cases in which the sheep have been sick for over a year. We have found no fever before the final stage, when the animal frequently dies from a terminal pneumonia, which is accompanied by a rise in the temperature. The animal will keep its appetite for long periods, and there may be no appreciable loss in condition. But if the disease runs a protracted course, emaciation may be extreme, accompanied by anæmia, which, however, rarely becomes severe. Recovery occurs so rarely, that most farmers kill the sheep as soon as they show definite symptoms.

Incubation period.—In a number of cases we have obtained reliable records of the source of infection and the space of time between exposure to infection and appearance of symptoms. The usual period of incubation is six to eight months. A typical case is the following : A ewe from an infected district was found far away, where nobody suspected the disease. This sheep was sold to a farmer, who took it with him, stopping at a neighbouring farm, where the sheep was kept for two days and nights in a small compartment with four lambs. When the owner killed the ewe a fortnight later he noticed that the lungs were large and unhealthy-looking.

All the four lambs fell sick, but no sign of disease was observed until after nine months in the first lamb, and after eleven or twelve months in the last. These lambs had, so far as was known, no possibility of contact with sick sheep except during the two days when they were housed with the sick ewe.

Age-incidence.—Sheep of all ages seem to be affected, no age-period being exempt, but the disease is rarely seen in lambs less than 7 months old. After that age the mortality rate increases, and farmers who for two years or more have been struggling with the disease, usually kill all their lambs in the autumn in order to avoid losing them during the winter and spring.

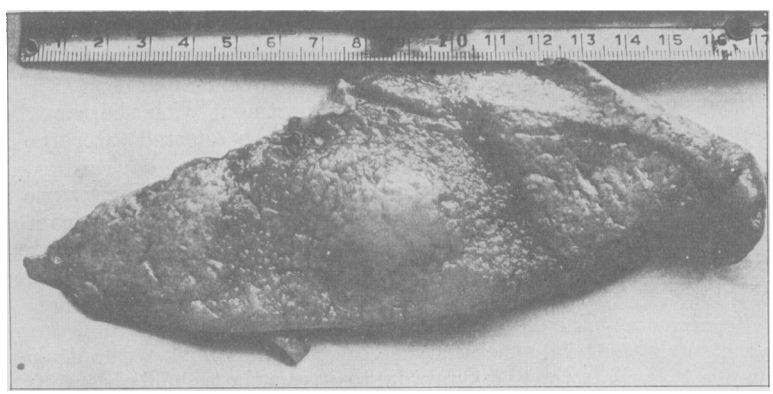

FIG. 1.—Initial lesion, hard and fibrous in the middle, with surrounding nodular tissue.

The question arises as to whether the disease is congenital. A few records from reliable farmers point strongly in this direction. In one case, for example, a newborn lamb was seen to get out of breath each time after suckling, and to avoid movements, and fluid was seen pouring out of its nostrils. We have never had the opportunity of examining such cases, which seem to be rare.

Morbid anatomy.—The initial lesion (fig. 1) may occur anywhere in the lungs. It may be as small as a cherry or as large as a hen's egg, and is frequently situated immediately under the pleura, though it may occur anywhere in the substance of the lung. It is not very distinctly limited, and the cut surface is greyish and is composed of numerous more or less elevated small nodules, usually 2–5 mm. in diameter. In fresh cases apparently sound tissue may be seen between the slightly elevated nodules, but as the disease advances, more and more nodules seem to be formed, until they are so closely set that no sound tissue can be distinguished between them. Around this lesion small, dispersed, greyish, slightly protruding nodules may be seen, decreasing in size and number with increasing distance from the chief lesion. In advanced cases large areas of the lungs are transformed into greyish, nodular, friable tissue, which breaks down easily between the fingers. In fairly recent cases it is often more or less waterlogged, whereas older lesions tend to show fibrous

changes, so that the initial lesion may be fibrous, whitish, and hard, when all other lesions are still soft, œdematous, and friable. A mucous, whitish, frothy fluid flows from the bronchi, the mucosa of which shows no apparent changes.

The enlargement of the lungs is usually striking (fig. 2), sometimes enormous, especially in cases of longer standing. This is chiefly the result of enlargement of the affected parts, which present considerable emphysema and increased water content, but in many instances a generalized enlargement of the lungs has been observed, in which lesions were only few and scattered, as if this general emphysema might be the first stage along with only small and scattered consolidations. The lymph-glands are not enlarged, except in cases complicated by pneumonia. The pleura is frequently affected, and covered by a thin membrane, which may cause adhesions between the lobes and the thoracic wall. In other organs no particular changes are seen.

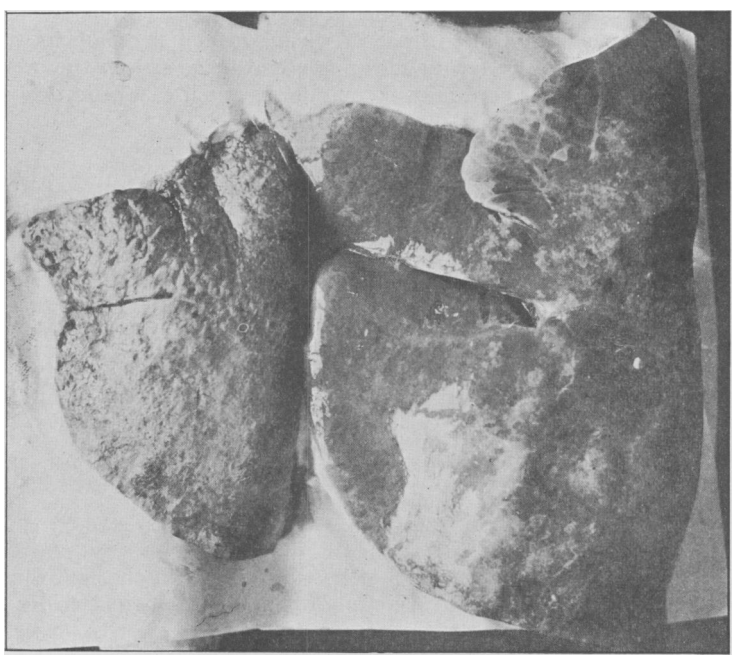

FIG. 2.—Showing great enlargement of an affected lung as compared with a normal lung.

Histology.—The histological picture is most characteristic. The sections may be picked out with the naked eye, showing intensely coloured patches with clear spaces between. The microscope reveals the dots as islands of epithelial proliferations, resembling adenomatous nodules (fig. 3). Not only are the alveoli covered with high columnar epithelium, but large, branched papillæ of loose connective tissue are formed, covered with a more or less regular layer of high columnar epithelium. Outside these epithelial nodules small tufts of epithelium may be seen in some alveoli. But apart from that the surrounding lung tissue is well filled with air, the alveoli are frequently wider than normal, and the septa may be very thin, so that no capillaries may be demonstrable in them. A greater or smaller amount of what appears to be desquamated respiratory epithelium is seen in the alveoli, and small groups of segmented leucocytes are usually seen somewhere in the alveoli and also in the connective strands of the epithelial papillæ.

As the disease advances, the epithelial tissue appears to proliferate, early epithelial alveolar proliferations growing up to solid adenomatous nodules (figs. 4 and 5), the growth evidently beginning in many alveoli simultaneously. In some alveoli the proliferations will be greater than in others, forming large papillary tufts which expand and break the alveolus in which they originated.

The epithelial proliferations apparently originate in the alveoli, thus furnishing an argument in the long-standing controversy on the nature of the alveolar lining, which here seems to react by desquamating the normal cell-lining and then rapidly to produce cylindrical, epithelial cells. These alveolar cells contain no cilia; on the other hand, cilia may be demonstrated in the bronchi, where papillary tufts are not infrequently seen projecting into the lumen. It will be easily understood that when this tissue has replaced a great proportion of the total lung, respiration must be considerably impaired.

Course of disease.—We know of no instance in which sporadic cases have not been followed by heavy losses, except when special measures have been taken by immediately isolating sheep coming from diseased flocks. The course on a farm is usually as follows: On a hitherto healthy farm a sheep is noted to be sick in the late winter or early spring (March-May). There may be one or two such cases, but the rest of the

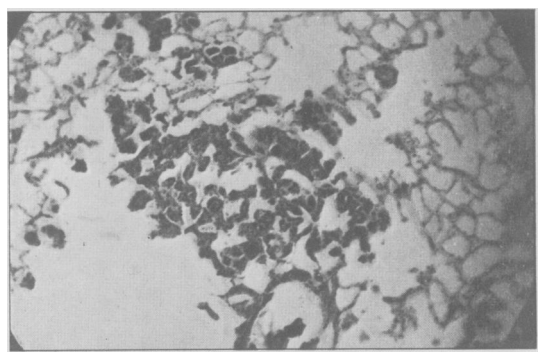

FIG. 3.—Adenomatosis. Low-power view of adenomatous nodule.

flock remain perfectly healthy throughout the summer, until the following autumn, when, after a time corresponding to the time of incubation, great losses inevitably begin. From this time onwards there are continuous losses, new cases appearing weekly. In January and February few new cases occur, a fact which is probably explained by the rare contacts during summer, when the sheep are at free range. In April, May, and June, the losses begin again and continue without interruption throughout the summer, until 50 to 60 per cent. are lost. The losses may reach 80 per cent. and more, and some farmers have slaughtered all their flock.

Resistance and immunity.—Different breeds show marked difference in resistance. One common breed, which is widely spread over the country, has proved particularly susceptible, 90 per cent. and even more having been lost on many farms. No absolutely resistant breed has been found, and only one seems to be fairly resistant. About 10 per cent. of this breed is lost, but as the strain is very rare the numbers are small and do not permit of conclusive deductions.

Ætiology.—This is unknown. No bacteria are found in the lesions, and cultures are negative, even though prepared on different kinds of media and incubated aerobically and anaerobically and with different carbon-dioxide-tensions. We have also tried virus cultivation on the chorion-allantoic membrane of hens' eggs, but with negative results. Transmission has been easily effected by keeping healthy and sick sheep

housed together, but by pulmonary injection of unfiltered material it was positive only in one case out of three. Attempts to set up the disease in five cases with Seitz-filtered material gave negative results.

Comparison with other known diseases.—McFadyean [1 and 2] has described a similar disease found in England about fifty years ago. Finding numerous nematodes of a species to which he refers as *Strongylus rufescens*, in and particularly around the lesions, he ascribed the disease to this parasite. Since his publication numerous authors have reported on verminous pneumonia, but the helminthological side of the

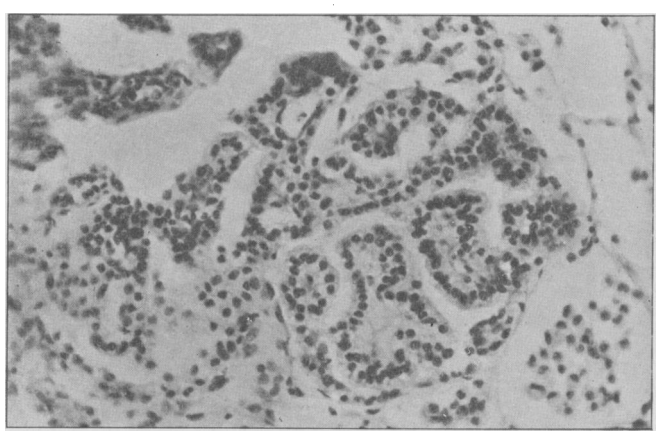

FIG. 4.—Adenomatosis of sheep's lung. Small adenomatous nodule surrounded by alveoli containing desquamated epithelial cells.

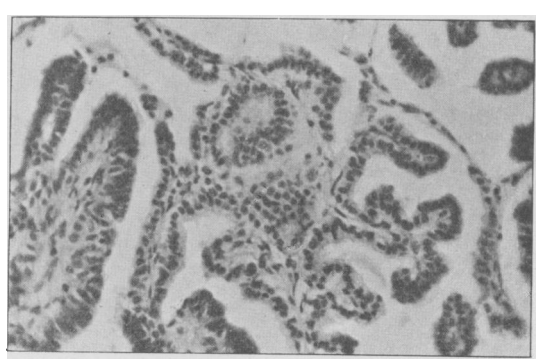

FIG. 5.—Formation of high papillæ in an adenomatous nodule.

question will be dealt with more adequately by Mr. Taylor. In short, we found the same anatomical lesions that McFadyean had associated with parasitic lungworms.

Comparing our findings with the descriptions given by Mitchell [3], Cowdry [4], Cowdry and Marsh [5], and de Kock [6], we incline to the opinion that our disease is identical with Jaagsiekte. The symptoms of our disease are the same as those described by the South African authors—the protracted course, dyspnœa, and nasal discharge—and the farmers there use the same method for diagnosis, namely, to incline the head of the animal to the ground and observe the fluid dropping from the nose. The terminal pneumonia is, according to de Kock, a very frequent feature. The lesions, as described by Cowdry and de Kock, are indistinguishable from our

findings, there being the same islands of epithelial proliferations and desquamation of round cells into the surrounding alveoli (fig. 6). The only histological difference which we find is a less interstitial reaction than that described by the South African authors, and the small nodules of connective tissue, described by McFadyean and Cowdry, are not apparent in our cases. Mitchell assumes the incubation period of Jaagsiekte to be from three to eight days, but, as de Kock has shown, it is very difficult in South Africa to obtain material which is certainly free from the disease, so that a typical Jaagsiekte lesion found a week after contact is just as likely to have been present before the contact.

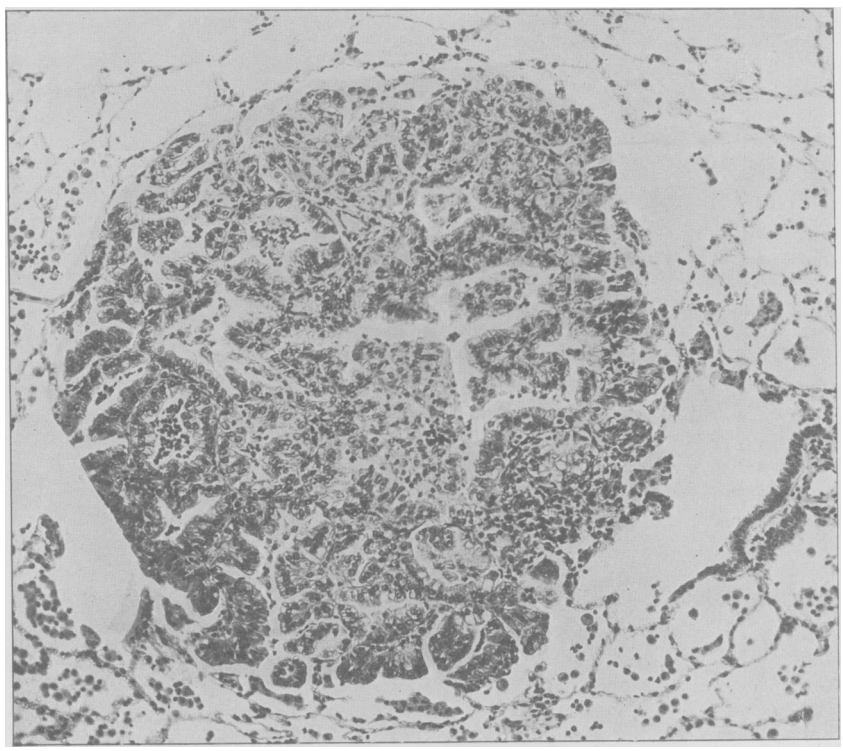

FIG. 6.—Adenomatous nodule from a section of Jaagsiekte (kindly sent by Professor Cowdry).

Cowdry and Marsh (l.c.) compared the progressive pneumonia of Montana with Jaagsiekte, and found many features of resemblance between the two, concluding that they are probably identical. Professor Cowdry has kindly sent me sections of his material for comparison, and from these sections we concluded that Jaagsiekte and our disease were probably the same, whereas the histological changes in the progressive pneumonia seemed to us to have rather the character of a chronic broncho-pneumonia, the epithelial proliferations being slight or negligible, although a considerable desquamation of the alveolar epithelial cells is to be seen. We would not deny the possibility that the progressive pneumonia might belong to the same category, but, in our opinion, the histological changes hardly justify the assumption that progressive pneumonia is identical with Jaagsiekte. We have seen one or two similar cases on infected farms, but have not made a definite diagnosis of adenomatosis on that histological finding, whereas the sections of Jaagsiekte which we have seen correspond exactly with our histological findings.

The objection may be made, that the epithelial proliferations are only a secondary phenomenon which may follow any chronic pathological process in the lungs. We have considered this possibility and have had lungs sent for comparison from all parts of the country. The two chief lung diseases which we found were contagious pneumonia and heavy *Muellerius* infestation. In these lungs we have never found changes which resembled adenomatosis, and we are convinced that the adenomatous disease is a disease *sui generis*, which can always be traced to a known source of infection.

Our opinion is, therefore, that Jaagsiekte and our disease are the same. The difference in mortality, which is much higher in Iceland than in South Africa, is probably explained by the difference in treatment. The sheep in South Africa are always grazing freely, and only rarely collected in kraals, whereas our sheep are housed for a long period in winter and thereby have far higher chances of infection. The South African authors, and Cowdry in America, point out the histological resemblances between Jaagsiekte and verminous pneumonia, but all agree that Jaagsiekte cannot be of helminthic origin, as no worms have been found in connexion with that disease, and apparently lungworms are very rare in South Africa. We incline therefore to the opinion that Jaagsiekte, the verminous pneumonia recorded by McFadyean, and our disease are all the same and are caused by some infective agent, the nature of which it has not been possible to demonstrate.

Adenomatosis in man.—Several cases are mentioned in the literature of adenomatous changes in human lungs. I shall only mention a few which resemble our cases of sheep disease.

Oberndorfer [7] describes a condition in an old woman, in which, besides a pneumonia, multiple adenomatous nodules were seen in the lungs, the alveolar epithelium being changed to cubical or cylindrical epithelium, forming papilliferous ingrowths into the alveoli. Metastatic growths were found in the bones and a diagnosis of lung cancer was therefore made. Oberndorfer says he had the impression that a rapid epithelial proliferation followed the transformation of the alveolar epithelium. "In our case", he says, "one could speak of multiple, beginning adenomas in the lung alveoli." Helly [8] describes a case of an old woman who had been suffering for a year from what was thought to be phthisis, and died suddenly. Multiple adenomatous nodules were found post mortem, with emphysematous tissue between. The description of the macroscopic and microscopic appearance of the lungs corresponds very nearly with the adenomatosis in the sheep. Löhlein [9] describes a similar case which he declared to be identical with Helly's, and at a congress in Germany Saltykow and Sternberg described the same kind of tumours at autopsies.

In Iceland we have seen no human cases which resembled the sheep disease and have found no evidence that it might be communicable to man. The occurrence of a similar condition in man shows that no worms are needed to produce such changes, for no nematodes are known as parasites of the human lungs. Aynaud [10] has suggested that the mere passing of worm larvæ through the lungs might be sufficient to start the adenomatous proliferations, as he found no lung worms in some of his cases, but only *Ancylostoma* in the small intestine. This suggestion is not corroborated by facts, as we do not know of adenomatous changes or cancer in the human population where ancylostomiasis or ascariasis is common.

Is the sheep disease a tumour growth? De Kock [6 and 11] has suggested that Jaagsiekte is a neoplastic process, and in fact there are many resemblances. When metastatic nodules are seen in lymphatic glands, as reported by Aynaud, the neoplastic nature of the process cannot be questioned. But Aynaud's is the only case reported in which metastasis has been found. Professor Peyron has given me the opportunity of studying Aynaud's sections, which showed undoubted metastasis in a lymph-gland, the epithelial proliferations having a papilliform or gland-like structure

among the remaining lymphatic tissue, which was, to a great extent, destroyed. In some of our cases we have found nodules up to the size of an apple composed like a pure cystadenoma, of numerous, large papillæ recalling the intraduct papilloma of the mammary gland in humans. The question whether Jaagsiekte and our disease may be regarded as neoplastic in nature may be discussed, but in my opinion only unprofitably so long as we do not know the cause of either. Aynaud, Peyron, and Falchetti [12] who have investigated numerous cases of presumed verminous origin in France (parasites were absent in half of their cases), come to the conclusion that the process is a real tumour growth. The histological changes seem to me to point to some agent which simultaneously has an effect upon a vast surface of the respiratory epithelium, transforming it to high, columnar form, thereby giving the newly formed epithelium a stimulus for continued growth. The growth starts simultaneously in numerous centres after the initial lesion has appeared, as if infectious material was spread from the initial lesion through the lung tissue, and since the lower borders are particularly affected it appears as if the infected secretion from the affected parts sinks to the lower parts of the lungs, there to produce fresh changes. This is not the usual process of tumour growth, although the microscopic appearance may greatly resemble it; evidently we have here a process which may be of great interest for tumour research, as there is a factor at work with a definite organizing power, which greatly stimulates the growth of certain tissue cells.

Conclusions

Comparing the so-called verminous pneumonia with our disease in Iceland, and with Jaagsiekte, we find histological changes of a very specific nature, which point to a specific origin. The South African authors deny the possibility that Jaagsiekte is caused by helminths, and we cannot find any correlation between lungworm infestation and our sheep disease.

The sections which Prof. Peyron showed me from his own and from Aynaud's cases are histologically also identical with ours.

We therefore think that the adenomatous changes, which in the literature are described as a result of worm infestation, are caused by some factor yet unknown, and cannot be explained by the action of worms alone. Whether the worms may play an intermediary part cannot yet be determined, but we at least have no reason to believe that they do.

It will be seen that we have not proceeded far in our research work. We think we have made a step towards correcting a widespread error with regard to helminthic pathology. But the experimental work with this disease is greatly hampered by the long incubation period, the difficulty of artificial transmission, and the resistance of laboratory animals to the disease. If we could get this disease down on a clear-cut experimental basis, and transmit it artificially to sheep or laboratory animals, it might prove of considerable scientific interest, as we have here a borderline between inflammation and tumour growth.

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The Lungworm Theory for the Origin of Epizootic Adenomatosis and the Question of the Existence of Adenomatosis in Great Britain

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MY experience of this disease has been small in comparison with that of Professor Dungal and Dr. Gislason, and my work on it has been limited to what could be accomplished during a stay of about five weeks in Iceland, and by the examination of a certain amount of material which had previously been sent to this country.

Professor Dungal has mentioned his reasons for believing that parasitic worms were the cause of the trouble. The pathological evidence obtained from the microscopical examination of affected lungs showing the presence of numerous parasitic worms and their larvæ in close association with the diseased tissue, was very suggestive of that conclusion. McFadyean also came to the same conclusion when investigating what appears to have been a similar disease which occurred in this country in 1888.

Some evidence was, however, obtained by Dr. Gislason to suggest that the worms might not be responsible: an examination for worm infestation which was carried out on 1,000 lungs from a diseased district, and on 1,000 lungs from a district in which the disease had not yet appeared, revealed an equal degree of infestation in each district.

On account of McFadyean's publications, however, and also on account of the strong pathological evidence in favour of the theory of causation by lungworms, it became all the more necessary to examine the association of these parasites with particular care.

Investigation in England.—Apart from the examination of sections of lung tissue, which has already been dealt with by Professor Dungal, and of hay suspected by Professor Dungal of carrying large numbers of the larvæ of *Muellerius*, the work at Weybridge consisted of the infection of sheep with lungworm larvæ originating from sheep in the diseased area in Iceland. The hay which was examined was found only to contain a few representatives of the strongyloid larvæ of horses and none referable to species of worms occurring in sheep.

In order to ascertain whether British sheep could be infected by Icelandic lungworms, two badly diseased lungs, heavily infected with *Muellerius*, were sent to Weybridge in ice from Reykjavik. On thawing out, the *Muellerius* larvæ were found to be very active and apparently normal. As many of these larvæ as possible were separated from the lungs and fed to slugs and snails of the species *Agriolimax agrestis*, *Helix aspersa*, and *Cepœa hortensis* between February 24 and March 25. During the third week of April it was ascertained that the snails were carrying the infective larvæ, and they were then fed to two lambs which had been born and reared in the buildings. Eight infected snails were given to lamb No. 949 and 13 to lamb No. 950. *Muellerius* larvæ did not appear in the fæces of the lambs until fourteen weeks later, when lamb No. 950 was slaughtered. Large numbers of the typical hard caseous and calcareous nodules were then found in the lungs, indicating the abortive development of numerous worms, but there was no sign of adenomatosis. The second lamb was