ENDOCRINE CONTROL OF GROWTH AND MUSCLE DEVELOPMENT.

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INTRODUCTION

It is not logical to associate scientific methods that improve growth rates, feed efficiency and carcass quality with over-production of meat. Over-production must be distinguished from better productivity or better profitability for the farmer. Scientific research must assist the producer to provide a quality product which is leaner and meatier at a price the consumer can afford.

Bovine species transforms nitrogen from its feed into proteins with a poor yield. A better knowledge of the physiology of growth and muscle development, especially the mechanism of protein accretion, will help to define methods for producing high quality meat with an optimal yield.

Several aspects must be considered : nutrition, genetic, environment and endocrinology.The influence of one of these aspects on the others cannot be ignored. In this brief review, we shall only consider the last aspect : endocrine control of growth. Optimisation of nutrition or genetic selection are "traditional" methods to improve meat production. The notion of endocrine control is more recent and its beneficial effects are more rapidly obtained than with genetic selection.

Anabolic agents were first used as growth promoters which increase nitrogen retention at the muscular protein level. They are natural or artificial hormones very efficient to improve meat production particularly in bovine and ovine species. But they are not easily accepted by consumers due to the risk of residues. A recent EEC guiding rule completely banned their use in meat production despite the numerous scientific evidences for the safety of estradiol, testosterone, progesterone and two synthetic molecules as trenbolone acetate and zeranol.

Taking this attitude into account, even if it is not founded on scientific grounds, new approaches must be proposed to improve meat production. The aim of this paper is to review the mechanisms of growth and muscle development in order to define new ways for growth promotion of cattle.

ENDOCRINE ASPECTS OF GROWTH AND MUSCLE DEVELOPMENT

Tissue growth is dependent upon the rate and extent of hyperplasia and hypertrophy of the constitutive cells. Cellular growth occurs as the result of nutrient uptake by the cells and the balance between anabolic and catabolic processes which regulate accretion of component and structural material of the cell. Endocrine system affects the availability, uptake and intracellular metabolism of nutrients.

A global view of this subject would have to consider not only hormones which are of concern but also the regulation of their synthesis and secretion, the relationships between endocrine systems, the target organs and their metabolic functions (scheme 1).

Most of the hormones involved in growth and muscle development processes are known as well as their regulation. Our knowledge about relationships between endocrine systems controlling functions such as growth, reproduction, general cellular metabolism, is more limited. While precise regulation of cellular, tissue or organ receptivities to hormonal signals are much less well understood.

Cellular aspects.

Growth of a tissue can occur from an increase in cell number (hyperplasia) and an increase in size (hypertrophy). Most of the hyperplasia, under physiological conditions, occurs prenatally. The number of muscle fibers in a muscle does not increase appreciably after a few weeks of age.

The rate of growth of muscle can be related to the rate of increase of the number of muscle nuclei through increased division of satellite cells.

Protein accretion in muscle cells results from an equilibrium between synthesis and degradation of proteins. While there is a considerable amount of knowledge on factors controlling protein synthesis, there are limited informations on the mechanisms of protein degradation. In addition, there have been only a few studies of fractional rate of protein synthesis and protein degradation in large animals (7,8,9).

Hormonal aspects

Somatotropin (Growth Hormone, GH) and somatomedins (Insulin-like Growth Factors ,IGF).

GH is known to be responsible for a wide range of metabolic (carbohydrates, lipids and proteins) and growth-promoting effects *in vivo*. Synthesis and secretion of GH from hypophysis are controlled by hypothalamus that secretes an inhibiting peptide, somatostatin or Somatotropin Release-Inhibiting Factor (SRIF) made of 14 amino acids, and a stimulating peptide, Growth Hormone Releasing Factor (GRF) 44 amino acids. A complexe feedback mechanism exists. IGFs, among other factors, are part of this regulatory system.

GH stimulates hyperplasia, hypertrophy and cellular differenciation through a large number of mechanisms. Thyroid hormones, insulin, glucocorticoides, androgenes, estrogens and various growth factors, in particular IGFs, are connected with these mechanisms.

GH acts on intermediate metabolism to stimulate protein synthesis. Mobilization of lipids, as free fatty acids for the liver, is accelerated, their oxidation is increased.

GH effects on carbohydrate metabolism are complex and may appear contradictory according to the physiological state of the animals : insulin-like effect (hypoglycemia) or anti-insulin effects (diabetogenic).

Most of the GH effects observed *in vivo* cannot be reproduced *in vitro*. Its somatogenic effects are mediated by IGFs produced mainly by the liver under the control of GH itself. In muscle, there is no conclusive data in favor of a direct action of GH on protein metabolism. Activation of chondrogenesis, protein synthesis and hyperplasia / hypertrophy of cells are indirect effects of GH which are mediated by IGFs.

IGF secretion seems to be controlled also by other hormones. Prolactin, insulin, have been implicated as stimuli for IGF production by the liver. Cortisol or triiodothyronine (T3) can act synergistically with GH.

Hence, the hepatic synthesis and release of IGF is under multiple hormonal control, the liver playing a central role in the endocrine control of growth.

Thyroid hormones (T3 and T4)

Thyroid hormones affect the growth, development and metabolism of probably all tissues in mammals and the specific effects depend upon the stage of development and the type of tissues involved. Normal growth in the post-natal individual is dependent on a euthyroid state. Thyroid hormones exert direct effects stimulatory to growth (increase of protein synthesis) or it may have permissive effects via other hormones such as GH. Indeed, they play a role in regulating pituitary GH production and they potentialize localized growth-promoting actions of GH. They may also play a role in restoring "normal" tissue response to growth-promoting agents. *In vitro*, T4 may be directly involved in the regulation of satellite cell proliferation and myonuclei accumulation (10).

Gonadal steroid hormones. Anabolic agents.

Anabolic steroids have been known for a long time but their mode of action is far from being elucidated.

According to their sexual properties, they can be classified into androgenic and estrogenic steroids. Progestagens, which also show anabolic properties, are less studied but are often classified in the androgen group as far as we are concerned with growth-promoting activity. However, within these groups, it is unlikely that all compounds are acting in the same way. For example, testosterone is thought to promote muscle growth by increasing the rate of protein synthesis (11), while it is generally accepted that the synthetic

steroid trenbolone decreases the rate of protein breakdown (12). To summarize all the hypotheses concerning their mechanism of action, we can say that the anabolic steroids could act either by interfering in the regulation of endogenous hormones (secretion or transport), either by inhibiting the biological effects of endogenous hormones by preventing their binding to their receptors in the muscle or by a direct action after binding of the anabolic agent to its specific receptor.

Mechanism of action of androgenic steroids

Androgens are certainly the growth promoters for which the most numerous hypotheses about their mode of action have been formulated.

High affinity binding sites have been discovered in skeletal muscle of a large range of species(13,14,15) suggesting that the anabolic activity of these agents would be due to a direct action onthe muscle after binding to their specific receptors. In this context, we can point out that a direct action of testosterone was shown in muscle cell culture (16). Androgens present an antiglucocorticoid activity <u>in vitro</u> by inhibiting the binding of glucocorticoids to their cytosolic receptors (17) : androgens could thus induce a better growth by antagonizing, at the receptor level, the catabolic effect of glucocorticoids in muscle (18). One point which emphasizes this hypothesis is that antiglucocorticoids can significantly reduce the catabolic activity, appreciated by measuring the rate of growth and muscle weight, of exogenous corticosterone in adrenalectomised rats (Danhaive, unpublished results). The question is of course to know whether glucocoticoids are responsible for muscle protein degradation at their normal circulating concentrations. Indeed, it appears that pharmacological doses of these catabolic agents are necessary to decrease growth in adrenalectomised rats (19).

But androgens could also act via a decrease in plasma level of corticosterone : it seems that the diurnal peaks peaks of the nictemeral pattern of corticosterone is significantly decreased in trenbolone treated rats (20).

It has also been proposed that androgenic compounds would be partially converted in estrogens which would be then responsible for the growth increase (21). If that mechanism was verified that could explain the difference of action between testosterone, which can be aromatized and trenbolone, which cannot be aromatized due to the absence of the C19 methyl group.

Another possibility is that androgenic steroids could influence the level of free endogenous androgens by displacing them from steroid binding proteins in blood and increasing thus their biological availability (22,23).

Finally, the regulation of the level of other hormones (ACTH, CRF, thyroid hormones, GH, insulin) by androgens has also been studied. But, until now, we have no evidence for such an indirect mechanism of action (20,24,25).

Mechanism of action of estrogenic steroids

The mode of action of estrogens is not better understood.

Estrogen treatment of sheeps and cattle increased significantly the concentrations of GH associated with a rise of insulin concentration (26,27). For this reason, everybody agreed that anabolic activity of estrogens might be connected with the central nervous system. Never theless, experiments on lambs showed that diethylstilbestrol and exogenous ovine GH had not the same biological effects and, moreover, that the increase in body weight in diethystilbestrol-treated animals were observed several weeks before any increase of GH levels in plasma (28). However, data on growing beef steers implanted with estrogenic agents show an increase of the secretion rate of GH and thus are in favor of a mechanism mediated by the pituitary gland(29). Moreover, considering that thyroid hormones are involved in growth and metabolism of skeletal muscle (30), it appears that T4 participates in the growth and anabolic actions of estrogens in ruminants. Indeed, estrogenic treatment of beef steers induces an increase of plasma T4, probably due to a reduction of peripheral conversion of T4 to T3 (31). However, as thyroid hormones are involved in protein synthesis as well as in protein breakdown, it would be rather hazardous to postulate that this plasma T4 increase can be correlated with an improved growth rate.

Very interesting observations are the decrease of corticosterone secretion in estrogen treated rats (32) and also the lower levels of free and active cortisol in man after estrogen treatment (33). Thus, estrogens could exert their anabolic activity by influencing the level of endogenous catabolic hormones.

Finally, as for androgen steroids, we may also expect a direct action of estrogens at the muscle level since the presence of estrogen receptors has been demonstrated in skeletal muscle (34,35). Muscle cells could thus be considered as a target of estrogen compounds.

Other mechanisms cannot be excluded : the synergic action of a combined treatment involving androgens and estrogens was associated in sheep with a decrease of plasmatic T4 and of the free thyroxine index (which reflects the free T3 concentration in plasma). Such combined implants abolish the estradiol-induced GH and insulin responses. These observations support an indirect mode of action (25).

In conclusion, the mechanism of the regulation of protein metabolism by the sexual steroid is thus still incompletely understood. It is rather amazing that these agents have been used for decades and that we have not yet a better knowledge of the biochemical processes which are responsible for improvement of the protein deposition at the muscle level.

Other hormones

Glucocorticoids, insulin, parathyroid hormone, calcitonin and perhaps prolactine (PRL) serve a supportive role in growth. In their presence, growth may proceed at normal rates, but they do not by themselves directly stimulate growth.

Thyrotropin-Releasing Hormone (TRH), which stimulates secretion of thyrotropin (TSH) and PRL increased growth rates in lambs and calves (36,37). This effect could be due to GH-like effect of PRL and thyroid hormone effect on growth.

Hormone concentration in blood is probably one of the parameters which could be correlated with growth. But patterns of secretion, particularly for GH, are doubtlessly important to govern growth function.

Tissue (cellular) responsiveness to hormones must also be considered even if there is a lack of data in this field.

CONTROL OF THE GROWTH OF MEAT-PRODUCING ANIMALS

There are two ways to influence the rate of growth and the carcass composition using methods based on endocrinology :
1) Endogenous hormones can be manipulated using for example modern genetics (transgenic animals) or immunological methods (vaccines against gonadoliberine, GnRH, or somatostatin, SRIF).
2) Administration of exogenous hormones or other substances, which can be natural or purely synthetic molecules, to facilitate the efficient production of lean red meat. Anabolic agents, somatotropin, GRF, growth factors (IGF) belong to this category of treatment.

Insertion of foreign GH gene into the animal genome

"Transgenic mice" have been produced (38) from eggs microinjected with metallothionein-rat GH fusion genes. This approach was proposed as a way to accelerate animal growth. More recently, the same research group (39) has established strains of transgenic mice containing a fusion gene including the promoter/regulatory region of the mouse metallothionein I gene and the coding region of the human GRF gene. Accelerated growth rates were observed relative to control littermates. Female transgenic mice carrying the human GRF gene were fertile in contrast to transgenic mice expressing human or rat GH, which are generally infertile.

Immunological methods of controlling growth.

Active and passive immunization procedures could be used in theory to influence an endocrine system, for example by neutralizing inhibiting feedback signals unfavourable to growth.

Spencer et al (40) described an elegant method for improving growth in lambs. This method is based on an autoimmunization against somatostatin (SRIF). The peptidic nature of SRIF allows to avoid the residue problem of classical

anabolic agents. But effective adjuvants, acceptable in term of public health consideration, have to be developed before the auto-immunization method will become applicable in growth promotion of animal on farms.

Closset et al present in the framework of this Meeting (41) the experimental results obtained by auto-immunization of young bulls with a synthetic vaccine, muramyl dipeptide (or tripeptide) chemically-coupled to SRIF (TECHLAND, Belgium, Patent 85269).

Experiments on active immunization against somatostatin continue to provide variable results which are not yet sufficiently encouraging to warrant commercial exploitation.

A clear relationship between the positive benefits of immunization and the plasma GH levels was not demonstrated. Mode of action of this anti-SRIF immunization could not be as simple as endogenous SRIF neutralization by antibodies leading to a rise in GH levels in plasma.

Anabolic agents

Estradiol, testosterone, progesterone, trenbolone acetate and zeranol, sometimes used alone but usually in selective combination, are efficient substances to increase growth rate and food conversion yield without adverse effects on carcass and meat quality. Despite the scientific evidences accumulated during almost 20 years for the safety of these five growth-promoters, EEC imposed at the end of 1985 a complete ban of their use in meat production. This irrational decision will probably have as consequences the production of meat at a higher cost in western Europ and the development of a black market possibly extending to dangerous substances such as the stilbenes.

Administration of somatotropin (GH), Growth Hormone-Releasing Factor (GRF), somatomedins (IGF) and other growth factors.

Genetic engineering and modern chemical synthesis of peptides have opened new possibilities for the control of growth since hormones, even with a complex polypeptidic chain, can be obtained as highly pure preparations at a raisonable cost by methods alternative to endocrine gland extraction.The mechanisms of control of GH biosynthesis and secretion and its effects, direct or indirect, in the control of growth and muscle development have been presented above. An impressive amount of research is performed on these various aspects in laboratory animals, in man and, more recently, in milk- or meat-producing animals. It is now well established that treatment of dairy cows with GH increases the milk yield and improves the feed conversion efficiency. Publications on the effect of exogenous GH administered for enhancing meat production are scarcer. But, so far, the experimental results are promising for improvement in daily live weight gain and food conversion efficiency. From experimental and clinical studies in laboratory animals and man respectively, it is apparent that GH administration induces an insulin-resistent state. It is not clear whether chronic GH administration in meat animals induces a somatotropin-resistent state. The pattern of GH administration (single daily injections or multiple injections)(42) and the doses, required to obtain maximal benefit for growth and carcass quality without noxious side effects, have to be defined. Low cost delivery systems efficient during several weeks have to be set up before new developments in the commercial use of somatotropin in animal production. Bovine somatotropin offers garanties about consumer safety. As a protein, it is rapidly destroyed when absorbed orally. Furthermore, somatotropins from animal origins (bovine, ovine, porcine, equine) are not biologically active in man.

Experimental data on the effects of GRF in domestic animals are still very scarce. Such treatment seems to influence GH levels, the response being variable with age (43) and improve milk production (44). Nevertheless, the effects of GRF on milk production appear less important than that of GH.Repeating injections of GRF caused a dramatic decrease in pituitary responsiveness to subsequent injection of GRF (45). Centrally administered GRF stimulates food intake in

sheep (46). Much remains to be done to determine the potential of GRF for improving animal performance.

IGF I from domestic animal origin (bovine, ovine) have been recently purified and their amino acid sequence determined (47,48,49). Bovine IGF I sequence appears identical to the human corresponding peptide. Surprisingly, biological and immunological properties of human and bovine IGF I seems to be different. These IGF preparations will permit to develop sensitive and specific assays of these growth factors in domestic animals. The genes for IGFs have been cloned (50,51,52) and genetically engineered IGF I will be soon available. Thus, the availability of sufficient amounts of IGF will allow to test whether administration of IGF may be capable of enhancing growth rate in meat-producing animals.

Before to conclude, let us mention growth-promoting treatments by non- hormonal substances : antibiotics and B-adrenergic agonists.

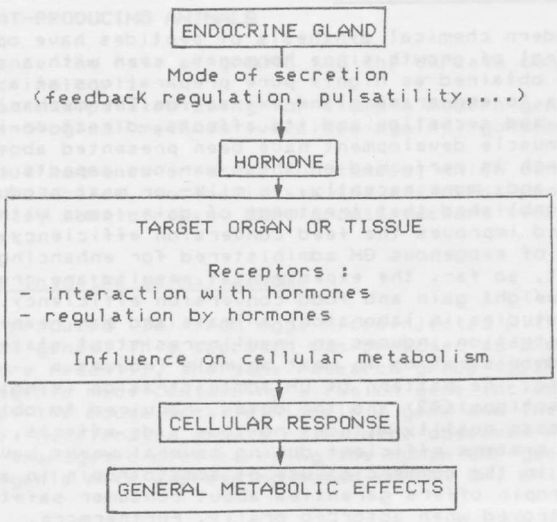
Antibiotics as growth promoters

They maintain animal health in situation of stress and under conditions of intensive production. In addition, antimicrobial feed additives enhance the growth performance by increasing growth rate and/or improved feed conversion (1).

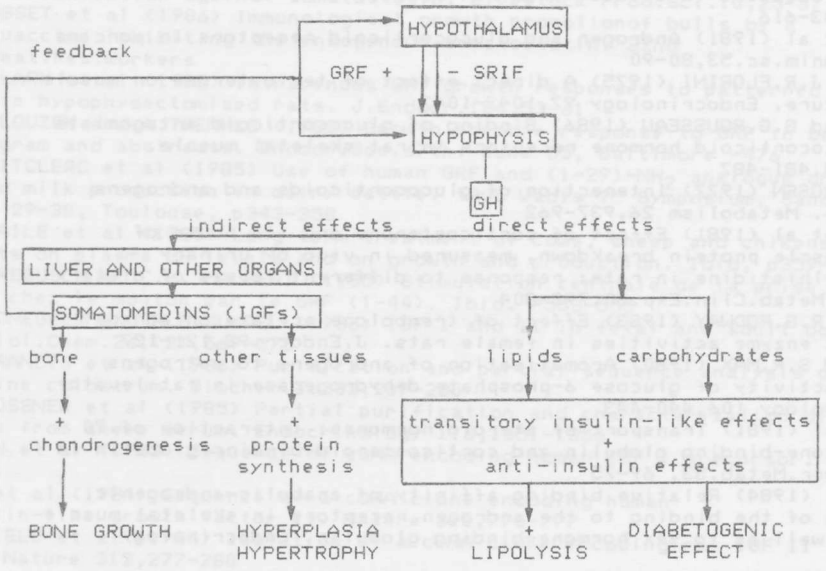
B-adrenergic agonists

Clenbuterol, a substituted catecholamine, and similar compounds reduce fat deposition and increase protein accretion in sheep (cited in (1)) cattle, pigs and poultry. These modifications of carcass composition are in agreement with consumer demand for a decreased fat content of meat. For these reasons, B-adrenergic agonists are sometimes called "repartitioning agents". The efficacy of such treatment appears promising but their mode of action, metabolism, side effects, residue levels and their toxicological meaning must be established before general application.

Scheme 1.



Scheme 2.



The following reviews are related to our subject :

(1) G.E.LAMMINGS (1986). Future Production and Productivity in Livestock Farming. 2nd International Conference of the DSA. Brussels, 23-25 April 1986.
(2) B.D.SCHANBACHER (1984). Manipulation of endogenous and exogenous hormones for red meat production. J. Anim.Sci. 59(6)1621-1630.
(3) R.E.ALLEN et al (1979) Cellular aspects of muscle growth : myogenic cell proliferation. J. Anim.Sci.49(1)115-127.
(4) M.E.DIKEMAN (1984) Cattle production systems to meet future consumer demands. J.Anim.Sci.59(6)1631-1643.
(5) A.TRENKLE and D.N.MARPLE (1983) Growth and development of meat animals. J.Anim.Sci.57(suppl 2)273-283.
(6) T.D.ETHERTON AND R.S. KENSINGER (1984) Endocrine regulation of fetal and postnatal meat animal growth. J.Anim.Sci.59(2)511-528.

Literature cited

(7) P.J.GARLICK et al (1976) Protein synthesis and RNA in tissues of the pig. Amer.J.Physiol.230,1108.
(8) G.E.LOBLEY et al (1980) Whole body and tissue protein synthesis in cattle. Brit.J.Nutr.43,491
(9) P.J.REEDS et al (1980) Protein turnover in growing pigs-Effect of age and food intake. Brit.J.Nutr.43,445
(10) D.H.BEERMANN et al (1983) Effect of exogenous thyroxine and growth hormone on satellite cell and polynuclei populations in rapidly growing rat skeletal muscle. Growth 47,426-436
(11) J.A.MARTINEZ and P.J.BUTTERY (1983) IVth. Symp.Protein metabolism and nutrition, Clermond-Ferrand. Ed. INRA Publ.,1983,II (les colloques de l'INRA no16),p77-80
(12) P.A.SINNETH-SMITH et al (1983) Effects of trenbolone acetate and zeranol on protein metabolism in male castrate and female lambs. Br.J.Nutr.50,225-234
(13) G.MICHEL and E.E.BAULIEU (1980) Androgen receptor in rat muscle : characterization and physiological variations. Endocrynology 107,2088-2098

(14) M.SNOCHOWSKI et al (1980) Characterization and quantitation of the androgen and glucocorticoid receptors in cytosol from rat muscle. Eur.J.Biochem.111,603-616
(15) M.SNOCHOWSKI et al (1981) Androgen and glucocorticoid receptors in porcine skeletal muscle. J.Anim.sc.53,80-90
(16) M.L.POWERS and J.R.FLORINI (1975) A direct effect of testosterone on muscle cells in tissue culture. Endocrinology 97,1043-1047
(17) P.A.DANHAIVE and G.G.ROUSSEAU (1986) Binding of glucocorticoid antagonists to androgen and glucocorticoid hormone receptors in rat skeletal muscle. J.Steroid Biochem.24,481-487
(18) M.MAYER and F.ROSEN (1977) Interaction of glucocorticoids and androgens with skeletal muscle. Metabolism 26,937-962
(19) S.SANTANDRIAN et al (1981) Effect of corticosterone and its route of administration on muscle protein breakdown, measured in vivo by urinary excretion of N-methylhistidine in rats: response to different levels of dietary protein and energy. Metab.Clin.Exp.30,798-804
(20) K.M.THOMAS and R.G.RODWAY (1983) Effect of trenbolone acetate on adrenal function and hepatic enzyme activities in female rats. J.Endocr.98,121-127
(21) J.F.KNUDSEN and S.R.MAX (1980) Aromatisation of androgens to estrogens mediates increased activity of glucose 6-phosphate dehydrogenase in rat levator ani muscle. Endocrinology 106,440-443
(22) M.M.PUGEAT et al (1981) Transport of steroid hormones: interaction of 70 drugs with testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J.Endocr.Metab.53, 69-75
(23) T.SAARTOK et al (1984) Relative binding affinity of anabolic-androgenic steroids: comparison of the binding to the androgen receptors in skeletal muscle and in prostate, as well as to sex hormone-binding globulin. Endocrinology 114,2100-2106
(24) P.A.SINNETH-SMITH et al (1984) Plasma somatomedin activity and tri-iodothyronine and thyroxine concentrations in female rats treated with the growth promoter trenbolone acetate. Biochem.Soc.Trans.12,251-252
(25) I.A.DONALDSON et al (1981) Growth hormone, insulin, prolactin and total thyroxine in the plasma of sheep implanted with the anabolic steroid trenbolone acetate alone or with estradiol. Res.Vet.Sci.30,7-13

(26) I.A.DONALDSON (1977) The action of anabolic steroids on nitrogen retention metabolism and the endocrine system in ruminants. Ph.D.thesis,University of Reading
(27) A.TRENKLE (1976) in Anabolic Agents in Animal Production (Edited by F.COULSTON and F.CORTE) Thieme,Stuttgart,Suppl.V 79-88
(28) L.A.MUIR et al (1983) Effects of exogenous growth hormone and diethylstilbestrol on growth and carcass composition of growing lambs. J.Anim.Sci.56,1315-1323
(29) R.GOPINATH and W.D.KITTS (1984) Growth hormone secretion and clearance rate in growing beef steers implanted with estrogenic anabolic compounds. Growth 48,499-514
(30) K.M.BALDWIN et al (1978) Enzyme changes in neonatal skeletal muscle. Am.J.Physiol.235,C97-102
(31) R.GOPINATH and W.D.KITTS (1984) Plasma thyroid concentrations in growing beef steers implanted with estrogenic anabolic growth promotants. Growth 48,515-526
(32) R.E.PETERSON et al (1960) Estrogen and adrenocortical function in man. J.Endocr.Metab.20,495-514
(33) M.VOGT (1955) Inhibition by hexoestrol of adrenocortical secretion in the rat. J.Physiol.130,601-614
(34) E.DAHLBERG (1982a) Characterization of the cytosolic estrogen receptor in rat skeletal muscle. Biochim.Biophys.Acta 717,65
(35) H.H.D.MEYER and M.RAPP (1985) Estrogen receptor in bovine skeletal muscle. J.Anim.Sci.60,294-300
(36) S.L.DAVIS et al (1976) Influence of chronic TRH injections on secretion of prolactin,thyrotropin and GH and on growth rate in wether lambs. J.Anim.Sci.42,1244-1250
(37) S.L.DAVIS et al (1977) Growth rate and secretion of pituitary hormones in relation to age and chronic treatment with TRH in prepubertal dairy heifers. Endocrinology 100,1394-1402
(38) R.D.PALMITER et al (1982) Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300,611-615
(39) R.E.HAMMER et al (1985) Expression of human GRF in transgenic mice results in increased somatic growth. Nature 315,413-416

(40) G.S.G.SPENCER and G.J.GARSSEN (1983) A novel approach to growth promotion using auto-immunisation against somatostatin. Livestock Prod.Sci.10,25-37
(41) J.CLOSSET et al (1986) Immunological growth promotionof bulls by a synthetic vaccine inhibiting the endogenous somatostatin. 32nd Eur.Meet.Meat.Res.Workers
(42) R.G.CLARK et al (1985) Intravenous GH: growth responses to patterned infusions in hypophysectomised rats. J.Endocr.104,53-61
(43) C.A.PLOUZEK and A.TRENKLE (1985) Growth hormone response to GRF in beef cattle.Program and abstracts. Endocr.Soc.67th.-June 85, Baltimore -476
(44) D.PETITCLERC et al (1985) Use of human GRF and (1-29)-NH_2 analogue on GH release and milk production in dairy cattle. "Quo Vadis ?" Symposium, Sanofi Group, May 29-30, Toulouse, p343-358
(45) C.A.BAILE et al (1985) Long-term treatment of cows, sheep and chikens with GRF: effects on plasma GH levels and on growth and production. Ibid, p359-370
(46) Y.RUCKEBUSCH et C.H. MALBERT (1985) Stimulation centrale de la prise de nourriture chez le mouton par le GRF (1-44). Ibid. P553-555
(47) A.M.HONEGGER and R.E.HUMBEL (1986) IGF I and II in fetal and adult bovine serum. J.Biol.Chem.261(2),569-575
(48) G.L.FRANCIS et al (1986) Purification and partial sequence analysis of IGF I from bovine colostrum. Biochem.J.233,207-230
(49) M.L.HOSSNER et al (1985) Partial purification and characterization of somatomedin from sheep serum. Endocrinology 116,1351-1356
(50) JANSEN et al (1983) Sequence of cDNA encoding human IGF I precursor. Nature 306,609-611
(51) BELL et al (1984) Sequence of a cDNA clone encoding human preproinsulin-like growth factor II. Nature 310,775-777
(52) WHITFIELD et al (1984) Isolation of a cDNA clone encoding rat IGF II precursor. Nature 312,277-280