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Some Recent Advances In Facial Eczema Research

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FOR many years there have been sporadic outbreaks in the North Island of a disease of sheep and cattle involving photosensitization of the affected animals and the production of a characteristic type of liver damage. From the spectacular, superficial damage—oedema, sloughing of skin, thickening of the ears—this disease has come to be known as "facial eczema." The outbreaks of 1935 and 1938 caused considerable stock losses, and since 1938 facial eczema has been under investigation mainly by members of the Animal Research Division.

Over the period 1938-51 progress was made on the field side, and from field observations it was concluded that the disease was probably nutritional in origin and was associated with abnormal growth conditions for pasture, especially where ryegrass was dominant. The disease was likely to be observed in a flock of sheep about a week after the commencement of flush pasture growth. Recognition of the dangerous conditions—very rapid growth in hot, moist periods, possibly following prolonged drying out—led to the institution of "facial eczema warnings" to farmers to keep sheep off such grass for some days to allow it to harden. These periods are most likely to occur in autumn. With this warning system satisfactory control of the disease during the minor outbreaks since 1938 has been possible. However, it is obviously desirable to know more about the disease with a view to easier and better control in the future.

From the earlier work on this disease, the following picture of facial eczema has emerged.

Facial eczema results from a characteristic type of liver damage and it is the impairment of some of the functions of the liver that leads to the more obvious symptoms of the disease. One of these functions is concerned with the removal of the bile pigment, bilirubin, from the blood; when the process becomes inefficient the animal becomes jaundiced—that is, certain tissues are stained yellow with bile pigment. This is common in facial eczema. Another liver function is the removal from the portal blood of phylloerythrin, a normal breakdown product of chlorophyll, the green colouring matter of grass. Interference with this function allows phylloerythrin to pass into the general circulation, and it is this pigment, by making the animal photosensitive, that is, sensitive to light, that causes the skin lesions from which this disease takes its name. It must be emphasised that it is the liver damage that produces the photosensitivity and jaundice effects and that it is only the animals with severe liver damage that become photosensitive.

Considerable work was also done on the pathology of facial eczema and on the definition of the lesions and the stages in their development.

However, as this paper is concerned with recent advances, we shall not discuss these earlier findings in greater detail.

One of the biggest handicaps to research on facial eczema has been and still is the failure to produce as required, toxic pasture. One explanation could be that the pasture is toxic for only a very short time. Grass has been cut and dried on farms where the disease was occurring; when this grass was fed to sheep at the Wallaceville Animal Research Station only on very few occasions was the type of

liver damage associated with facial eczema produced. Even then the damage was generally only slight. The Department of Agriculture took over farms where facial eczema appeared to occur frequently only to find that the disease seemed to disappear.

For some years the facial eczema research farms, first at Wairoa and later at Manutuke near Gisborne have followed a system in which over the "facial eczema season" several tagged sheep are drafted on to a paddock each week and after a period of, say, four weeks they are killed and their livers are sent to Wallaceville for histological examination. Grass is cut daily, dried, and bulked in week or two week lots, the idea being that if facial eczema liver lesions are observed in any animals it becomes possible to pinpoint the appropriate "toxic pasture" period and a sample of this grass is available. In this way evidence was obtained that grass cut and dried on one of the paddocks at Manutuke during the third week of April, 1951, should have been toxic. By November, 1951, it had been shown that feeding this bulked sample of grass to a sheep for four weeks gave moderately severe facial eczema liver lesions. After this confirmatory experiment there was left about 200 lb. of dried grass as moderately toxic material for work on facial eczema.

The securing of this toxic grass is a major advance in facial eczema research, because it has at last provided us with grass sufficiently toxic for chemical extraction experiments. The isolation of the toxin is an essential part of the facial eczema investigation and is at present our main objective.

Two hundred pounds may sound a lot of grass until it is realised that it would hardly have been sufficient to feed two sheep for four weeks. The long test period is associated with the low level of toxicity which, in turn, may be due to two factors. The method by which the grass is dried may lead to loss of toxicity, and, also, the bulking of samples will lead to dilution of any toxic grass that may be present.

Those of us working on facial eczema at Wallaceville and at Ruakura had for some time been convinced that for any real progress to be made in studying this disease it was imperative to find a smaller test animal than the sheep, which is not only an expensive animal to use in the numbers such work requires, but which also eats a prohibitively large amount of grass before effects are produced. We had already found the guinea pig to be a very satisfactory animal for studying the liver disease caused by eating the leaves of broom-corn millet (*Panicum miliaceum*). Because of our considerable experience in working with it, the guinea pig was chosen as the first small animal to be fed on the dried facial eczema pasture.

For those who are unfamiliar with the beast, it might be mentioned that the guinea pig can live quite happily on an all-grass diet.

Guinea pig feeding trials on dried grass samples from the 1950 facial eczema season have been carried out at Ruakura, but the grass has not been sufficiently toxic for any worthwhile conclusions to be drawn. Feeding trials with the 1951 sample began in December, 1951, at Wallaceville and liver damage was produced. In January, 1952, similar work was started at Ruakura. In the Ruakura experiments 10 animals were fed over a period of 2 to 6 weeks. They were then killed and histological examination of their livers was carried out by J. V. Evans at Wallaceville. It is not our intention here, nor are we competent, to give a complete account of the histological work done at Wallaceville. It is obviously an important part of the whole story. Put briefly however, it may be stated that in all cases there was definite and characteristic liver damage, the livers showing diffuse fibrosis with bile duct hyperplasia. These lesions are of the same type as are found in facial eczema. In all except the animals killed after two weeks,

liver damage was also clearly visible to the naked eye, the most obvious effect being a diffuse whitish flecked appearance throughout. The livers were also increased in size. The severity of all these effects increased with the length of the feeding period. In no cases have similar lesions been observed in any of the guinea pigs we have fed on a number of dried normal pasture samples.

From these results it seems very likely that whatever it was in the grass that produced this liver damage in these guinea pigs must be the same thing or something very closely related to it, that gave facial eczema liver damage in sheep fed on it. That is, the guinea pig is probably affected by the facial eczema-producing substance. Also, if we can use as our criterion the time needed to produce effects in the sheep and guinea pigs fed the same dried grass sample, it looks as if the guinea pig is probably comparable in sensitivity to the sheep.

It is difficult to over-emphasise how important to facial eczema research it is to have a suitable small animal as our test. A little reflection will show some of the more obvious reasons. First of all there is the quantity of grass required. Assuming that the dried pasture would be as toxic as the material we now have, we would need to feed about 100 lb. dry wt. to a sheep over a period of 4 weeks to produce much effect. To contemplate any chemical extraction work it would be desirable to feed extracts at twice that level to allow for losses in manipulation, and even the most optimistic chemist would agree that there would probably need to be at least two dozen feeding experiments before the nature of the facial eczema agent was established. Simple arithmetic gives the impressive total of 2 tons of dried toxic pasture for such an undertaking. And we think it would be a bold man who undertook to supply such a quantity. In the same way, it would be necessary to have a semi-industrial scale laboratory to handle the extraction work. Using guinea pigs as we do, within the weight range 200-300 grams, the amount of grass fed over a 4-5 week period is reduced to about 2 lb., and to achieve the amount of work mentioned earlier would require about 1 cwt. of dried toxic pasture. This is more than we have at present but it offers a much more hopeful prospect for the future. Another direct result of the use of the small animal is that it becomes feasible to test grass grown under controlled conditions in an endeavour to produce "facial eczema pasture." More will be said about this later.

In brief: Facial eczema pasture can be cut, dried and stored and still retain some toxicity. The guinea pig is a satisfactory test animal. With these two advances the way has been cleared for chemical extraction work in the laboratory.

Such work has already yielded results. A solution containing the toxic substance has been obtained from the dried grass by extracting with suitable organic solvents; this has been shown by putting the extracts on to normal dried grass or guinea pig food, removing the solvents and showing that the appropriate liver lesions were produced on these diets. There did not appear to be much loss of toxicity during this treatment. Attempts at further fractionation have so far been disappointing owing to loss of toxicity, and suggest that we are dealing with a rather unstable substance. A likely explanation of the losses appeared to be that the method used in concentrating and drying the extract destroyed the toxin. A method has now been found of drying the extracts without serious loss, so that a dried material having a concentration of toxin of about 20 times the original dried pasture has been obtained. Results to date lead to some useful conclusions.

Either normal dried grass or guinea pig food was adequate to maintain guinea pigs in good health. When extracts were added to these diets liver lesions were produced. This means:—

1. That facial eczema is not a simple deficiency disease.
2. That facial eczema is due to a toxic substance present in the pasture sample. This has, of course, been postulated for many years, but this is probably the first time that the fact has been demonstrated experimentally. No toxicity has been detected in the residue remaining after extraction of the toxic dried pasture; this portion represents 90-95% of the total bulk of the grass.
3. Also, because of its solubility in organic solvents, the facial eczema toxin is not protein in nature. It may be concluded, therefore, that facial eczema is not caused by the direct action on the animal of a virus or a micro-organism.
4. Again, because the liver damage can be produced in the guinea pig, which is a rodent, it is clear that facial eczema liver damage is not peculiar to ruminants.

It might be added that no significant amount of the fluorescent alkaloid, perloline, has been detected in this dried grass.

The factor that now limits our progress towards isolating the facial eczema toxin is the shortage of suitable dried pasture. To make the most efficient use of the sample we have it is necessary to do one experiment at a time and know the results of it before planning the next step. As we are at present using a four-week feeding period it's a slow business. We are trying to break this bottleneck in two ways; by devising a quicker test and by producing more toxic pasture.

To turn now to the animal side of the picture.

The big difference between field conditions and laboratory feeding in this work lies in the fact that in the field the sheep is exposed for a short time to a highly toxic pasture; in the laboratory we are obliged to feed a much less toxic material for a long time. In the first case one observes "knockout" effects on the liver, with the production of jaundice and photosensitivity. In the guinea pig feeding experiments the liver is damaged much more insidiously and although the same type of liver damage is produced the animal is able to adapt itself and does not show such effects externally. In fact, to the observer the animals appear in perfect health. The guinea pigs would probably get jaundice and so on if we fed extracts at high enough levels but we have so little toxic grass available that we cannot afford to try the experiment. For the present we rely for our criterion of liver damage on *post-mortem* examination of the animal; if the liver shows the flecked appearance mentioned earlier, and is also increased in weight, we assume, pending histological confirmation by Wallaceville, that we have a positive case and carry on with the next chemical extraction.

We are at present looking for a biochemical test that can be used on guinea pigs in the hope that we can reduce the time necessary per experiment. In affected animals there appears to be elevation of the blood amino-acid level but this is apparently not sensitive enough for diagnostic purposes. A more hopeful approach has come from the study of serum proteins. Dr. Lyttelton, of Grasslands Division, has made electrophoretic studies of the serum proteins of normal guinea pigs and an animal showing facial eczema liver damage. Quite large changes were observed in the albumin and alpha-globulin fractions, with a smaller change in beta-globulin. If these results can be confirmed on a further animal, this observation may be very useful. Dye clearance tests have also been adapted for use on guinea pigs. A solution of the dye, bromsulphthalein, is injected into the blood and the rate at which it disappears is a measure of the efficiency with which the liver can handle it. In many human liver diseases this test is an extremely useful and sensitive one, but it is too early to say how it will work in guinea pigs with facial eczema liver lesions.

There is some evidence of impairment of rose bengal removal from the blood of sheep with facial eczema, and this dye clearance test is also being used on guinea pigs. Another approach which has been tried is the use of a smaller test animal; this has been tackled in two ways. We have tried even smaller guinea pigs and also, now that we can prepare toxic extracts and hence are no longer tied to herbivorous animals, we have considered the mouse. If the mouse were as satisfactory and as sensitive as the guinea pig we would stand to make quite a saving in toxic pasture. A mouse weighs about 20 grams; the guinea pigs we use at present are 200-300 grams. Unfortunately, mice fed high levels of facial eczema grass extracts over several weeks have given no visible evidence of liver damage. This may mean that the mouse is more resistant than the guinea pig to this toxin; alternatively it may be that the mouse is unable to absorb the toxic material from mixtures so far prepared. For the present it appears that the mouse will not be of much use to us.

On the other hand, preliminary experiments with smaller guinea pigs have been very satisfactory and animals weighing 120-140 grams have proved to be at least as sensitive on a proportional basis as larger guinea pigs. Although such animals are only about 2-3 weeks old, they are gratifyingly robust and, as they eat only half as much as our former test animals, they will probably be used in future chemical fractionation work.

But as has been emphasised throughout this paper our great handicap is shortage of toxic pasture. In an endeavour to overcome this and also to enable a study of conditions necessary to produce this disease, experiments have now been started aimed at growing pasture under controlled conditions of temperature, moisture, etc. We have four glass frames about 9 ft. square; in them there is sward and soil transplanted from an area where facial eczema occurs frequently. The air and soil will be maintained at known temperatures and the pasture dried out thoroughly; water applied freely should then produce flush growth. Guinea pigs grazed on this pasture will be examined after 2-3 weeks for signs of liver damage.

This approach may seem a little strange to people accustomed to think in units such as the sheep and the acre but we feel it is the next logical step in our endeavour to find what we can about facial eczema. Ultimately, of course we must go back to the sheep to check what is found, but in the meantime there is a great deal of work to be done.

Discussion

Dr. L. R. WALLACE: Does the digestive system of the guinea pig approach that of the ruminant in any way?

Dr. PERRIN: The guinea pig is a rodent and has the single stomach of the non-ruminant animal. However, like all herbivorous animals, including ruminants, it has a large caecum in which it is likely that otherwise undigested material is attacked by micro-organisms.

Mr. HURRAN: Has the possibility of injecting the toxin been considered?

Dr. PERRIN: Yes, but at the present stage of the work, when our extracts are bulky and contain such a wide range of chemical compounds, we feel that injection rather than ingestion would be too dangerous to the animal.

Dr. I. J. CUNNINGHAM: The rate of absorption of the toxic materials may depend on the dilution of the material, as is the case in the absorption of anti-vitamin A extracts.

Mr. R. J. LANCASTER: It may be that the grass contains something which is converted into the toxin by digestive processes.

Mr. J. B. SWAN: Has facial eczema been seen in horses?

Dr. C. P. McMEEKAN: There have been no cases in the last ten years.

Dr. I. J. CUNNINGHAM: There is a report of one affected liver from a horse, diagnosed by Dr. Hopkirk at Wallaceville.

Mr. J. GERRING: Is the left lobe of the liver the affected one in guinea pigs as is the case with sheep?

Dr. PERRIN: In most of the guinea pigs we have fed toxic grass or extracts the damage appears to involve all of the liver. In some cases, however, where some areas are affected more seriously than others, the left lobe does seem to be more damaged.