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THE PROGRESS OF ENDOCRINOLOGY WITH SPECIAL REFERENCE TO ANIMAL PRODUCTION

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ENDOCRINOLOGY is one of the youngest branches of science and one in which knowledge is expanding at a phenomenal rate. It is concerned with all matters pertaining to the hormones—entities which Selye defines as "physiologic organic compounds produced by certain cells for the sole purpose of directing the activities of distant parts of the same organism." The endocrine system, jointly with the nervous system, is responsible for regulating and co-ordinating important body activities. It is concerned in growth, reproduction, lactation and in the maintenance of a steady internal equilibrium in metabolism, all of major interest to students of animal production. It seems pertinent, therefore, to enquire as to the progress of endocrinology and the significance and application of this increasing knowledge to animal production.

A general investigational pattern can be detected in the past study of most endocrine organs. The organ is removed and deficiency symptoms observed, or possibly deficiency symptoms are in some way connected with hypofunction of the organ. Extracts of the gland are prepared and their effects on test animals observed. Replacement therapy is tested. Purification of the glandular extracts is attempted with its main objective the isolation of the hormone and the study of its chemical and biological characteristics. Synthesis of the hormone closes one chapter of the study. Let us trace this pattern in a specific case—that of the thyroid gland. Symptoms of hypothyroidism—cretinism and myxoedema have been recognised for hundreds of years, but were only connected with thyroid deficiency in the second half of the 19th century. In 1891 an English Physician, Murray, showed that the administration of thyroid to a myxoedematous patient brought about a marked improvement in health. About the same time it was found that the feeding of thyroid would raise the low basal metabolism characteristic of hypothyroid conditions. In 1919 Kendall reported the preparation from thyroid tissue of a highly active crystalline compound which he called "Thyroxine." Extensive study of the hormone has shown that it is essential for normal growth and development, and regulates the general rate of metabolism through its influence on tissue oxidation. Finally Harrington and his co-workers determined the true structure of thyroxine and synthesised it. This hormone proved to be an amino acid (tetraiodothyronine).

Before we consider the application of endocrine knowledge to animal production let us first see to what stage knowledge concerning other endocrine glands has been brought by this almost classical pattern of investigation.

The hormone of the adrenal medulla—adrenaline was the first to be isolated in crystalline form. This was in 1901 and four years later adrenaline was synthesised. Its powers of inducing the mobilization of sugar through glycogenolysis, stimulating smooth muscle contractions and increasing blood pressure are too well known to need elaboration. Of different origin from the medulla and functionally independent of it, the adrenal cortex produces steroid hormones. These assist in the regulation of carbohydrate metabolism through influencing the rate of the conversion of non-sugars to carbohydrates and control the elimination or retention of potassium, sodium and water in the tissues. Several sterols have been isolated from the adrenals—some (e.g. corticosterone) predominantly affecting carbohydrate metabolism and others chiefly mineral metabolism. An increasing number of these naturally occuring cortex hormones are being synthesised, but much work has yet to be done in this field.

Both male and female gonads also have been found to be steroid-producing endocrines. The male sex hormone, produced by the interstitial cells of the testes has been isolated, named testosterone, and synthesised. It stimulates the development of male characteristics and maintains the accessory sex organs.

In the female the ovary produces at least two hormones. One, responsible for the development of female characteristics and accessory sex organs, ''heat''-inducing, influencing the growth of the mammary glands, and probably having a major, if indirect, role in the initiation of milk secretion is believed on good evidence to be the sterol estradiol which has been isolated from the ovary and synthesised. The other, progesterone, isolated from corpora lutea, has likewise been synthesised. It has the properties of further stimulating the development of the uterus and mammary glands and is necessary for maintaining pregnancy.

The pancreas, parathyroids and pituitary produce hormones that are proteins or protein-like in nature.

In 1889 Mering and Minkowski demonstrated experimentally the relationship between hypo-pancreatic conditions and diabetes, but it was not until 1921 that Banting and Best showed that the injection of an extract of the pancreas lowered blood sugar in depancreatized dogs. Since then the hormone, a protein, has been produced in crystalline form, and its role broadly defined as the acceleration of sugar combustion and glycogen synthesis.

Progress has been slower in the case of the parathyroid gland. Ample evidence has been produced to show that this endocrine organ plays an important role in the regulation of calcium and phosphorus metabolism in many animals. This is accomplished through the influence of the hormone on the activity of osteoblast and osteoclast cells which may respectively cause mineral deposition in boney structures or bone absorption, and possibly through some regulation of the renal threshhold for phosphorus. A hormone has not yet been isolated in pure form but the evidence available suggests that it is a simple protein.

The anterior lobe of the pituitary gland produces hormones which regulate the activity of other endocrine organs. Two of these have been isolated in forms giving the characteristics of pure proteins.

One, the luteinizing hormone (L H) in the male stimulates the development of the interstitial cells of the testis and the secretion of the male sex hormone. In the female this factor is instrumental in bringing about ovulation of mature follicles and formation of corpora. It is interesting to note that available evidence suggests that the same hormone is produced in the male as in the female, but with vastly different results.

The second hormone isolated, is the corticotrophic hormone which regulates the production of Adrenal cortex hormones. Although their isolation in pure form is not yet confirmed, two other factors, the follicle-stimulating hormone and the thyrotrophic hormone have been generally accepted as authenticated hormones. The former stimulates the seminiferous tubules of the testis in males and in the female causes growth and development of immature follicles in the ovary, while the latter regulates the activity of the thyroid gland.

Some evidence has been produced suggestive of pituitary regulation of the pancreas. Further supporting evidence is required before a separate pituitary hormone performing this function can be accepted as proven.

Although the existence of pituitary trophic factors in connection with the parathyroid and adrenal medulla have been postulated the weight of evidence is at present against pituitary control of these endocrines.

The anterior pituitary lobe also produces hormones which act directly on non-endocrine target tissues. One example of these is the somatotrophic or growth hormone, which promotes the development of soft tissues and bone and cartilage growth, and has been isolated as a pure protein. Another is Prolactin—the lactogenic hormone, the first pituitary hormone to be isolated as a pure protein, which activates the epithelial cell of the mammary gland alveoli to secrete milk. A considerable amount of evidence has been accumulated in favour of the existence of a pituitary mammary growth factor tentatively called mammogen but the chemical work necessary to prove or disprove the claim that it is a separate pituitary factor has yet to be done. Still other anterior lobe hormones have been postulated including further carbohydrate, fat and protein metabolism factors, thymotrophic and renotrophic principles and a reticulo-endothelial system stimulating hormone. As yet the evidence in support of each is insufficient to warrant their consideration as separate from known hormones.

Extracts of the posterior lobe of the pituitary may exhibit four main pharmaceutical properties. They may cause vasoconstriction with resultant increase in blood pressure; they may have an anti-diuretic action; they may cause uterine contractions (oxytocic effect) and, especially interesting from a dairyman's point of view—they may bring about what we call the "letting down" of milk in a lactating animal.

Whether these properties of extracts are a reflection of the production by the posterior lobe of one, two, or more protein-like hormones is not yet known. It is interesting to note that the realization of the possible role of the posterior pituitary gland in the "let down" phenomenon has greatly stimulated work in this field.

A protein-like extract of the intermediate lobe of the pituitary has the property of causing the pigment granules of certain animals such as the frog or toad to disperse thus darkening the skin. It seems certain that in some species this lobe secretes a hormone but no specific role for this factor in mammals has been established.

Although the thymus and pineal glands have long been suspected of endocrine function, there is still no definite proof that they produce hormones.

I have confined this brief and quite incomplete survey to the better known endocrine organs. To quote further examples would be tedious —or more tedious. Enough has been said to illustrate the considerable progress that has been made along the more familiar lines of investigation. In many cases hormones have been isolated synthesised and their properties, both chemical and physiological, intensively studied. In other cases, as for example the parathyroid and posterior lobe of the pituitary, work is at a less advanced stage. In a branch of study such as this speed of progress is very much dependent on team work. In the investigation of the role of an endocrine organ the general physiologist may determine the effects of the removal of that organ and the efficiency of crude substitution procedures. The problem of preparing extracts and isolating the pure hormone has then to be undertaken by the chemist who may have to enlist the aid of the physicist to assist him in his task. The physiologist in turn may have, as it were, the ball passed to him again with the request that he develop a biological method for testing the potency of the various extracts the chemist may prepare in his search for the pure hormone. A reverse pass may follow—the physiologist asking the chemist to devise chemical means for quantitative assay of material containing the hormone. The physiologist continues the work in studying the biological characteristics of the pure hormone. As in a passing rush in rugby football, progress upfield may be rapid if the team is composed of experienced players handling the ball with skill and precision, or halting, as when the ball is dropped, by a weak link or when an unfit member cannot keep up with the play. So in the endocrine field steady advance in knowledge has been made chiefly through the work of scientists from different fields—anatomists, physiologists, biochemists, organic chemists, physical chemists to mention only a few—concentrating on a particular endocrine problem, each one solving problems which held up the work of others.

At this point we may well ask in what way does animal production benefit from the accumulation of knowledge in the endocrine field?

The most obvious answer, of course, is that study of the endocrine system has provided further knowledge of the physiology of animals, and, in particular, a better understanding of reproduction, lactation and the adaption of metabolism to a changing external and internal environment. These phenomena are so much a part of animal production that efficiency in animal production is determined to no small degree by endocrine influences.

We examine current animal husbandry practices in the light of this further knowledge; we use it in argument to back up our advocation of what we consider to be sound methods; we are better equipped to take up the study of certain problems in animal production as, for example, those of reproduction and lactation. However, there is no need to labour this point to a Society such as ours. We readily agree that if a process or function is economically important in animal production it is of tremendous advantage to have an extensive background of knowledge concerning that process or function.

The endocrine system is primarily a regulatory system. Is it possible for us as animal husbandmen to regulate this regulatory system—to the end that the efficiency of animal production is increased? To take but one example, if growth and development are greatly influenced by the growth hormone of the pituitary and the thyroid hormone, is it possible to change the rate of growth, its efficiency or its pattern in farm animals to our advantage by artificially ensuring that animals are influenced by more or less circulating growth hormones? Work with small animals has given some suggestive and encouraging results, but because of differences in the reaction of different species or of different strains within species to treatment, only work with farm animals themselves will give us the required information.

Let us examine some of the problems which are met in venturing into this field and see what prospects progress in endocrine knowledge offers for their solution.

If we wish to increase the amount of circulating hormone to bring about a desired result our first problem is that of the availability of that hormone. And because of the large size of most of our farm animals the quantities of material required must be relatively large. We may add that, at least eventually, the cost must be low. Where supplies of hormones are limited to those produced by laborious extraction procedures from glandular material there seems little hope of practical application involving large numbers of animals. The search therefore is on for alternate sources of hormones. Some success has been attained with other animal material—estrogens and androgens are obtained from urine, a gonadotrophin having chiefly luteinizing properties from human pregnancy urine and one capable of ovarian follicle stimulation from the blood of pregnant mares. The latter, called for short P.M.S., has been used with a small measure of success in experiments with sheep, goats and cattle in attempts to induce follicle development and ovulation in sterile or seasonally anestrous females, and in sows to induce estrus during lactation and thus enable early breeding. For the most part improvement in the supply position would seem dependent on the development of cheap methods for synthesizing or the partial synthesis of hormones. The immediate outlook is not bright for those of a protein nature. The fact that many of the steroid hormones have been synthesized raises hopes that cheap progestins, androgens and adrenal cortex hormones will in time become available. In one case considerable progress has been made. It was discovered that the iodination of certain proteins under suitable conditions resulted in the production of thyroid-active material containing thyroxine. This led to the development of a method for the production of a cheap substitute, thyroprotein, for dried thyroid or the hitherto costly synthetic thyroxine, and opened the way for studies of the effect of various degrees of hyperthyroidism on growth, milk production and fertility in farm animals and egg production in poultry. It is noteworthy that under certain conditions mild hyperthyroidism, induced by feeding thyroprotein to dairy cattle, results in increased production of milk with an abnormally high fat content and that despite the known dangers of overdosage, the commercial application of this procedure is being actively explored in England and the U.S.A. A further advance has been reported lately from England in that a new and relatively cheap method for synthesizing thyroxine itself has been discovered, so, in the near future, we may find thyroprotein replaceable by pure thyroxine for large-scale animal work. The supply problem for the thyroid hormone at least seems near solution.

A further development has already assisted in meeting the problem of large-scale supply of hormones, i.e. the production of compounds different chemically from the natural hormones but having the same or many of the same physiological characteristics. The outstanding example here has been the discovery by Dodds and co-workers that some of the stilbene derivatives, notably "stilbestrol," possess high estrogenic potency. As some of these useful compounds are produced quite readily, we have now available a cheap source of estrogen for large-scale animal work.

In veterinary practice stilbestrol has found a minor place in the treatment of pyometra, but the results from its use in cases of sterility featuring ovarian hypo-function have not been consistently satisfactory. Perhaps one of the most spectacular experimental developments involving the use of stilbestrol has been the induction of lactation in dry non-pregnant dairy cattle. After a period of treatment with estrogens, during which mammary development takes place, some animals will come into copious lactation presumably under the influence of pituitary prolactin, the secretion of which has been stimulated by the estrogen. Unfortunately some undesirable effects are sometimes associated with the treatment—nymphomania, changes in conformation particularly in the pelvic region and pelvic fractures. These, together with an unpredictable variability in response, make the commercial application of the technique a doubtful proposition. That such a startling possibility should be so near to practical application is itself a tribute to progress in the field of applied endocrinology.

One of the problems in planned regulation of the endocrines which is associated with the supply position is that pertaining to the relation of one hormone to another. In many respects the hormones do not work independently. Rather are some of the results they achieve the effects of a change in the respective concentrations of several hormones. Ovulation is the result of more L.H. and less F.S.H. rather than all L.H. and no F.S.H. Sometimes two hormones work synergistically—estrogen plus progestin will give faster and more complete mammary development than the same hormones given separately—the same hormones may work antagonistically in other respects—estrogens induce heat—sufficient progestin will inhibit heat even although estrogen be present in the system as in pregnancy. For some tasks, as for example mammary development, we may not be able to achieve optimum results until the major hormone involved plus synergising hormones are all available in adequate supply for use in large animal experiments.

Given an adequate supply of hormones, another problem immediately confronts us in animal work. How is the hormone to be administered? The technique of frequent injections used so often with small animals has undesirable features in normal animal husbandry. The development of the pellet implantation technique seems to be one improvement. Solid pellets of hormone with or without a "filler" are implanted subcutaneously and the animal receives a continuous supply of the potent material by slow absorption from the surface of the pellet. Several steroid hormones—androgens, adrenal cortex hormones and estrogens have been successfully administered in this way.

Another possibility was suggested by the discovery that the aliphatic esters of the estrogenic substances estrone and estradiol have a duration of effect after subcutaneous injection proportional to the number of carbon atoms in the fatty acid chain. The longer the ester carbon chain, the longer the effect of a single injection—this due to slower absorption. By the application of this principle, lactation has been induced in virgin heifers by a single injection of a combination of short (quick-acting) and long (slow-acting) esters of diethylstilbestrol.

Feeding may be a convenient method of administration, yet many hormones, e.g. pituitary and parathyroid hormones, are not effective given in this manner. Certain steroid hormones also are not effective orally but investigation of allied compounds having a similar hormone-like action has, in some cases, produced orally effective ones. For example, the male sex hormone testosterone is comparatively inactive taken by mouth but the artificial androgen methyl-testosterone has high oral potency.

Certain hormones have been found to have a local action when placed on mucous membranes or skin. Of interest in this connection is the observation that the teats of dairy goats lengthen under the local action of estrogens. We may speculate as to what use may be found for local action of mammary growth stimulating or lactogenic principles infused into the udders of dairy stock.

We have considered some of the problems associated with the task of increasing the supply of hormones within the body. However, it may be desirable to effect the opposite result, the partial or complete elimination or inhibition of hormones. An effective procedure is to remove the endocrine organ producing the hormone and this method has long been widely applied in castration to eliminate the influence of the male sex hormone in domestic animals, to make for greater ease in handling and more rapid fattening. Animal husbandmen may have a strong claim to have been very early in the field of applied endocrinology! However, it is seldom practicable to influence hormone output in this way because of the difficulty of adapting surgical techniques for gland removal to large numbers of large animals. What a fortunate circumstance it was that testes become located in so accessible a position! One development in this respect is suggestive of the possibilities that may be ahead. It has been shown that certain compounds, notably those containing a thiocarbonamide grouping are antithyroid drugs, capable of inhibiting the formation of thyroxine within the animal body. Further investigation has made available relatively non-toxic substances such as thiouracil which are active when given orally. In the case of the pancreas it has been found that the compound alloxan has the property of causing degeneration of the insulin-producing cells of the islet tissue thus inducing diabetes. The fact that inhibiting substances have been found for some endocrine glands suggests that further developments in this field may add to our power to regulate the endocrine system. With the thyroid gland we are already in a fortunate position. We have relatively cheap thyroprotein to give hyperthyroidism, and thiouracil to induce hypothyroidism. Both substances are potent orally. Some of the animal work involving a hyperthyroid condition has already been mentioned.

The effects of thiouracil and allied goitrogens, particularly with respect to the growth and fattening of pigs, lambs, cattle and poultry, are under investigation. Good results are reported in poultry, but reports are so far rather inconsistent in the three other species, those with the pig during the last 4-6 weeks of fattening appearing the most promising in that claims have been made that more effective weight gains have been produced.

We normally think of hormones as being produced by endocrine glands. We have had to extend this conception to cover the fact that products of the chemists' skill in synthesis not found in nor produced by the animal body may possess the characteristics of animal hormones. But we can proceed further. It is now well established that substances having these properties are to be found in some of the foods commonly eaten by our live stock. The full significance of this in animal production is by no means clear. However, at least one practical problem has arisen. Reports have come from Western and South Australia describing a condition of low fertility in ewes and abnormal development of the reproductive organs and mammary glands in wethers. The phenomenon has been associated with the grazing of the Dwalganup strain of subterranean clover—incidentally one not used commercially in New Zealand. It seems certain that the observed effects are due to the presence in the grazed pasture of estrogenic substances, young green clover being particularly potent. Since the early Australian reports, the presence of estrogenic compounds in green pasture has been reported by English workers. The fact that in New Zealand occasional lines of wethers when slaughtered show a proportion of animals with abnormal mammary development and even milk secretion amply justifies a careful watch being kept on this aspect of nutritional physiology.

There is another side to this story—as it has been suggested that at least part of the milk secretion stimulating properties of good spring pasture may be linked with its content of hormone-like substances.

Perhaps one may be pardoned for speculating a little at this point. We now know that an animal may consume hormone-like substances in pasture. Conversely we know that the animal excretes hormones in the urine, e.g., the pregnant animal excretes estrogens and progestin both in combined form, and, strangely enough, we may cite the cow as excreting relatively large amounts of androgens in the dung. Is it possible that these animal hormones affect the growth of plants or affect the micro organisms in the soil?

Some evidence of hormone inhibiting substances being present in animal foods has come from the thyroid field. A naturally occurring goitrogen has been isolated from turnip and swede roots. This does not mean that these foods should be avoided, but it does suggest that this aspect of animal nutrition should not be overlooked. Iodine deficiency can no longer be regarded as the only likely cause of goitre in farm animals.

With the increase in knowledge of endocrine physiology has come a better appreciation of the way in which the nervous and the endocrine systems work together in regulating various functions of the body. It was early recognised that the secretion of adrenaline by the adrenal medulla was at least in part controlled by stimulation from the sympathetic nervous system. There is strong evidence to support the belief that the hormone of the posterior pituitary which brings about the "let-down" of milk is secreted in response to nervous stimuli. I believe that it is fair comment to suggest that increased knowledge of this latter endocrine-nervous mechanism, particularly in combination with interested scientists with talent in extension work, has brought about a renewed and critical interest in milking technique with advantage to the efficiency and productiveness of the dairy industry.

Time does not permit consideration of the many other problems in this field and I have been able to mention but a few of the attempted applications of endocrine knowledge.

In many respects we cannot but feel disappointed at the many instances of only partial success in the applied work, and with results that are indicative of future possibilities rather than of immediate gains. That surely is a reflection of the fragmentary nature of our knowledge and our anxiety to use what we have at the earliest possible moment. However, those fragments are being pieced together and the gaps are being filled. We cannot fail to be impressed by the potentialities of the tools that are coming to hand and the increasing opportunities for their employment.

While the application of endocrine knowledge may not have produced the type of results expected by those whose thinking has been coloured by reading of the 1889 report of the 72-year-old French physician who claimed rejuvenation under the influence of extracts of dog testes, progress has been real and sure. If the next twenty years are as productive of increased knowledge and improved technique for applying it as have been the past two decades, it seems likely that adjustments of endocrine balance through methods other than breeding may asist very materially in increasing the efficiency of animal production.