INH PROPHYLAXIS AND TREATMENT IN BOVINES

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The project described in this paper is being carried out on a dairy herd. The herd is kept as a source of fresh milk for the employees of a company and has for many years been maintained as a closed unit, except for the occasional purchase of a new bull. The herd, which now numbers 130 head, including calves, is run on about 10 acres of land. The bulk feed is grown in the neighbourhood and the animals are fed in the milking shed or in the paddocks. Thus they are in very close contact with one another. Water for the cattle is provided in concrete drinking troughs.

During February 1957 the owners applied to have the herd tuberculin-tested and were alarmed when, on the tests being read, it was found that about 60% of the animals gave a positive or suspicious reaction.

It was decided to use iso-nicotinic acid hydrazide (INH) on the herd to determine its value, if any, as a chemotherapeutic and prophylactic agent.

MATERIAL AND METHODS

The first step was to re-test the whole herd and give each animal a metal ear-tag for easy identification — the test was carried out on 19 - 21 March 1957, using both bovine and avian tuberculins, and the overall results were as follows: herd total, 115; positive reactors, 69; suspicious reactors, 16; and negative, 30.

When the incidence of reactors is as high as these results show, suspicious reactions may be considered as positives. This means that the test revealed that 74% of the herd were reactors to the single intradermal test. To avoid confusing the issue, the tuberculin test was interpreted purely on skinfold increase at the site of injection after 72 hours, using the following limits: skinfold increase under 2 mm., negative; skinfold increase 2 - 4·9 mm., suspicious; and skinfold increase 5 mm. and more, positive.

All positive and suspicious reactors, as well as the negative animals, were to be given a daily dose of INH for 6 months, after which the herd would be re-tested and the position reviewed. All calves born after the start of the test were to be given INH within 7 days of birth.

The dose of INH used was 45 gr. for a full-grown Friesland, graded down to about 15 gr. for a calf. When considered in terms of average human dosage, the dose used on the smaller animals is high while that given to the adult animals is relatively low.

The drug was supplied in crystalline form, which milking cows took mixed in their concentrate ration. Those animals not receiving concentrates were passed through a crush-pen and individually dosed, it being found most convenient to wrap up each dose in a small piece of paper and throw the pellet into the back of the mouth.

The treatment of the herd started on 5 May 1957, and on 18 August 1959 all adult animals were taken off treatment, but all calves and heifers are remaining on daily INH treatment until about the age of 2½ years. During this experiment no changes were made in the general management of the animals, neither were any special hygienic or isolation measures used.

RESULTS

Single intradermal tuberculin tests were carried out on the following dates with the overall results shown in Table I: 18 - 21 March 1957 — bovine and avian tuberculins used, 11 - 14 November 1957 — bovine and avian tuberculins used, 18 - 21 February 1958 — human tuberculin used, 26 - 29 May 1958 — human and bovine tuberculins used, 6 - 9 December 1958 — bovine tuberculin used, and 7 - 10 July 1959 — bovine tuberculin used.

Attempts were made at the beginning of the project to discover open tuberculosis cases, using milk and sputum-cup samples, but unfortunately all efforts proved fruitless. Detailed postmortem examinations were carried out on animals that died or were destroyed after the trial began. Full laboratory and biological tests were carried out on all samples collected at these autopsies.

The salient points to arise from the trial to date are as follows:

1. The Possibility of Raising Calves free of Tuberculosis in Herds where the Disease is Rife

Since treatment of the herd began, 70 calves have been born and these have always been negative to the tuberculin tests carried out at various times, with the exception that, at the test done on 7 - 10 July 1959, 8 calves showed suspicious reactions, and 3 showed positive reactions to bovine tuberculin. At each subsequent re-test of these calves, all reactions were found to have decreased. Two of the calves that showed the greatest reactions were slaughtered, but autopsy revealed no tuberculous lesions, although both showed cysticercosis. At first it was thought that this infection of 'measles' was sensitizing the calves to tuberculin. However, it was noticed that the calves that had sawdust bedding in their pens were the only ones to show tuberculin sensitization, and as soon as this bedding was replaced by 'duckboards', no further new calves showed an allergy to tuberculin. Following this up, it was found that the sawdust bedding had been obtained from a sawmill some miles away. At this mill the sawdust was simply thrown into heaps in the open air to which numerous children, fowls and wild birds had free access.

Samples were selected from the original sawdust heap where bedding was obtained for the calves. These specimens, collected in sterile receptacles, were aseptically handled and, before seeding on media, were treated in the laboratory for ½-hour, 1-hour and 2-hour periods, with 4% sodium hydroxide. A number of acid-fast species were isolated, the majority falling into the fast-growing *M. fortuitum* group; one resembled an avian type. We wish to draw special attention to this avian type.

White guinea-pigs were selected and injected intramuscularly with cultures obtained from single colonies of both groups. Subsequently, the infected calves were subjected to the intradermal tuberculin test, from 18 to 25 days after injection. Mammalian tuberculin was injected into the skin behind the right ear and avian tuberculin behind the left ear. Control guinea-pigs from the breeding section were similarly skin tested; each injection produced a small whitish bleb. The results were read 24 - 48 hours after the test.

In the pigs injected with the avian-type bacillus there was a striking positive skin reaction to the avian tuberculin; there were comparatively poor but definite reactions to mammalian tuberculin. All the pigs injected with the fortuitum group and all the controls remained completely negative.

The guinea-pig reactors which underwent postmortem examination showed an abscess at the point of injection, enlarged or slightly caseated inguinal glands, swollen iliac glands and moderately enlarged spleens with, in one case only, raised tubercles on the surface.

TABLE . TUBERCULIN SKINFOLD MEASUREMENTS N A DAIRY HERD

Tuberculin test	*Tuberculin used*	*Date of test reading*	*Total herd strength*	*Positive reactions*	*Suspicious reactions*	*Negative reactions*	*% negative in herd*	*Total skinfold increase in mm.*	*Average skinfold increase in mm.*
1st	Bovine 99	21.3.57	115	69	16	30	26·1	869·9	7·56
2nd	Bovine 5	14.11.57	126	69	26	31	24·6	862·2	6·84
3rd	Human 8	21.2.58	129	41	28	60	46·5	430·9	3·34
4th	Human 10	29.5.58	125	55	30	40	32·0	522·8	4·18
	Bovine 7		125	17	52	56	44·8	310·4	2·48
5th	Bovine 131	9.12.58	121	33	49	39	32·2	403·6	3·33
6th	Bovine 134	10.7.59	130	35	48	47	36·2	388·6	2·99

The mycobacterium recovered so far from the lesions of guinea-pigs examined at autopsy closely resembles the avian organism. It is being studied for further classification.

With regard to this organism, a point of exceptional interest was the strong isoniazophilic tendency apparent in a preliminary sensitivity test made on 5 - 50 μ of isoniazid incorporated per ml. of media, which produced growth several days earlier than on the non-INH control tubes. This might be an explanation in modern chemotherapy for the emergence of previously unknown mycobacteria in human pathology. In veterinary science, these organisms might be an additional cause of the inexplicable occasional reactions in areas where bovine tuberculosis had been eradicated.

This, together with the fact that calf sensitization to tuberculin ceased as soon as the sawdust bedding was done away with, suggests that these avian-like organisms in the bedding were the cause of the sensitization, and that the INH prophylaxis was still effective in keeping the calves free of bovine tuberculosis. It is also interesting to note that in June 1960, 7 calves that had shown sensitization to bovine tuberculin previously were re-tested using both bovine and avian tuberculins; this showed that, while skin reactions to the bovine tuberculin had decreased somewhat, the reactions to avian tuberculin were some 4 times larger.

2. The Clinical Effect of the Drug

Use of the drug stopped coughing and led to improved bodily condition and weight of the animals. All animals slaughtered for postmortem examination were in really excellent condition. Overall milk production increased very noticeably.

3. The Apparent Cure of Bovine Tuberculosis using Isoniazid

Of the 69 animals that gave positive reactions to the tuberculin test on 21 March 1957, before the treatment with INH began, 25 have either died or been destroyed for autopsy purposes to date, and of these 23 have undergone postmortem examination with the following results:

Three were found to have tuberculosis. Of these 1 had been treated for only 28 days. The organisms isolated from the other 2 were found to be biologically attenuated, although typically of bovine type. In the remainder (20) no tuberculosis could be found macroscopically, nor could the organisms be grown from any material that appeared suspicious. Subsequently, 9 further postmortem examinations were done. In some of these, although smears from lesions showed acid-fast bacilli, cultures could not be grown, and in 2 cases where cultures were obtained these organisms were found non-pathogenic for guinea-pigs.

DISCUSSION

When all cattle positive to the tuberculin test are merely removed from a grossly infected herd, such as the one studied in this trial, it is well known that the disease smoulders on in the herd even when the strictest hygienic precautions are taken. However, if the remaining negative animals can be protected by the use of INH much will have been achieved. Some may pick up enough infection to turn a negative into a positive reaction in the early stages, but these infections do not appear to proceed beyond this initial allergy-producing stage.

Infection with avian bacilli, however, results in calves becoming sensitive to tuberculin, especially avian tuberculin, without any macroscopic signs of disease, and this may be an important factor in confusing control of tuberculosis in bovines.

The great question, of course, is how long INH prophylaxis has to be kept up. It is not an easy matter to determine. The purpose of this paper is, however, to show how dramatically a highly infected herd can be improved in condition and how the spread of the disease can be checked by using isoniazid as a curative and prophylactic agent.

Further trials are necessary to determine: (1) optimum dosage of INH, (2) length of treatment necessary, and (3) what happens to a previously tuberculous animal when INH therapy is discontinued.

SUMMARY

A highly infected tuberculous herd of dairy cows, heifers and calves was submitted to isoniazid (INH) therapy over a period of 2½ years. This therapy acted both curatively and prophylactically. The value of the remedy in building up a clean herd is stressed.

Avian infection can, however, bedevil the whole picture.

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