THE SECOND HAMMOND MEMORIAL LECTURE

**THE RÔLE OF REPRODUCTIVE RESEARCH IN
ANIMAL PRODUCTION***

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In the first Hammond Memorial Lecture, presented by Dr McMeeken, he reviewed the rôle of science in animal industry on a global basis and discussed in general terms its application in the future.

In this second lecture, I would like to deal with some of the more specific fields of research in which Sir John was interested and to attempt to project into the future the potentialities of some of the more recent work.

INCREASED PRODUCTION THROUGH ARTIFICIAL INSEMINATION

Throughout his whole life in research, Sir John's primary interest was in methods of increasing production in domestic animals and it is almost certainly true to say that his intense interest in reproduction and growth was secondary to this aim. It is, therefore, quite understandable that, when asked what he considered the most important way in which he had influenced this objective, he replied, 'by the introduction of artificial insemination'.

It was largely through his influence and that of the late Dr Arthur Walton and of Joseph Edwards that the then Minister of Agriculture—Richard Hudson—was persuaded that this was a method of livestock improvement which would give a rapid return in the form of increased production of both milk and meat, which at that stage of World War II was so vitally important. Although technically a success and increasing in popularity at an almost frightening rate, A.I. proved somewhat of a disappointment in that it did not fulfil the prediction of an immediate increase in production. In fact, the yields of the first 1500 heifers produced by A.I. varied little from those of heifers produced by bulls bought in the local market. The use of A.I. did, however, separate certain bulls of considerable genetic merit from others which were of little value and it merely became a question of devising suitable methods of identifying these differing animals. The programmes of progeny-testing devised by Robertson and Rendel are now too well known to describe here, but the application of these methods and the foresight of the Milk Marketing Board in setting up the Bureaux of Records, which list the breeding potential of all bulls with sufficient daughters on which to make an assessment, have lifted livestock improvement from an art somewhat nebulously attributed to certain breeders with a reputed inherent instinct for selecting the superior sire to that of a much more exact science. With the advent of frozen semen, a very considerable export trade for bull semen is now being built up and this will inevitably grow enormously as the

* Delivered at the Zoological Society of London on 9th December 1970.

more undeveloped countries acquire facilities for semen storage and handling. The value of semen exports is, at the moment, running at about £250,000 per annum and building up rapidly. There is a potential multi-million pound export market for semen but, if we are to exploit this market, much greater drive is required, and, above all, the facilities for testing for transmissible disease which are provided by the Ministry of Agriculture will need to be greatly expanded.

There have been a few changes, however, which are causing some degree of concern. The widespread use of A.I. has greatly accelerated the change from a cattle population of many breeds to one where the Friesian has become the predominant milk breed and the only one in which large numbers of bulls can be progeny-tested. It is inevitable, therefore, that the numerically smaller breeds are at a distinct disadvantage in that they are unable to identify sufficient bulls of genetic merit and are also exposed to a degree of inbreeding which can only become more severe.

The extremely widespread use of individual bulls has caused the Ministry of Agriculture to look more closely at the production of genetically defective progeny. Bulls which produce more than two defective offspring may no longer be licensed for A.I. if the defect is considered to be hereditary. This has raised the problem of the animal which may be extremely valuable from an assessment of his progeny but has produced, say, two or three defective offspring out of several thousand. Added to this problem is the fact that in some cases it is uncertain which progeny defects are definitely of genetic origin. There is an urgent need for breeding experiments to look into many of these borderline factors. The influence of drugs and pesticides which may have teratogenic effects appears also to have been largely overlooked, but this is a very difficult and expensive problem to investigate in the large animal.

It has been estimated that, by the application of systematic progeny testing and widespread use of proven bulls within these schemes, an annual increase in milk production of the order of 1.5% should be achieved. This represents about 12 gallons per lactation per year, an estimate probably on the high side if applied to the country as a whole but, if even half this level was reached, it would represent a national bonus amounting to more than £2 million per annum.

What is more difficult to assess is the genetic merit of bulls used now as against those used in, say, 20 years' time, or, in other words, what genetic progress has been made. Plans are now in hand to investigate this problem. Large stocks of semen from a number of adequately progeny-tested sires will be laid down and every 5 or 10 years sufficient of this semen will be used to obtain a new progeny assessment. In this way, it will be possible to compare a bull's daughters with those of his contemporaries over a period of perhaps 20 years and determine if the degree of genetic improvement, which the bulls showed initially, is repeatable against later contemporaries. Such a scheme may sound simple, but I can assure you that the complications of making such an assessment are considerable.

Because of the long generation interval in cattle, genetic improvement is inevitably slow and any technique which could shorten this interval would

obviously be of great value. It is possible that administration of pituitary hormones before normal puberty may advance spermatogenesis sufficiently to obtain precocious samples of semen for the initiation of a progeny test. It is, in fact, already known that the administration of LH to such immature animals will boost androgen production to adult levels, but these fall equally rapidly on withdrawal of the treatment (Text-fig. 1).

TEXT-FIG. 1. The effect of the injection of LH before normal puberty on fructose and citric acid production in ejaculates obtained from identical twin calves fed on differing planes of nutrition (Davies, Mann & Rowson).

PRENATAL LOSSES

A rather disappointing aspect of A.I. has been the inability of the application of this technique to increase fertility or to reduce prenatal mortality to any great extent. Even with the high rate of fertilization which is known to occur in cattle, the calving rate to a single service is rarely more than 55 to 60%. There is considerable evidence to show that the responsibility for such embryonic mortality lies with the female, but the cause in most cases remains obscure. It is known, for example, in both cattle and sheep, that the transplantation of an embryo which is physiologically 2 or more days out of phase with uterine development will result in a drastic increase in embryo mortality, but what causes such losses is still not clear. Recent experiments on egg transfer carried out under conditions where the corpus luteum would normally be maintained beyond the usual cycle length, indicate that failure of pregnancy in such cases is not due to the inability of a living but out-of-phase embryo to maintain the corpus luteum as one of pregnancy. This would suggest changing embryonic requirements within the uterus during the early stages of pregnancy and this is a factor which certainly warrants investigation. It is, however, quite evident that some bulls are more fertile than others but, at the moment, there is no method of

assessing this potential fertility other than by trial and error. When within normal limits, semen quality and activity is little guide and the technique of heterospermic insemination devised by Beatty and his colleagues is too difficult to apply as routine practice.

There is a considerable body of evidence that, in the human, genetic defects in the developing embryo are involved in early abortion and such defects may equally well occur in the domestic animals as has been suggested by Bishop and his colleagues. It is known, however, that in most domestic species, the loss of the embryo occurs very early in gestation and the influence of any genetic defect, if present, must, therefore, apply largely during the first week or so of pregnancy. The position is, in fact, a little confusing for, if one recovers eggs from the uteri of donor cattle and transfers these to synchronized recipients, a pregnancy rate far above what is considered normal has, so far, been obtained. It could be argued, therefore, that this high conception rate is due to the elimination of fertilization failures, plus possible genetic defects, but it is known that, in normal circumstances, fertilization failure is low and if genetic defects are largely responsible then these would have to occur and be recognizable as abnormal eggs by the time the eight-to thirty-two-cell stage was reached, since most of these transfers were carried out at this stage of development.

Hammond frequently referred to the 'balance of hormones' being involved in infertility and it is, in fact, well known that the movement of the egg through the oviduct can be profoundly influenced by hormones with a consequent effect on fertility and this is of particular importance to scientists interested in human population control.

In this respect, a rather peculiar phenomenon is seen in the mare, where only the fertilized eggs appear to be transported through the oviduct, the unfertilized ones accumulating in its lumen throughout the breeding season. It would appear possible that, once fertilized, the surface of the egg of this species undergoes some form of physical change, rendering it more receptive to the action of tubal cilia (Plate 1).

Relatively recently, it has been shown that binding of protein to steroids can be of great value, not only in the assay of steroid levels in body fluids but also in the production of antibodies to such steroids. It should, thus, become possible to neutralize the influence of some of the natural steroids produced by the body at certain stages of the cycle and to study the effect of this treatment on egg movement and fertility. In addition, the application of more sensitive methods of steroid and gonadotrophin assays which are now being employed allows the research worker to detect varying and minute levels in peripheral blood rather than that draining the organ in question. While the scientist can readily pinpoint conditions which will certainly produce infertility if varied from normal, an understanding of the relationship of these conditions to farm practice is largely lacking. Experiments to study infertility in large animals by deliberately introducing certain conditions such as those carried out by Hignett and his colleagues on the influence of mineral intake are extremely expensive to conduct and, for this reason, research in this field has been very much neglected. This is unfortunate if one considers the annual losses in cattle, due to infertility alone, which were estimated at £7 million per annum by the National Veterinary

Medical Association as far back as 1940. The relationship of nutrition to fertility is, in fact, not at all clear except under extreme conditions. It is, however, quite certain that a reduced food intake is reflected by a lowered response to injected hormones. In order to investigate these factors more broadly, it has been suggested that what is termed a 'metabolic profile' of the herd should be obtained covering a larger range of factors and, in fact, studies of this nature in both fertile and infertile herds are in progress.

If one takes a broad look at the picture, any increase in production due to decreasing prenatal loss must inevitably be small and the gain be slow in materialization. On the other hand, any increase in the number of offspring per animal could, under certain conditions, provide an immediate and extremely valuable contribution to increased production. I think one must consider, therefore, whether we have got our priorities right. Should we not be turning more attention to factors involved in a direct increase in production rather than those associated with prenatal loss, where the dividends, judging by the past 20 years of research, are likely to be minimal? It is something of a biological enigma that the cow, which normally has a single calf, is provided by nature with four teats and by man with a milk-producing capacity sufficient to rear three or four offspring, while the sheep, which in many breeds is quite capable of producing three lambs, is only equipped with two teats and often has an inadequate milk supply. Artificial rearing, which is now highly successful, has largely solved the problem of additional offspring, but the main one of increased prolificacy still remains. The use of gonadotrophins is unreliable due to variation in response and—as will be discussed later—a number of other factors, while the heritability of twinning is considered to be extremely low, although a multiplicity of factors could be involved here. Twinning is not, for example, simply a case of breeding for two ovulations; uterine limitations are also clearly involved. It would be of interest to know if these uterine limitations are largely imposed by caruncle numbers and whether it would be possible to select on this basis. Such an approach was impossible until the egg-transfer technique was developed because, in order to establish the number of caruncles, it is first necessary to slaughter the animal. The recovery of eggs before slaughter and their transfer, if a satisfactory caruncle count was determined, could overcome this problem. So far as I am aware, however, little is known of the variability of such counts and knowledge of their heritability does not exist. The importance of this factor will become clearer in the later part of this lecture.

Differing priorities obviously also apply to differing parts of the world and this very point was made by Dr McMeeken last year, when he pointed out that even a small sum of money spent on fencing may, in certain countries, show a greater return in production than vast sums spent on sophisticated research in others.

I think that physiologists often tend to overlook the tremendous contribution to production made by the veterinary profession in the elimination or reduction of disease, particularly tuberculosis and *Brucella* infections. Tubercular peritonitis with blockage of the oviducts, for example, was a not uncommon finding 25 years ago. Trichomoniasis, vibriosis and other venereal diseases have been

almost eliminated. By implementing the recommendations of the Northumberland Report on Foot and Mouth Disease, the risk of spread of this disease by semen will also be eliminated, since only frozen and quarantined semen will be used after December 1971.

EGG TRANSFER

It is hardly surprising that, along with his great interest in using A.I. as a method of genetic improvement through the male, Hammond should have been intensely interested in exploiting the genetically valuable female by egg transfer. It is obvious that there are much greater limitations on the application of this technique to widespread livestock improvement but, nevertheless, it could play an important rôle, particularly in beef production. Much of the work carried out in this field has, so far, been confined to investigations of methods of obtaining optimum pregnancy rates and on the use of the technique as a tool for research into the physiology of reproduction. There have, however, been a few cases of its practical utilization for special purposes, one of the most notable being in Australia where Moore & Shelton rapidly multiplied a group of thirty-seven polled Merino ewes by transferring their eggs to uterine foster mothers to produce 172 lambs, following a single gonadotrophin treatment.

From a fundamental point of view, it has been shown that, in sheep and cattle, pregnancy rates at least equal to those of normal mating can be achieved providing certain quite simple criteria are met. The factors governing success vary with the species but generally involve the use of suitable flushing media, varying methods and stages of egg recovery and, above all, the transfer of eggs to recipients which are relatively closely synchronized so far as the stage of the cycle is concerned with those of the donor animals. Variations from exact synchronization of ± 2 days can be tolerated in some species, but beyond this, few pregnancies occur. This is a point to be considered in prenatal mortality for if, under certain conditions of feeding and management, a state of asynchrony exists between the physiological development of uterus and embryo then, despite the presence of a perfectly normal conceptus, the pregnancy will not continue. There is some preliminary evidence that the necessity for synchronization of the cycles of donor and recipient is more acute in the cow than in the sheep and one cannot help but wonder whether this is related to the natural fertility of these species. It would appear from data so far available that a variation of ± 1 day can influence pregnancy rates following egg transfer in the cow, whereas it requires a variation of ± 2 days to produce a similar effect in the sheep. If this is related to the natural pregnancy rate of 55 to 60% for the cow and 75 to 80% for the sheep, pregnant to a single service, it is probable that any factor which causes the embryo and uterus to become out of phase in physiological development would be reflected more severely in the cow with its more exact synchronization requirements than in the sheep (Text-fig. 2).

STORAGE OF EGGS

The storage of eggs before transfer is an obvious requirement and has been

investigated by various workers. Successful transfers have been carried out in sheep after 72-hr storage *in vitro* although the percentage of success was not high.

Some 12 years ago, it was also shown that the sheep egg would continue development if transferred to the oviduct of rabbits and this permitted the successful export of eggs to South Africa and Japan.

Recently, Lawson has investigated this aspect of storage more thoroughly by leaving sheep eggs in the rabbit oviduct for periods of 3, 5 or 7 days and then testing their viability by re-transfer to recipient sheep. These investigations have shown that excellent results can be achieved after 3 days' storage, but that results decline from 5 days onwards. Although foetal membranes frequently develop normally, in the case of the eggs stored in the rabbit for the more

TEXT-FIG. 2. The effect of the degree of synchronization on pregnancy rates obtained in cattle (---) and sheep (—). Synchronization requirements appear from evidence so far to be more acute in the cow than in the sheep. The figures against the symbols are of the number of animals.

prolonged period and then re-transferred to sheep, the embryo often dies and the membranes eventually resorb, resulting in a return to oestrus after 30 to 50 days. The satisfactory storage rate of 3 to 4 days does mean, however, that the technique could be used for the export of sheep eggs to almost anywhere in the world for very little cost.

Similar experiments are in progress with cow eggs and these appear to survive equally well within the rabbit oviduct and continue development on re-transfer to the recipient cow. One aspect to consider in inter-species storage of eggs is that the temporary recipient may well be immune to certain diseases and it is possible that natural antibodies present might destroy infective bacteria or virus carried on the stored egg. The rabbit, for example, is naturally immune to foot and mouth disease, but would the natural antibodies destroy the virus on eggs taken from infected cattle? Nobody knows, but this should be investigated.

Recently, the successful inter-continental shipment of pig eggs has been

achieved following *in vitro* storage. A new export field is, therefore, being opened up.

EGG TRANSFER AND RESEARCH

Egg transfer has provided an extremely valuable tool for research. By its use, it has been possible to demonstrate a clear-cut unilateral utero-ovarian-embryo relationship in cattle, sheep and pigs. It has been widely used in investigations on the mechanism of action of the luteolytic factor in these species and, more recently, has been extensively used to investigate the ability of the uterus to carry additional young.

It can be demonstrated that, if an embryo is transferred to one uterine horn of the sheep or cow and confined within that horn, the animal having a corpus luteum in each ovary, then the corpus luteum on the pregnant side will be maintained as that of pregnancy and the other regress in the normal cyclical manner. That this is a local luteolytic action can be demonstrated by removal of the uterine horn on the non-pregnant side, when the corpus luteum on that side will then persist. Extension of this work has shown that the uterus in these species probably acts in two ways: (1) a short-term effect which depends on the anatomical relationship between the uterus and the ovary containing the corpus luteum and (2) a general and more long-term effect which can be demonstrated by transplanting the endometrium to other sites in the body, usually resulting in extended cycles. It has been established in the sheep that the embryo acts in an anti-luteolytic manner preventing the luteolytic effect of the non-pregnant endometrium acting on the corpus luteum. Very recent research has suggested that there may be minute unilateral connections between the uterine vein and ovarian artery enabling blood draining the non-pregnant horn to pass into the artery to be carried directly to the corpus luteum. The uterine vein is abundantly equipped with valves and differences in pressure between vein and artery might well be overcome because of their effect.

Unilateral effects also occur in the male and Mann and his colleagues have been using the unilateral injection of androgens into one seminal vesicle or vas deferens as a measure of potency based on chemical assay of the injected gland and using the gland on the other side as a control (Plate 2).

Ten-fold differences in the fructose content, which is an androgen indicator, have been demonstrated between the injected and non-injected sides.

PRODUCTION OF TWINS BY EGG TRANSFER

In the cow, progress in the development of egg transfer has been slow until a few years ago when it was discovered that the synthetic medium 199 proved excellent for the storage and transfer of eggs in this species. It seemed obvious, therefore, that Hammond's dream of the transfer of pure beef eggs to the poorer yielding dairy cow to increase meat production should be carried a stage further in an attempt to induce twinning by the transfer of two eggs to suitable recipients. The initial work on this was disappointing in that only 12.5% of animals receiving two eggs produced twins. In all these cases, however, both

PLATE 1

(A) Fertilized sheep egg and (B) anion exchange resin sphere of similar size and density. Passage of egg through oviduct normal, but spheres frequently remain within lumen.
(C) Scanning electron microscope photograph of a recently fertilized rabbit egg. $\times 8500$.
Note irregular surface giving grip to cilia. (By courtesy of Dr H. Dott.)

(Facing p. 120)

PLATE 2

Seminal vesicles and ampullae of calf showing hypertrophy of one side following unilateral injection of androgen.

(A) Unilateral and (B) bilateral twin calves obtained following the unilateral or bilateral transfer of two eggs. In the case of unilateral twins, only the tail of the membranes usually extends into the contralateral horn.

PLATE 4

(A) Damaged zona following removal of blastomeres (B). (C) A 7-day blastocyst in which the zona was damaged by injection of blastomeres at the eight-cell stage and the zona sealed with mucin following transfer to the oviduct of a pseudopregnant rabbit.

(Facing p. 121)

eggs were transferred to one uterine horn and it was discovered in subsequent experiments that the cow egg, in these circumstances, does not normally migrate and that both embryos were implanting in a single uterine horn with consequent competition for nutrients and resultant embryonic loss.

A comparison of the number of cotyledons which develops in animals with two embryos implanted on one side, as against one in each uterine horn, showed that many more attachments occurred in bilateral pregnancies with consequent effect on prenatal nutrition. By the transfer of a single egg to each uterine horn, it has now been shown that a twinning rate of 73% can be obtained (Plate 3). The impact of such results if translated into beef production in this country is obvious.

PRODUCTION OF CHIMERAS

The production of twins in cattle has interesting scientific implications in that, in about 95% of cases, the foetal membranes fuse and there is an interchange of blood-producing and other types of cell between embryos with resulting chimerism. Differing breed chimeras are, therefore, now being produced by the transfer of an egg of one breed to one horn of the uterus and of another breed to the other.

It will be of interest, where these breeds differ widely in production and carcass quality, to see if there is any influence of the occurrence of both blood types in each twin. Moreover, as chimeras are tissue-tolerant, it should be possible to investigate milk production at the cellular level by the reciprocal interchange of half the mammary gland, leaving the normal half to provide a perfect control, the blood supply to both being constant.

The results of attempting to produce differing breed twins by egg transfer to an already pregnant animal have, so far, proved of fundamental interest, in that it would appear that there may possibly be some physiological or immunological influence within the uterus resulting in the loss of either the natural or transferred egg in more cases than one would normally expect. Work in sheep, where eggs of a different breed were transferred to an already pregnant uterus, have shown a similar tendency. If this does prove to be the case, it would complicate the production of twins in cattle through the A.I. centres, where it has been hoped to transfer a second egg to the contralateral horn of an animal already inseminated and made pregnant in the normal manner.

PRACTICAL APPLICATION OF EGG TRANSFER

For any field-scale application of egg transfer, large supplies of fertilized eggs will be needed and the present system of recovery from the uteri of gonadotrophin-stimulated donors will be inadequate. It is highly likely that the solution to this problem in future years will lie in the fertilization *in vitro* and culture of follicular eggs harvested from slaughtered animals. The development of this technique will involve methods of capacitating spermatozoa so that they are readily available for fertilization. It is not established with absolute certainty that capacitation is necessary in the bovine, but experiments with tetracycline-

labelled spermatozoa would suggest that it is. While it would be possible to capacitate within the animal and then to remove and freeze the capacitated spermatozoa, the recovery rate would be low and evidence would be required that freezing and thawing did not affect capacitation. Alternatively, it might be possible to capacitate *in vitro* as has been done with other species. Active research is also being pursued in investigations into lysosomal enzymes and their relationship to capacitation and this line of investigation could prove invaluable to fertilization *in vitro*. There will still remain the formidable problem of storage of fertilized eggs until they are required for use. In addition, the present non-surgical techniques require improvement so that a pregnancy rate equal to that obtained surgically can be achieved.

As stated earlier, the most obvious way to apply the technique in practice, once the problems mentioned have been overcome, would be through the A.I. centres. For example, where dairy cows had been inseminated with semen from a beef bull, it should be relatively easy to deposit a fertilized beef egg in the opposite uterine horn to that in which the normally ovulated egg was developing and, thus, obtain a high proportion of twins. It is quite a simple matter to detect on which side the natural ovulation has occurred by examining the ovaries for the developing corpus luteum, which at the appropriate time of transfer, i.e. 4 to 5 days, would be quite pronounced.

Exploitation of the genetic material of individual animals would probably be best obtained by orthotopic grafting. In order to achieve success by this technique, the homograft reaction has to be overcome, but with the intense research now being conducted in the human field in order to solve the problem of organ grafting, a solution will inevitably be found. It should then be a relatively simple matter to destroy the potential eggs within the ovaries of recipient animals by X-irradiation and to graft pieces of ovarian tissue from genetically valuable donors. Such a technique has the advantage that it would be a 'once-for-all' operation and, so long as oocytes were available within the grafted ovaries, the grafted recipient would continue to produce the offspring of the donor animal. Successes along these lines have already been achieved in small mammals in Professor Parkes' previous laboratories at Mill Hill.

SIZE AND PRODUCTION

In all attempts to correlate phenotype with milk production, only one factor appears to be consistently related, this being the size of the animal. If one relates this fact to Hammond's findings that the size of the placenta controls the size of the offspring, it would be of interest to develop the embryos of some of the smaller breeds, such as the Jersey, in the uteri of a large breed, such as the Friesian, both to look at the development of the offspring and to see whether, in fact, production is affected.

The influence of placental development on size and the possibilities of using egg transfer to exploit this has not gone unobserved by horse breeders, but one can imagine the reaction of the Jockey Club to anyone trying to register a thoroughbred out of a shire, despite the evidence of its true identity by blood typing.

To digress for a moment; it has always puzzled me, in view of the evidence of increased carcass weight obtained by the use of injected or implanted oestrogens, why pastoralists have not looked into the question of a possible anabolic effect of phyto-oestrogens in beef-producing pastures. The objections, which are held to the administration of synthetic oestrogens into beef animals, are unlikely to be sustained if they were introduced by the grazing of oestrogenic pastures. I realize that there are difficulties in such a suggestion since some plants only contain oestrogens for relatively short periods of time and the anabolic effects of level of intake are largely unknown, but it is a point surely worth investigating.

A striking discovery has recently been reported by Steelman and his colleagues, who discovered that a substance produced by the intermediate stage of an unusual type of tapeworm had anabolic effects similar to those of growth hormone. The increase in weight of small mammals, which resulted from treatment, was largely due to protein and if similar effects are found in the domestic animals, the production potential of this substance would appear to be enormous.

UTERINE CAPACITY

There is little point in using gonadotrophins in attempts to increase production unless one knows what the uterine limitations are and the composition of these limitations. Egg transfer, as mentioned earlier, has, therefore, been used to measure the ability of the sheep uterus to carry multiple offspring by the transfer of above-normal numbers of eggs (five) from a common genetic source to the uteri of various breeds of sheep. The normal potential fertility of each ewe was determined by counting ovulations on the ovaries at the time of transfer of the eggs. The results indicated that Finnish and Suffolk sheep are already producing at close to their uterine capacity but, most important, that the Romney Marsh is capable of carrying about double its normal potential lamb crop. Selection for ovulation in this breed is, therefore, obviously vitally important and this work will, no doubt, be noted in New Zealand where the predominant sheep is the Romney Marsh and where the lamb crop is low. It would also appear that this breed may be extremely suitable for stimulation by low doses of gonadotrophin.

Three other aspects of egg transfer research and their possible influence on production are probably worthy of brief mention.

Production of identical twins

Theoretically, the removal of one blastomere from a two-cell egg and its introduction into a new zona, followed by the transfer of both eggs, could result in the production of identical twins which are invaluable for experimental studies. Experiments in the rabbit have shown that the transfer of eggs up to the eight-cell stage, where all but one cell has been removed, can result in pregnancy and normal young, but, so far, the transfer of eggs where a blastomere has been placed in a new zona has failed. It is believed that, with better methods of manipulation of the single blastomere during transfer to a fresh zona, successes

may well be achieved. If, however, as suggested by some, the zona acts as a barrier until sialo mucins are deposited around the developing cells, then some physiological plumbing may be necessary by coating the pierced zona with mucins through temporary transfer to the rabbit oviduct (Plate 4).

Sex selection

The sexing of embryos by identification of sex chromatin is relatively simple in the rabbit but, because of the granular nature of the nucleus of the cells of the embryos of domestic animals, it is necessary in these species to revert to an examination of the karyotype. Although this is possible by removal of a few cells from the conceptus before transfer and identification of the sex chromosome, it is a rather tedious process with somewhat limited practical implications. A more convenient method of obtaining the same result would obviously be sex determination by the separation of the X- and Y-bearing spermatozoa, but all attempts at this have failed and the theoretical concept on which such efforts at separation have been made is highly suspect. To expect the difference in mass between the X and Y chromosomes to be greater than individual differences in the mass of the cells themselves is stretching the imagination to an impossible degree, nor would there appear to be any sound evidence that the electrical charge on X- or Y-bearing spermatozoa should be different. The recent claim that X-bearing spermatozoa tend to agglutinate more readily and, therefore, sediment more rapidly requires further investigation.

The production of mosaics

Attempts are, at present, being made to produce mosaics by the injection of adult, foetal and embryonic cells into developing eggs and blastocysts. The feasibility of such a technique has already been demonstrated by Gardner. The technique of injecting such cells into the blastocyst and egg of some domestic species is relatively simple and the blastocyst at this stage is considered quite incapable of an immune response.

There are many unanswered questions in this work. Will adult cells become de-differentiated and incorporate in the developing embryo? Will it be necessary to use cells obtained from a blastocyst or embryonic disc of a similar stage of development? Most important, but most unlikely, will cells from one species incorporate into embryos of another and will tissue tolerance be established between the cell donor and the offspring resulting from the transfer of such injected blastocysts to suitable recipients? From a practical point of view, what will be the quality and quantity of milk produced from an udder consisting of a mosaic of cells?

These experiments sound rather theoretical and unlikely to succeed, but no more so than those of Gurdon who showed that the transplanted nucleus of a fully differentiated cell of the intestine of the frog was capable of acting as a blueprint for the normal development of the egg of this species. Nor should one dismiss completely the possibility of what is sometimes termed 'genetic engineering' being used as a method of increasing animal production. Fifty years ago, even A.I. was looked upon by many with repugnance yet to-day it is accepted as routine practice. In another 50 years, it is quite possible that the

introduction of chromosomes into the egg may be received with equal equanimity.

EXPANDING PRODUCTION

The rapidly increasing population of most European countries and expansion of housing programmes will inevitably mean that more food has to be produced from fewer acres of land. At the present time, we, in Britain, are losing some 55,000 acres of agricultural land per annum. This, together with economic pressures, is inevitably going to result in an increase in so-called factory farming. Under this system, groups of animals all of an approximately equal age are required at varying periods of the year. Individual suppliers are, therefore, going to become more and more interested in producing stock in batches. In order to do this, it becomes necessary to synchronize matings by the use of progestagens or other suitable agents.

The technique of batch farrowing following the use of methallibure in the pig is now a routine procedure and its effectiveness is partly due to the fact that, being a non-progestagen, the sow is fertile at the withdrawal oestrus. Unfortunately, this does not appear to be a suitable agent for ruminants. The use of progestagens in ruminants, while giving reasonably effective synchronization at the withdrawal oestrus, appears to reduce fertility sharply, unless the animals are left until the second cycle thus losing time and, by this stage, some degree of scatter of oestrus has occurred. There is a great need for the development of a non-progestational synchronizing agent similar to methallibure, but which is effective in other domestic animals. This, in itself, raises a problem in the sheep, where it is well established that the first ovulation following seasonal anoestrus occurs without the ewe exhibiting oestrous behaviour. It appears that a falling progesterone level followed by the normal FSH oestrogen and LH pattern is required for normal oestrus and it is, therefore, doubtful if a non-progestational agent alone would fulfill these requirements in this particular species. There is also a certain element of danger in the use of such drugs, since it has been shown that some fed to an animal in the early stages of pregnancy, can induce teratogenic effects. King, for example, has shown that the accidental feeding of methallibure to pigs during certain stages of pregnancy can produce drastic abnormalities. If one relates this finding to the Ministry of Agriculture's policy of rejecting A.I. bulls which produce more than two defective offspring out of many thousands, the importance of greater knowledge of the effect of drugs is obviously vital. Experience in other fields has already exposed the danger of widespread use of chemical agents and care will have to be taken before new drugs can be generally accepted.

In his address to the British Association in 1953, Sir John remarked "while pure science goes very deeply into a very limited problem—so that the definition of a scientist has become one who knows more and more about less and less, the function of an applied science is to synthesize this detailed knowledge into a constructive whole, so that it can be used for a specific purpose". If this were true in 1953, it is even more true to-day, when, owing to the extremely rapid accumulation of knowledge, fields of research by individual workers have, of necessity, become narrower. It inevitably follows that the translation of present-

day fundamental research into practical productivity has become very much more difficult and scientists have occasionally come in for some criticism for what some people regard as pursuing a too fundamental line of research. It is, however, quite impossible to predict whether a fundamental line of research may or may not reveal knowledge likely to be of great practical value, but such a philosophy is often difficult to put over to the farmer. This was a facet of Sir John's character where he was particularly brilliant and those of us who had the privilege of working with him have always tried to relate a fundamental approach to a practical outcome.