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(54) Title: Treatment of Animals

(57) Abstract:

The invention provides a use of an antibiotic in the treatment of an animal, by administering the antibiotic to the animal through implantation thereof into the animal body.

AP105

(56) Documents cited: US 4 374 121 US 4 159 322 US 4 077 406

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THIS INVENTION relates to the treatment of animals.

According to a first aspect of the invention, there is provided a use of an antibiotic in the treatment of an animal, by administering the antibiotic to the animal through implantation thereof into the animal body.

The antibiotic may be implanted subcutaneously into the animal body, and may be implanted in controlled release form so that a prophylactically effective or immunizing quantity of the antibiotic is released into the animal body over a period of time, eg at least 10 days, to permit the animal body to build up immunity against a disease.

The prophylactically effective quantity of antibiotic which is released may be at a relatively low non-therapeutic dosage level, eg between 0,1 and 2 mg antibiotic per kilogram animal body mass per day. The bloodstream of the animal may simultaneously be challenged, eg by way of injection, with virulent organisms of the disease, thereby

allowing the animal to build up the immunity against the disease.

The Applicant believes that the use of the antibiotic according to the first aspect of the invention will be particularly, but not necessarily exclusively, effective in rendering animals immune to heartwater, anaplasmosis, mastitis, and/or redwater.

The animals may be ruminants such as cattle, sheep, goats or the like.

In one embodiment of the invention, the antibiotic may be in solid form, eg in tablet, capsule, pellet, rod or the like form. In another embodiment of the invention, it may be in the form of a paste. In both these forms, the antibiotic will hence be in a form in which it is released slowly over a period of time and in controlled fashion into the body.

The antibiotic may be tetracycline or a derivative thereof. For example, it may be a tetracycline derivative, viz doxycycline hydrochloride ie the hemihydrate, hemiethanolate of (4S,4aR,5S,5aR,6R, 12aS)-N-(2-carbamoyl-1,4,4a,5,5a,6,11, 12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacen-4-yl)-dimethylammonium chloride, an

antimicrobial substance obtained from oxytetracycline and methacycline and which is long-lasting.

According to a second aspect of the invention, there is provided a use of an antibiotic for the manufacture of a medicament for treating an animal, with the medicament being administrable to the animal body by implantation.

The medicament may be in solid form. Instead, it may be in the form of a paste.

According to a third aspect of the invention, there is proviced a substance or composition for use in a method of treatment of an animal body by implantation thereof in the animal body, the substance or composition comprising an antibiotic.

According to a fourth aspect of the invention, there is provided a medicament for use in a method of treatment of an animal body by implantation in the animal body, the medicament including an antibiotic as an active ingredient.

The medicament may be in unit dosage form, and may be in solid form, eg in the form of a pellet, tablet, or the like. Typically, it may be in the form of a tablet about 1 cm long and 2,5 mm in diameter.The medicament may hence include at

least one excipient, such as a binder, eg polyvinylpyrrolidone, and/or a lubricant, eg magnesium stearate and/or a mixing agent, eg alcohol, and/or a filler.

According to a fifth aspect of the invention, there is provided a method of treatment of an animal body, which includes implanting an antibiotic into the animal body such that a prophylactically effective quantity of the antibiotic is released into the animal body in controlled fashion over a period of time.

The treatment may be effected once during the lifetime of the animal, eg immediately after the birth of the animal or at a time when the animal is introduced into a geographic area in which the predetermined disease is prevalent.

The quantity or dosage rate may be sufficiently high to be prophylactically effective, yet sufficiently low not to inhibit entirely the natural ability of the animal body to build up immunity against the disease. Typically, the dosage rate may, as mentioned hereinbefore, be between 0,1 and 2 mg antibiotic per kilogram bodyweight per day, eg 0,2 to 0,5 mg/kg per day, for a predetermined period of time.

The invention will now be described by way of example, with reference to the following non-limiting tests, formulations and graphs 1 to 10:

TEST 1

To each of six fully grown sheep was initially, on day 0, administered by subcutaneous injection, 1 mg per kg bodyweight per day of LIQUAMYCIN 100 (trade mark), the active ingredient of which is oxytetracycline. Each sheep was also injected intravenously with 5 ml Welgevonden Supply antigen blood containing virulent heartwater organisms, ie Cowdria ruminantium organisms. The daily subcutanoeus administration of the LIQUAMYCIN 100 at the same dosage rate was thereafter continued for a further 25 days, with rectal temperature readings being taken each morning. On day 40, each of the sheep was again injected intravenously, with 5 ml of the Welgevonden Supply antigen blood containing virulent heartwater organisms, ie re-exposed to the disease. All six sheep survived the disease. The sheep were then again, on day 60, injected with 5 ml of the same blood, ie again re-exposed to the disease.

All six sheep survived this re-exposure to the disease, indicating that they had built up immunity to the disease. Temperature readings were ceased after day 90.

Graphs 1 to 4 show the temperature readings versus time for two of the treated sheep (Sheep A and B) as well as two control sheep (Sheep C and D). Sheep C was intravenously injected with the antigen blood on day 0 but was not pretreated with the tetracycline at the low immunizing dosage rate. Instead, it was treated with a therapeutic dose of the LIQUAMYCIN 100, viz 20 mg per kilogram bodyweight when a temperature rise was noticed, ie on day 11. Temperature readings were ceased in respect of Sheep C on day 18, and recommenced on day 29 after Sheep C had been re-exposed with 5 ml of the antigen blood on day 27. Temperature readings were ceased on day 52, with Sheep C hence also having built up immunity to the disease by being treated with the therapeutic dose of the tetracycline. In some cases, more than one therapeutic dose will be required.

However, the therapeutic dosage route has risks associated therewith, eg the timing of the dosage is critical. If the therapeutic dosage is administered too early, immunity is not built up; if the therapeutic dosage is administered too late, the animal will die. There is even the risk that an animal will die even when injected with the correct therapeutic dosage at the correct time - see Graph 4 in respect of Control Sheep D. Sheep D was also injected with the antigen blood on day 0; a temperature rise was experienced on day 11; it was injected with a 20 mg/kg

therapeutic dose of LIQUAMYCIN LA on day 11; however, Sheep D died on day 12.

TEST 2

Solid tablets having the following formulation were made up

(i)	doxycycline hydrochloride	- 75 parts by mass
(ii)	polyvinylpyrrolidone	- 3,2 parts by mass
(iii)	magnesium stearate	- 1 part by mass.

These solid ingredients, in powdered form, were admixed. Sufficient alcohol, ie ethanol, was added to the powdered admixture to granulate the mixture. After evaporation of the alcohol, the granules were tabletted in known fashion. The tablets were 5 mm in diameter and about 3-5 mm long, with each tablet having a mass of about 100 or about 150 mg.

Three sheep (designated E, F and G) were treated by subcutaneously implanting on day 0 sufficient tablets into the ears of the animals, viz 3x150 mg tablets into the right ear and 2x150 mg tablets into the left ear of Sheep D, 1x150 mg tablet into each ear of Sheep E, and 2x100 mg tablets into each ear of Sheep F, to release a total of 10 mg/kg active ingredient, ie doxycycline hydrochloride, into the animal's body over a period of 25 days. The long-acting tablets released the active ingredient slowly in controlled fashion over the twenty-five days, and were fully dissolved or exhausted by day 25. Hence, 5 mg/kg is introduced per

ear, ie 0,4 mg/kg per day. The tablets were implanted in both ears rather than in one only, to minimize reactions in the ears themselves which could adversely influence the absorption of the active ingredient. Reactions were indeed experienced in both ears in each case, but all three animals survived both the initial exposure on day 0 as well as the subsequent exposure on day 35 of 5 ml of antigen blood as described hereinbefore with reference to Test 1, injected intravenously, hence indicating that immunity had been built up. Hence, immunity was achieved by subcutaneously releasing into the body immunizing or prophylactic, ie bacteriostatic, quantities of the antibiotic. It is hence critical that the release rate be below the bacteriocidal or therapeutic dosage rates as this would result in killing off of the organisms without immunity being built up. It is also important that the release rate be sufficient to enable the immunity to build up. If it is too low, the animal will die when subjected to the organisms. The Applicant hence believes that subcutaneous implantation of the antibiotic in solid or paste forms provides a very effective means of obtaining the desired release rate.

Graphs 5 to 7 show temperature profiles versus time for these animals.

TEST 3

Tablets having a diameter of about 2 mm and a length of about 1 cm, with a mass of about 75 mg, were made up as for the 5 mm diameter tablets and having the same composition. These tablets or pills were easier to implant subcutaneously due to their smaller size. They were implanted in three sheep in the same dosage rates as in Test 2, viz to give a total of 10 mg active ingredient of doxycyclic hydrochloride per kilogram animal body mass over 25 days. Two 75 mg tablets were implanted into each ear of each animal. These sheep, designated H, I and J, survived an initial exposure to 5 ml of antigen blood as hereinbefore described, injected intravenously, with both the implantations and the exposure being effected on day 0. These sheep have not yet been subjected to re-exposure.

Graphs 8, 9 and 10 show temperature profiles for these sheep.

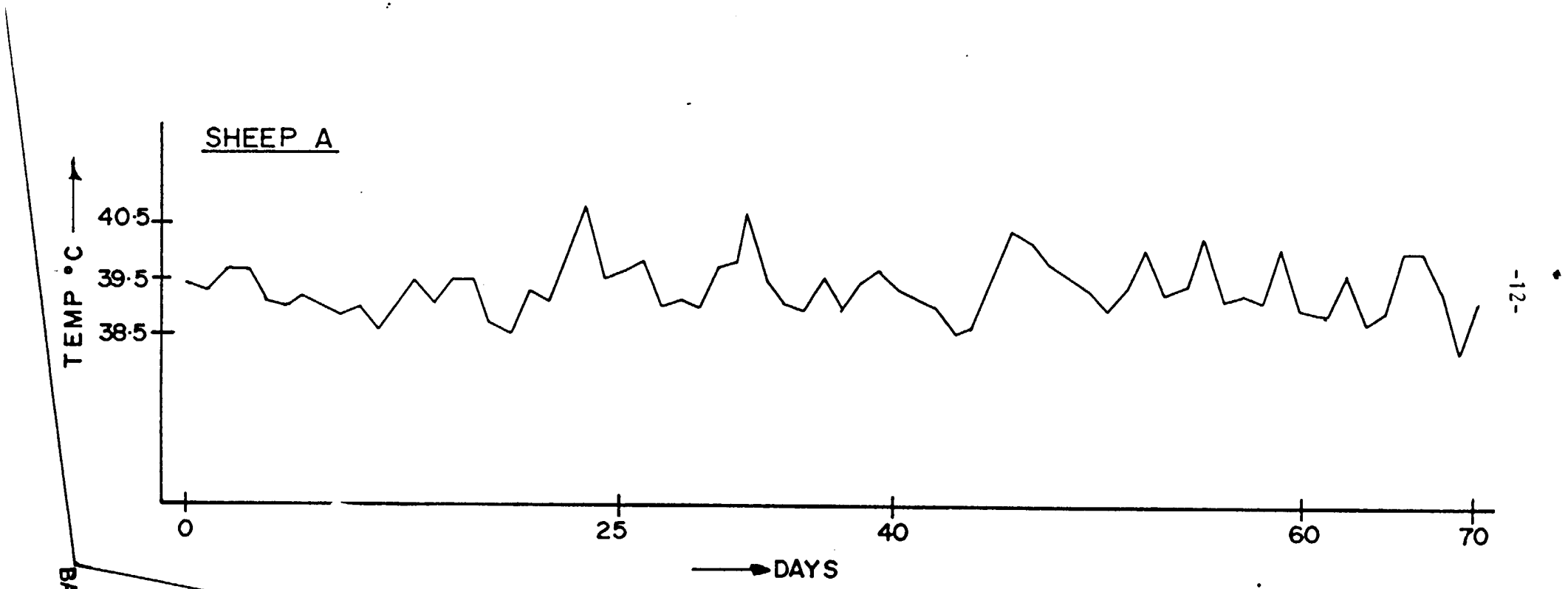
Applicant believes that, on the basis of the above tests, the prophylactically effective doses could possibly be lowered even further, eg to about 5 mg active ingredient per kg bodyweight or 0,2 mg per kg per day.

Instead of being implanted subcutaneously in the ear, the implantation can be effected in any other suitable body location.

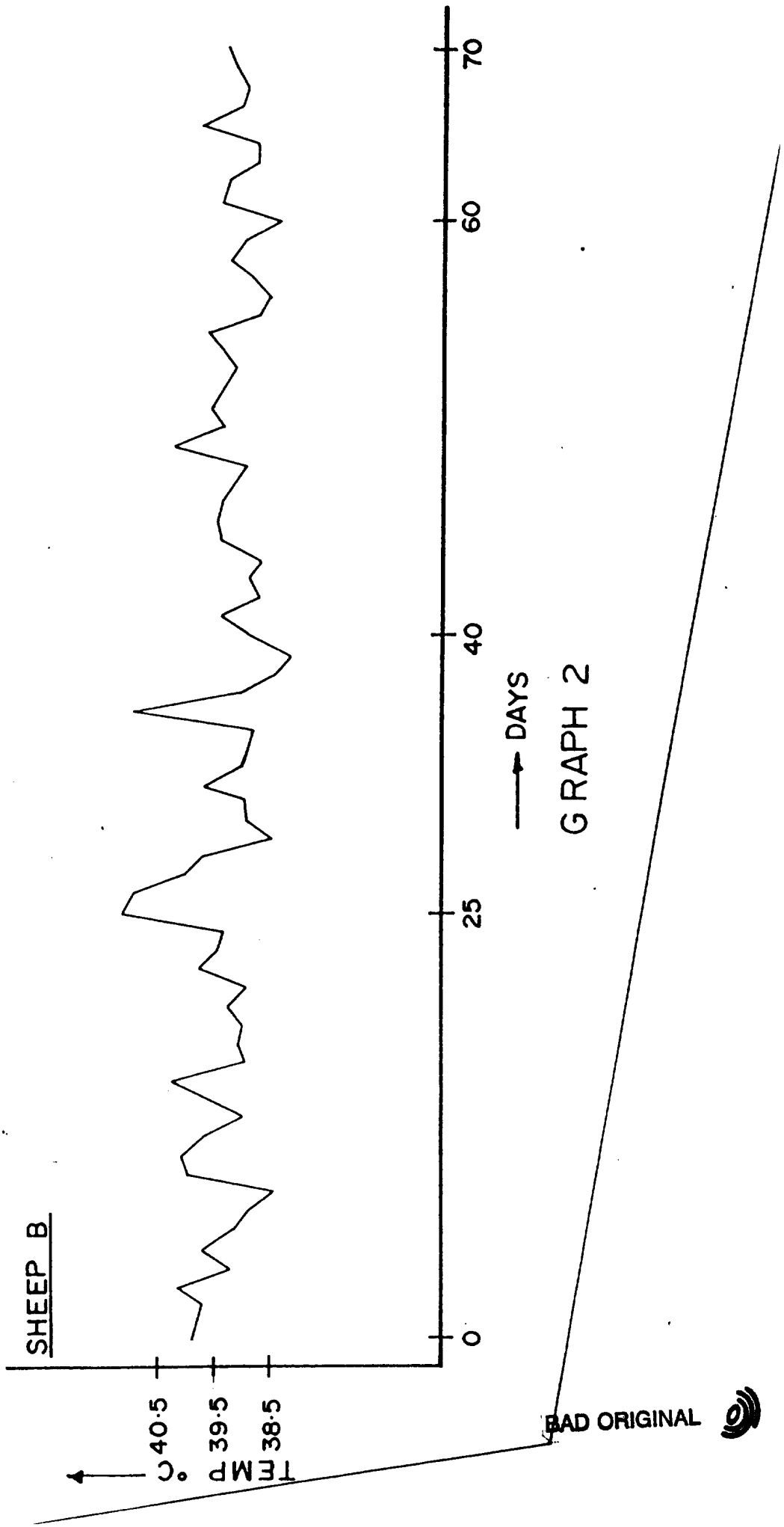
Still further, instead of the controlled release tablets as hereinbefore described, a controlled release gel or paste can be implanted. For example, the gel or paste can then comprise:

(i)	Doxycycline hydrochloride	-	20 mg
(ii)	Magnesium stearate	-	17 mg
(iii)	Polyvinylpyrrolidone	-	15 mg
(iv)	N-methyl-2-pyrollidone	-	35 ml
(v)	Water to render injectable	-	35 ml
(vi)	Na formaldehyde sulphoxalate	-	0,2 mg
(vii)	Ethanolamine	-	to ph 6.6, 5.

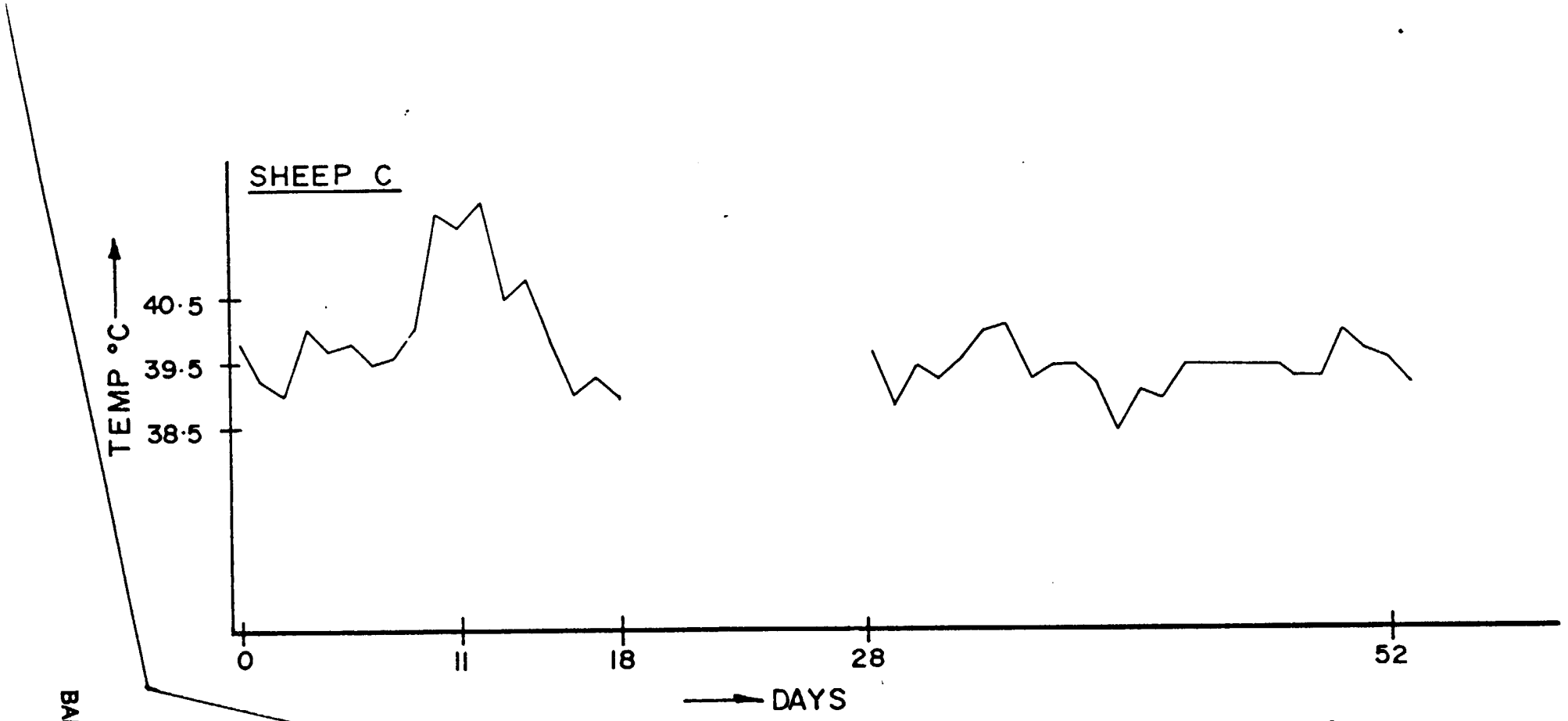
The Applicant also believes that the method and means, ie subcutaneous implantable long-acting tablets and gel as provided by the present invention, provide a quick, easily implementable and effective method and means for prophylactically treating animals for immunity against diseases such as heartwater, anaplasmosis, mastitis and redwater. Hitherto there has been no satisfactory means of building up immunity against these diseases. In addition, by providing the antibiotic in prolonged or slow controlled release form, ie in solid or gel form implanted subcutaneously, the need to treat animals daily while building up immunization, is avoided. This naturally leads to savings in time and labour.



GRAPH I



GRAPH 2



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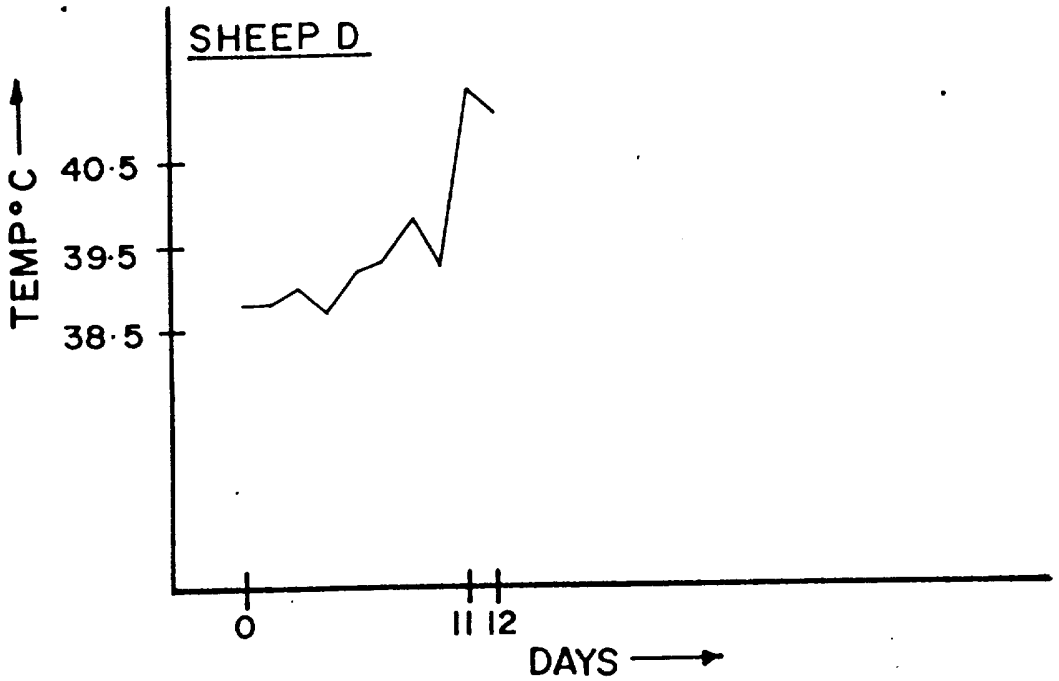

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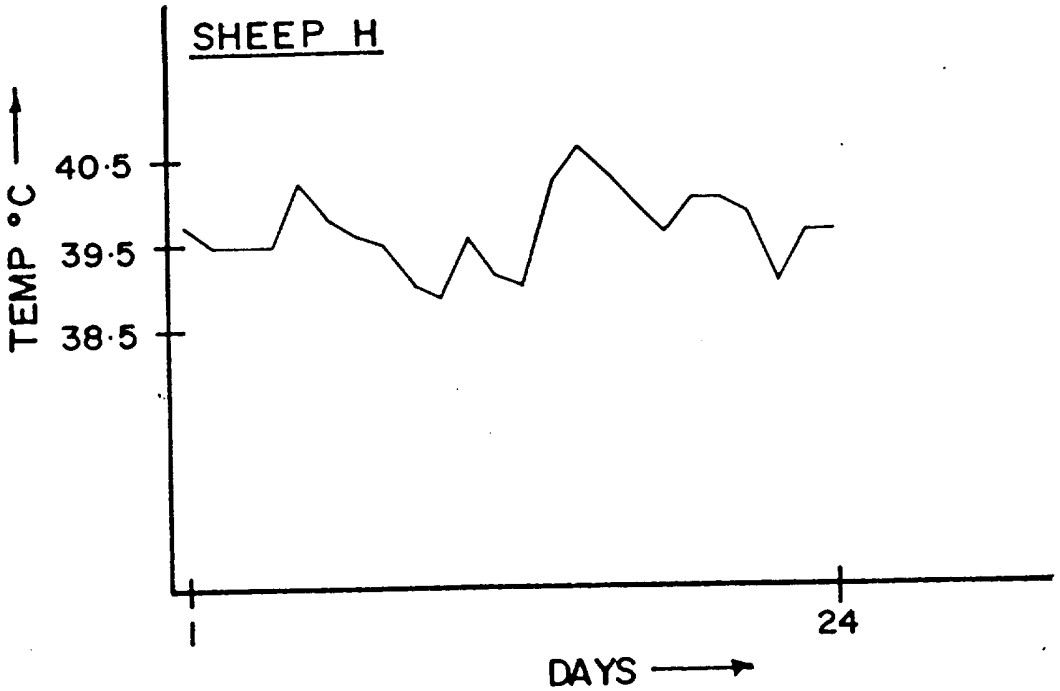

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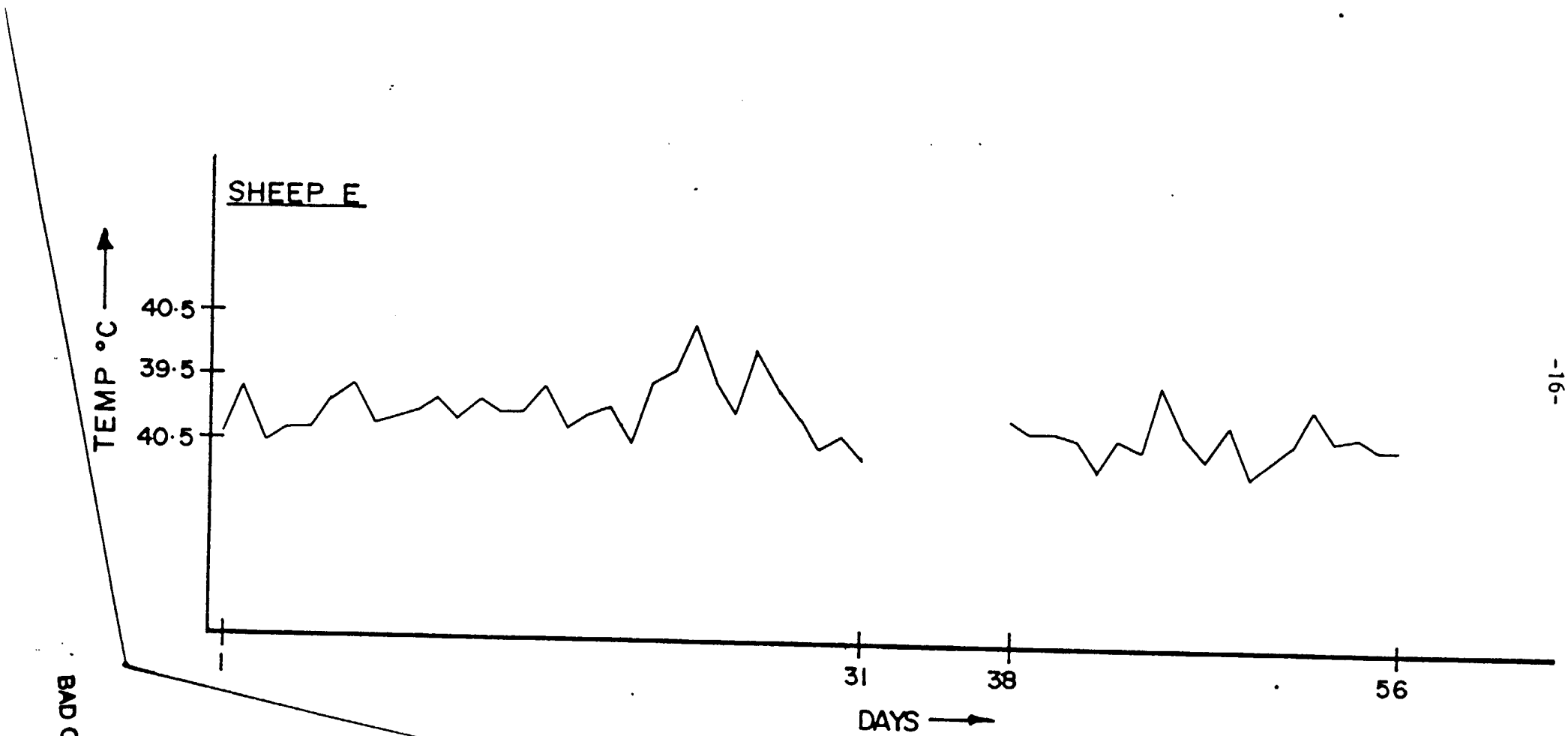
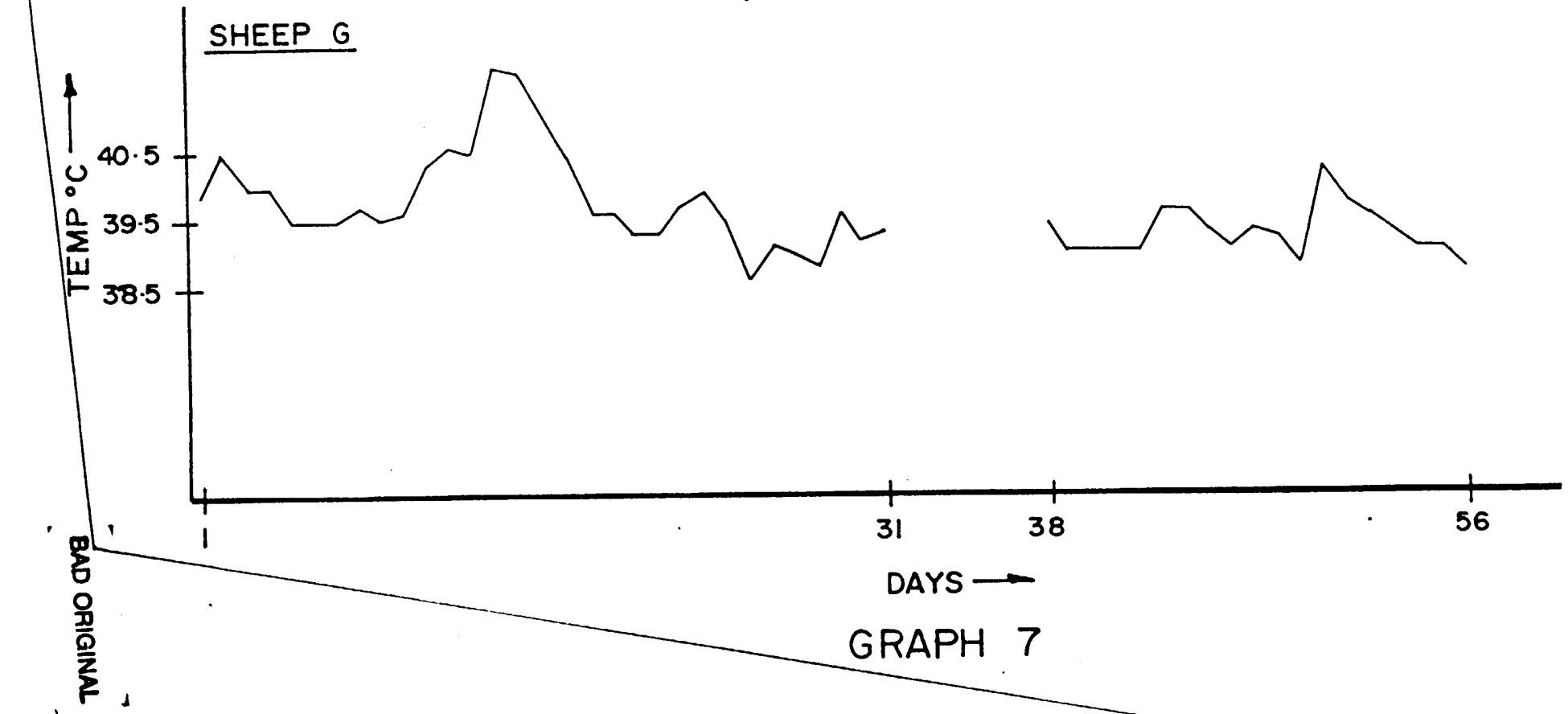


GRAPH 5

GRAPH 6



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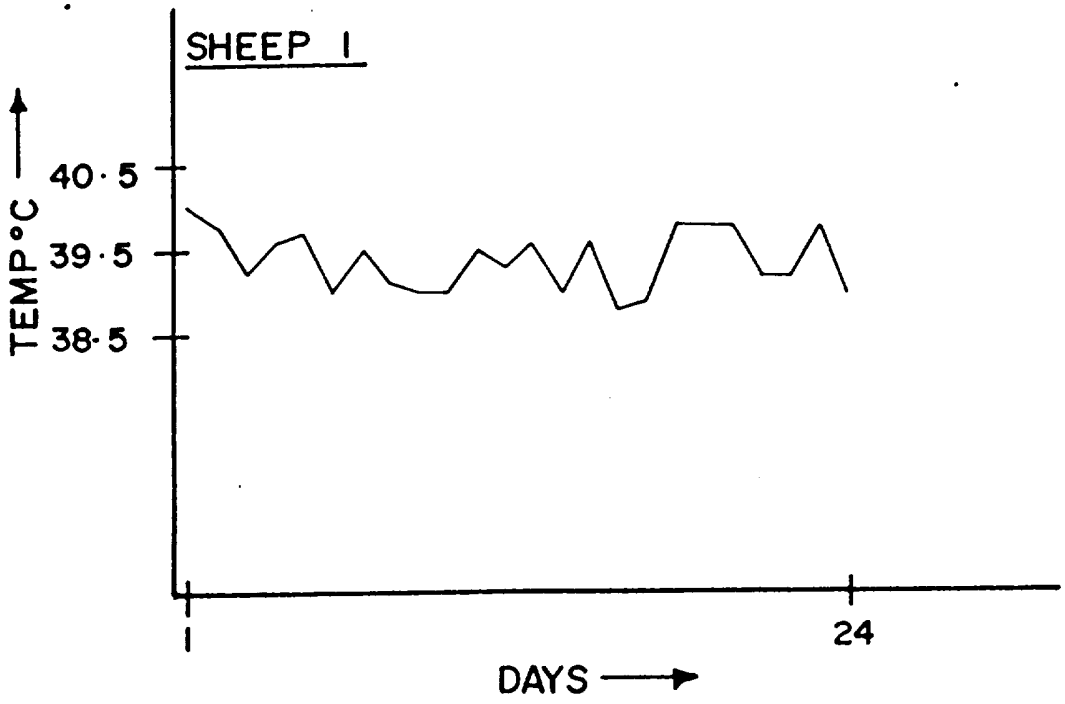
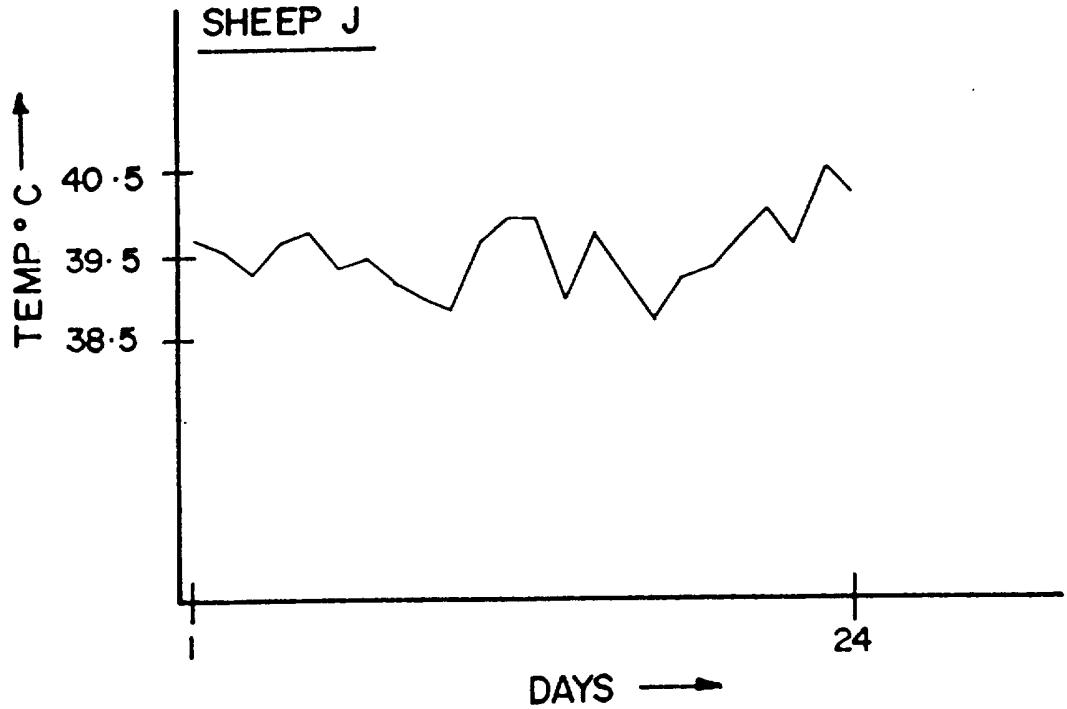


GRAPH 9



GRAPH 10

1. A use of tetracycline or a derivative thereof in the treatment of an animal, which comprises

implanting subcutaneously into the body of an animal a solid implant comprising tetracycline or a derivative thereof;

allowing tetracycline or its derivative to be released into the animal body over a period of time; and

challenging the bloodstream of the animal with virulent Cowdria ruminantium organisms, with the amount of tetracycline or its derivative which is released being sufficiently high to be prophylactically effective, but below a therapeutic dosage so as not to inhibit entirely the natural ability of the animal body to build up immunity against heartwater, so that the animal thereby builds up immunity against heartwater.

2. A use according to Claim 1, wherein a tetracycline derivative is used, the tetracycline derivative being doxycycline hydrochloride, with the period of time being about 25 days, and with the doxycycline hydrochloride being released at a controlled rate of between 0.1 and 2 mg/kg animal body mass per day.

3. A use according to Claim 2, wherein the implant is in tablet form, and also comprises polyvinylpyrrolidone as binder and magnesium stearate as lubricant, with the amount of doxycycline hydrochloride released being between 0.2 and 0.5 mg/kg animal body mass per day.

4. A substance or composition for use in a method of treatment of an animal body by implantation thereof in the animal body, the substance or composition comprising powdered tetracycline or a derivative thereof, as active ingredient; a powdered binder and a powdered lubricant, with the active ingredient, binder and lubricant being in compressed solid unitary form.

5. A substance or composition according to Claim 4, wherein the tablet comprises

doxycycline hydrochloride, as active ingredient	-	75 parts by mass
polyvinylpyrrolidone, as binder	-	3.2 parts by mass
magnesium stearate, as lubricant	-	1 part by mass

6. A method of treating an animal to render it immune against heartwater, which comprises

implanting subcutaneously into the body of an animal a solid implant comprising tetracycline or a derivative thereof;

allowing tetracycline or its derivative to be released into the animal body over a period of time; and

challenging the bloodstream of the animal with virulent Cowdria ruminantium organisms, with the amount of tetracycline or its derivative which is released being sufficiently high to be prophylactically effective, but below a therapeutic dosage so as not to inhibit entirely the natural ability of the animal body to build up immunity against heartwater, so that the animal thereby builds up immunity against heartwater.

7. A method according to Claim 6, wherein a tetracycline derivative is used, the tetracycline derivative being doxycycline hydrochloride, with the period of time being about 25 days, and the amount of doxycycline hydrochloride being released at a controlled rate of between 0.1 and 2 mg/kg animal body mass per day.