CONTROLLED RELEASE IN PRACTICE: A FARMER'S VIEW

A. HEITMAN*

In the Introduction to this Symposium, Keith Ellis refers to the direct release of materials into the rumen, the blood stream and the intestines. It must be kept in mind that farmers will only use instruments that are easy to operate and if they are not easy to operate the jobs will not get done. The reluctance to administer drugs will be even greater when there is some doubt as to the effectiveness of the drug in question. A large number of farmers only vaccinate for pulp kidney when the lambs or sheep are actually dying in the paddocks.

On the subject of instruments for administration, I don't know of anyone who has used an injecting gun all day and not given himself at least one painful jab. I am very keen to see needles eventually given away altogether. I have observed that there are a large number of operators who poke a needle in anywhere they can reach. This leads to carcass wastage and often ineffective drug use. Visit an abattoir and see for yourself the large number of sores and lumps that need to be cut out of a carcass as a result of a needle being incorrectly used. So I must impress on those concerned with research and the manufacture of our new drugs the need to avoid drugs that require injection by needle.

The degree of trauma that a sheep goes through and the production that is lost because of bad and painful handling is difficult to measure. When the Australian Merino Society first began its large-scale artificial insemination programme, we were anxious to do the job quickly and easily. We used a machine for holding ewes which was air-operated and very good at holding the sheep still. Results were from 40-60 per cent lambing, even with the semen placed correctly at the neck of the cervix. Now, several years later, we use a new, simple technique where the ewe stands quietly in a race and is inseminated gently and painlessly. The result has been a 50-70 per cent lambing. I suggest the handling necessary for the administration of drugs by injection is detrimental to animal production.

Let me now turn to instruments used for the oral dosing of bullet-type implants. For these, we need an automatic gun and perhaps shot instead of bullets. The 'gun needs to be able to take at least two shots at a time for multiple doses of different types of active agent. It should be possible to hand-load the gun for two or more shots or to load it automatically for one type of shot. Using an active agent in the form of shot would make loading easier and reduce damage to the gullets of so many sheep, particularly lambs. The damage done to these animals must be tremendous when you consider some of the new selenium bullets with their square ends. I hope to see the day when I can have a bag of shot around my neck attached to an automatic gun and all the sheep with their heads over the pen and the mouths open and 'waiting.

The successful use of the cobalt bullet and the varying success of selenium, copper, and magnesium bullets have been mentioned already. I would like to suggest that zinc and molybdenum bullets should also be tested. Most of these trace elements have long since disappeared from our Western Australian soils and more work should be put into the use of trace elements for maximum production, perhaps administered in a compound implant.

I have often wondered why some sheep do not take to licks and others appear to be gluttons. I am positive that licks are only second choice although a lot

* P.O. Box 82, Mingenew, W.A. 6522.
Animal production in Australia

Easier to use. I prefer to administer the animal's requirements according to my formula and not according to their choice.

Eli Lilly Research Laboratories have developed a commercial implant called "Compudose" which has been used to give increased growth rates in cattle in feedlot situations over 200 to 400 days. Average gains have been 5% in suckling calves, 10% in growing calves, and 17% in finishing cattle. An average improvement in the feed conversion ratio for finishing cattle of 8% has been claimed ("A New Concept for Improving Growth Rate and Feed Efficiency in Beef Cattle" Eli Lilly and Company, Indianapolis, 1979). I hope that we will see this type of product for sale in Australia in the future. For the sheep farmer I can see huge financial returns in wool growth and carcass gains. I foresee a small implant that could be placed in the loose skin on the sheep's neck. This could give us faster growth rates up to lamb marketing of, say, 35 kg and any lambs not finished could still be used for growing wool or sold as hoggets or shippers at a later date.

I am sure that this is a good time for more research into simple, effective, easy-to-administer controlled release systems and this could well lead to a great leap forward in animal production. Farmers will use these devices because they are easy to administer and the sheep may only have to be yarded once a year. The annual dose could well contain all the necessary worm drenches for the year's programme, growth stimulators and, dare we hope, the year's supply of trace elements as well.

THE FUTURE
KEITH J. ELLIS

The intention of this final section of the Symposium is to explore the potential for future research and application, and to discuss some of the implications of the acceptance of the technology. In considering such matters it will be necessary to speculate about many issues. It must be stressed that many of the suggestions are as yet unproven, but an important feature in developing any new technology is the need to seek beyond current thinking.

An important consideration when formulating materials for use with controlled-release technology is the payload, or carrying capacity of the system and this is limited by the practical size of the device. This in turn pre-determines either the maximum amount of "active" which can be released each day, or the effective lifetime of the device. While this will rarely have an effect on the use of devices for the delivery of pharmacological agents, it can severely limit the applicability of the technology for the supply of essential nutrients which may be required in large quantities. However, one should not discard the potential of this technology without first determining experimentally the daily requirements using this regime. Many listings of daily requirements of nutrients refer to the amount which should be supplied in a supplementary feed where the intake is not necessarily continuous. Any single, large dose may pass through the gut in a concentrated slug, and as it passes sites of absorption or action the biochemical processes could become grossly overloaded, resulting in an inability to fully utilize that material. The result then is similar to that observed with nutrients which are considered to have a low "availability", a large proportion of the administered dose is not utilized. With a controlled-release form of administration however, a concentration which is much less than the peak following single dosing can be maintained continuously in the gut, and the absorption mechanisms are much more likely to be capable of handling a high proportion of the material.
Animal production in Australia

Magnesium supplementation to control grass tetany provides an example, whether given in a once-daily drenching programme or by supplementation with hay, the minimum effective prophylactic dose is considered to be in excess of 10 g/d (Allcroft and Burns 1968), but the variable-geometry magnesium capsule appears to be effective at a daily dose of about 2.5 g/d (Laby personal communication). Thus although the technology can have definite payload limitations, these need not necessarily rule out the use of a slow-release device.

Pharmacological agents are generally used in small amounts and are therefore less likely to exceed the payload limitation of a suitable device. In addition, this is the group of "actives" which, along with growth promoting agents, will probably lead to the greatest application of controlled-release technology. Conventional drugs can be administered in a way which mimics existing practice with the sole aim of reducing the frequency of dosing and hence saving time. An obvious example would be to use one of the existing anthelmintics in a capsule prepared in such a way that the dose is given in a pulsed manner at predetermined intervals. This then would constitute an "easy-care" option.

In addition, the same drug could be released continuously, but at a much lower dose level. The consequences cannot be reliably predicted, but it could be speculated that much less drug might be required, tissue levels might be different and unwanted side effects could be lessened. As an example of the latter it is pertinent to consider the influence of controlled-release administration of anthelmintics on the development of drug resistance in parasites. Since it is not known for certain how drug resistance occurs, it is not possible to state categorically what effect the prolonged exposure to low levels of anthelmintics would have on a parasite population; the definitive experiments remain to be performed.

When talking about sustained-release systems the tendency is to think of long term administration i.e. the order of months. However there are numerous examples of short term application, (hours, days or weeks). Hormone sponges for synchronising ewes are a form of sustained-release technology, and it is feasible that procedures currently depending on repeated administration of any drug (e.g. for induction of lactation, or chemical defleecing) will in future be more effectively performed by means of a controlled-release device.

The technology is not necessarily limited to farm management of large numbers of animals. For example, slow-release antibiotic devices are valuable, for veterinary use. Since treatment of bacterial infections can require repeated injections, the application of antibiotics to farm animals is often limited to only the very valuable stock. One can only speculate on the increased number of animals which might be treated if a suitable, yet inexpensive, single-dose product became available.

One future development to which attention must be drawn can be described by the term "Alternative Pharmacology". Almost invariably the screening processes used in the evaluation of new drugs rely on the effectiveness of a single, large dose. Possibly there are many drugs discarded on the basis of this testing procedure, either because they were ineffective or because of the large doses which were indicated. Of these failures, some might have been very successful if administered in a chronic, low intensity (or controlled release) manner. I believe it is high time that scientists and pharmaceutical companies began to look seriously at their screening procedures.

Extension of this thinking can lead to a variety of biological or environmental forms of manipulating animal health and production, some of which might overcome the problems of unwanted side-effects and tissue residues. To use the
example of intestinal parasites once more, one could ask what effects might follow from subtle changes in the pH or in the concentration of chelating agents in the abomasum. Until recently, infusion has been the only method available to the animal scientist of testing such an hypothesis, and although not impossible to perform, this has limited widespread experimentation using continual administration of "actives" to grazing animals. The range of controlled-release devices being developed certainly present scientists with experimental tools with which to test new "actives". No doubt many will be unsuitable, but the successes could be spectacular.

Finally, the implications of this technology to the user must also be considered. Because of the need to administer "things" rather than solutions, there is a need for a different approach to the handling and dosing of animals. Furthermore, one must be sure that every animal is dosed correctly, since one missed dose of a controlled-release device could be equivalent to many omissions of a conventional dosing. While it is a fact that any commercial device will have a very high retention once in the intended site, there will always be a risk of rejection (e.g., regurgitation) during or immediately following the administration. However, the time which will be saved in the long term allows for more care and time to be spent on the initial dosing. To assist with oral dosing of devices to cattle, a good head-restraining device is mandatory, while for sheep, a handling device which elevates the animal would be an advantage. Thus, some modifications to existing animal handling facilities might become necessary.

Most devices can be administered by a single operator. However, the good manager may well use a second person to record the dosing of individual animals because of the potential long-term effectiveness of the devices. Since the costs of any administration will probably be larger than those of any existing dosing, inadvertent multiple-dosing will be economically disadvantageous.

Looking to trends in other areas of farm management, we can see that controlled-release technology is admirably suited to a computer-based management programme. By this means the farmer would know at a glance which stock were not protected against any particular disease or deficiency condition at any time.

CONCLUSIONS

There can be little doubt about the feasibility of making controlled-release devices with practical application to the animal industries. As with any innovation, there have been problems associated with the development of inexpensive and yet reliable devices, but one can confidently predict that none of these problems will be insurmountable provided that the resources of the manufacturing industries can be fully utilized.

Examples of the progress that can be made may be seen in the application of controlled-release devices to medicine. Refillable, mechanical pumps which can be implanted in many different organs (including the brain) are now a reality (Blackshear 1979). The incorporation of analytical components to sense changes in the release rates are now being developed.

I believe controlled-release technology will become an important adjunct to the grazing industries, with advantages arising both from the "easy-care" approach and, perhaps more importantly, from the biological implications and alternative chemotherapy which the technology allows.

However, conservatism and resistance to change could delay the successful, widespread acceptance of the technology. The time is ripe for graziers to demonstrate their interest, for scientists to try out new ideas, and for drug
companies to adopt alternative screening procedures.

REFERENCES


