EXOGENOUS GROWTH HORMONES IN ANIMAL PRODUCTION

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Summary

There is now substantial evidence that exogenous hormones may be used to effect improvements in productivity of farm animals – poultry, swine and ruminants. At present, steroids and related compounds are used widely throughout the World to improve growth of meat-producing animals – principally cattle. Growth hormone and related hormones have been shown to improve productivity of farm animals and it is expected that growth hormone will be available for use in animal production systems, at least in the Northern Hemisphere, by 1988. Major use of the hormone in dairy herds is anticipated and the effects of growth and perhaps wool growth may be exploited as well.

For the purpose of this overview on the use of "growth hormones" in animal production it has been assumed the "growth hormones" are hormones or hormone analogues which improve the productivity of farm animals or show promise of doing so. Brief mention has been made of the potential for immuno-manipulation of endogenous hormone secretion.

I. INTRODUCTION

To date most improvements in animal production have been achieved by improvement in husbandry/feeding practices and by deliberate selection/breeding of superior animals. As a result, dramatic improvements in productivity have been obtained. In spite of this it is now clear that even further improvements may be obtained either by manipulating the genomes of animals (see Lockett 1985) or, in the shorter term, altering the hormonal status of the animal.

Hormones regulate all body functions and accordingly body tissues of animals are controlled directly and/or indirectly by a complex of hormones. The potential for improving productivity of man's domestic animals has been appreciated for many years but exploitation of the stimulatory effects of hormones on animal productivity has not occurred until quite recently. Currently, a number of hormones and hormone analogues are being used in animal production systems and there is substantial interest in exploiting the use of other hormones.

Much of the commercial interest in using hormones to improve productivity has arisen from observations made during quite basic studies on the modes of actions of hormones in the animal body. To some extent, the commercial application of hormones for improving productivity of farm animals has proceeded faster than research into physiological changes permitting increased productivity.

II. GROWTH HORMONE

The importance of growth hormone for normal growth in mammals was recognised nearly 60 years ago and studies with rats conducted during the

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1930's showed that growth hormone stimulated growth (Evans and Simpson 1931) and increased the ratio of muscle protein:body fat (Lee and Schaffer 1934). Since that time it has been shown that growth hormone is required for normal growth in ruminants (Tindal and Yokayama 1964a, 1964b; Vezinhet 1973). Furthermore, the physiological effects of growth hormone have been studied extensively (see Table 1).

Table 1. Biological activities of growth hormone (adapted from Machlin 1976)

	Biological Activity	Details
Stimulated by growth hormone	Cell Division	numbers of cells in muscle, liver, spleen, mammary and other tissues; DNA polymerase
	Protein Anabolism	nitrogen retention; uptake of amino acids; incorporation of amino acids into protein; RNA polymerase; elongation of mRNA; polyamine synthesis
	Lipid Metabolism	fatty acid release from adipose tissue; oxidation of fatty acids
	Carbohydrate Metabolism	tissue glycogen deposition; pancreatic release of insulin; peripheral insulin resistance; plasma glucose concentrations
	Mineral Metabolism	deposition of Ca and P in bone; Ca turnover; retention of Na, K, P
Inhibited by growth hormone	Lipid Metabolism	fat synthesis; adipocyte size

In short growth hormone promotes growth (stimulating cell division, skeletal growth and protein synthesis) exerts lipolytic effects (promotes release of fatty acids from adipose tissue and increases oxidation of fatty acids) and also exerts diabetogenic activity (induces peripheral insulin resistance and the transport of glucose into body tissues (see Hart and Johnsson 1985). It appears that these effects of the hormone result in the production responses induced by exogenous growth hormone – see below.

Until recently the relative scarcity of purified hormone precluded extensive studies on the effects of exogenous growth hormone on productivity of farm animals. The recent resurgence of interest in use of growth hormone to improve productivity of farm animals, resulting from appreciation of the commercial applicability of exogenous hormone, has led to production of sufficient hormone of pituitary origin to allow meaningful studies on product ion responses in farm animals. The physiological bases for these responses also are being examined.

Development of procedures for production of large quantities of "genetically-engineered" or recombinant DNA-derived growth hormone (Goeddel et al. 1979) has led to considerable expansion of research effort on the effects of exogenous growth hormone on productivity of farm animals. Indeed, several commercial companies in North America, Britain, Europe and Australasia are actively promoting research in this area. It appears that growth hormone will be available for extensive use in the field within the next 2-3 years (see Mix 1985).

(a) Effects of growth hormone in growing animals

Some effects of exogenous (homologous or heterologous) growth hormone on production parameters in domestic animals are summarised below. In general, exogenous growth hormone has been found to increase liveweight gain, increase the proportion of lean tissues and decrease the proportion of fatty tissue in the carcases of treated animals. Significantly, in most studies with mammalian farm animals increases in the efficiency of utilisation of food for liveweight gain have been measured.

i)   Effects in chickens   Although the role of growth hormone in controlling growth in chickens remains unclear, available evidence suggests a similar role to that in mammalian species. It is clear that growth hormone is required for normal growth and other hormones interact with growth hormone to allow full expression of growth potential. There is however equivocal evidence that exogenous growth hormone increases growth in the chicken once optimal growth has been obtained. This may be due to the use of heterologous (ovine or bovine) growth hormone, but in most studies where purified chicken growth hormone (either pituitary-derived or "genetically-engineered") has been used, effects on growth have not been recorded.

Table 2. Effects of intravenous injection of purified chicken growth hormone on body weight gain (g) on, cockerels 4 weeks old at commencement of treatment. Values are percentage increases in body weight relative to saline-treated birds (adapted from Leung 1985)

Daily dose of chicken growth hormone (µg)	Day of treatment			
	3	6	10	14
5	20.7*	13.5*	9.2*	7.7
10	19.6*	11.2*	9.2	7.7
50	15.3	9.8	6.6	6.5

* $P < 0.05$.

There are a limited number of exceptions where growth responses have been observed following treatment of chickens with purified chicken growth hormone. Marsh and Scanes (1984) noted significant increases of 10-20% in body weights of chickens given daily injections of purified chicken hormone and similarly a significant increase (8%) in body weights of chickens injected with chicken growth hormone plus thyroid hormone. More recently Leung (1985) reported results of studies with cockerels 4 weeks of age,

Intravenous injections of 5 μg/d or 10 μg/d, but not 50 μg/d, of purified chicken growth hormone significantly but transiently stimulated growth (Table 2). No effects of treatment on body composition nor efficiency of food utilisation were recorded in this study.

ii)   Effects in pigs   In most studies with pigs exogenous growth hormone has been found to stimulate growth, alter body composition and improve the efficiency of food utilisation in young pigs growing rapidly (see Table 3).

Table 3.   Summary of some effects of exogenous porcine growth hormone on growth, feed conversion efficiency (FCE) and carcase composition of growing pigs (adapted data presented by Hart and Johnsson and cited from various sources)

Dose ranges (mg GH/kg/d)	Treatment period (weeks)	Difference from controls (%)			
		Growth	FCE	Carcase content	
				Muscle[†]	Fat[§]
0.033 – 0.67	4–15	–1 to 16	7 to 19	0 to 25	0 to –21

[†]Protein content of muscle or area of "eye" muscle;   [§]back fat thickness.

Machlin (1972) noted 'toxic' effects of doses of growth hormone $\geqslant 0.22$ mg/kg liveweight but did not define the nature or bases of these effects. Possibly, the above report of toxic effects of porcine growth hormone influenced later researchers to use lower doses of hormone. In studies with doses ranging from 0.015–0.06 mg/kg of genetically-engineered human hormone Baile et al. (1983b) observed small effects on growth, small decreases in the efficiency of feed conversion and no changes in carcase composition. Similarly, Chung et al. (1985) recorded only small (but significant) positive effects on growth and feed conversion efficiency and no change in carcase composition in pigs treated with 0.022 mg/kg/d porcine growth hormone.

Clearly, further research is required to resolve optimum doses and potential problems with toxicity of growth hormone in pigs. Furthermore, the observation of Machlin '(1972) that relative growth responses and improvements in efficiency of food utilisation were higher for pigs offered restricted than adequate amounts of food deserves further study.

iii) Effects in cattle   Early studies on the effects of growth hormone on growing cattle were reported by Brumby (1959). Since that time Sejrsen et al. (1983) and Bauman (1984) have reported effects of exogenous bovine growth hormone on growth and body composition in young dairy cattle.

Long-term treatment (12 to 21 weeks) with exogenous growth hormone increased growth rate by about 10% in all studies. Preliminary results reported by Bauman (1984) indicated a marked improvement in the efficiency of food utilisation together with greater protein and lower fat contents of carcases of treated than control calves.

There is now limited data on metabolic/physiological effects of exogenous growth hormone in growing cattle. Eisemann et al. (1984a) measured

effects of daily injections, over 12 days, of bovine growth hormone on plasma concentrations and whole body irreversible losses of non-esterified fatty acids in growing Hereford heifers and Eisemann et al. (1984b) reported data on nitrogen retention in the same study. In this study there was no significant effect on growth rate but plasma concentrations of and whole body irreversible losses for non-esterified fatty acids as well as nitrogen retention were significantly increased by treatment. Similar observations on nitrogen retention and growth rate had been reported previously by Car et al. (1967) for Simmental steers and by Moseley et al. (1982) for Holstein steers.

More recently Leenanuruksa et al. (1985) examined the effects of exogenous growth hormone on arterial concentrations and arterio-venous differences across leg muscle tissue of metabolites together with blood flow to muscle tissue in growing dairy heifers. Arterial concentrations of glucose and 3-OH-butyrate tended to increase and of non-esterified fatty acids increased significantly during growth hormone treatment. A significant increase in blood flow to leg muscle tissue occurred following treatment and marked changes in arterio-venous differences of metabolites were measured. Growth hormone decreased arterio-venous difference for glucose, increased arterio-venous difference for 3-OH-butyrate, caused a change from uptake to output of non-esterified fatty acids and increased lactate release.

Effects of growth hormone on exchanges of amino acids across hind limb muscle tissue have been measured in growing calves (Jois et al. 1985a, 1985b). Treatment with growth hormone did not affect markedly plasma concentrations nor arterio-venous differences of plasma and blood free amino acids but significantly increased arterial concentrations of blood free amino acids. Most interesting effects of growth hormone on arterio-venous differences of peptide-associated amino acids in both plasma and blood were measured. Whereas peptide-associated amino acids in plasma and blood were released from muscle tissue during control (saline) periods, growth hormone either reduced the release or induced an uptake of peptide-associated amino acids.

The results of the above studies on metabolic/physiological effects of growth hormone in growing cattle are consistent with reported changes in body composition, and in some studies growth, induced by treatment with exogenous growth hormone. Overall growth hormone promotes protein accretion and lipolysis and apparently effects growth promotion.

ii) Effects in lambs   Several studies have been conducted to evaluate the effects of growth hormone on growth and carcase characteristics in growing lambs. Wagner and Veenhuizen (1978) reported increased growth (20%), increased protein (25%) and decreased fat (37%) in carcases as well as increased efficiency of feed utilisation (14%) in wether lambs treated twice daily with c 0.19 mg/kg liveweight of ovine growth hormone for approximately 100 days. More recently Muir et al. (1983) reported results of a study in which wether lambs were treated for 56 days with 7 mg (c 0.25 mg/kg/d) ovine growth hormone in a slow-release base (designed to maintain high circulating levels of hormone). In this study growth rates were not affected by treatment but carcase protein (8% increase) carcase fat (9% decrease) contents and efficiency of food utilisation (7% increase) were affected by treatment.

Table 4.

The above results are contradicted by results of several studies conducted in the intervening period. Muir et al. (1983) found that injections of growth hormone resulting in sustained and marked increases in plasma concentrations of the hormone had no effect on wool growth in rapidly-growing lambs. In a series of studies in which purified ovine growth hormone (daily doses of c 10 mg) was administered to Merino sheep over relatively short periods (4 weeks) wool growth was suppressed during administration of growth hormone but showed prolonged acceleration (beyond that measured before treatment with growth hormone) after cessation of treatment (Wheatley et al. 1966; Wallace 1979; Wynn 1982).

The depression in wool growth observed during growth hormone treatment was associated with increased nitrogen retention in the studies of Wheatley et al. (1966) and Wynn (1982). The latter worker interpreted this observation as evidence that growth hormone promoted muscle protein accretion thereby depriving the wool follicle of amino acids essential for wool growth. It was further proposed that the accelerated wool growth occurring after cessation of hormone treatment resulted from increased availability of amino acids from muscle protein breakdown.

In view of the contradictory results it will be necessary for further studies to clarify the influence of exogenous growth hormone on wool growth. It would be of interest to examine the time course of response, in terms of wool growth, by monitoring wool growth throughout a prolonged period of administration of growth hormone. Furthermore, effects of age, breed/strain of sheep as well as nutritional status on wool growth responses to growth hormone should be evaluated.

(c) Effects of growth hormone on milk production

Brumby and Hancock (1955) were amongst the first to report galactopoietic effects of growth hormone in the dairy cow. Although this galactopoietic effect has been studied most extensively in dairy cows (see below) there have been reports that exogenous bovine growth hormone is galactopoietic in sheep (Jordan and Shaffhausen 1954; McDowell and Hart 1983; Hart et al. 1984b) and goats (Mepham et al. 1984). Similarly, "genetically-engineered" porcine growth hormone was shown to increase milk production in lactating sows (Harkins et al. 1985).

In recent years there have been numerous studies on the galactopoietic effects of exogenous growth hormone in the dairy cow. The commercial relevance of increasing milk yield in the cow has no doubt prompted the resurgence of research effort. Broadly, two types of studies have been performed. On one hand short-term studies lasting a few days or weeks have been performed using pituitary-derived (Bines et al. 1980; Peel et al. 1981, 1982a, 1983; Fronk et al. 1983; McDowell et al. 1983) or "genetically-engineered" (Bauman et al. 1982) bovine growth hormone. On the other hand, there have been a limited number of studies where growth hormone has been administered for periods varying from 10-27 weeks (Brumby and Hancock 1955; Machlin 1973; Eppard and Bauman 1984; Peel et al. 1985). A summary of effects of growth hormone on milk yield and composition is given in Table 5.

Table 5. Summary of effects of exogenous bovine growth hormone on milk yield, milk composition, body weight and feed intake of lactating dairy cows

	Short-term treatment	Long-term treatment
Milk yield	10-40% increase	20-50% increase
Milk fat content	small increase	no change
Milk lactose content	no change	no change
Milk protein content	no change or small decrease	no change
Feed intake	no change or small decrease	increase
Liveweight	decrease	no change

Limited supplies of growth hormone have restricted the number of long-term studies. In recent years the substantial interest in use of growth hormone has prompted several commercial companies to promote research into long-term effects of exogenous growth hormone in the dairy cow. A number of these studies currently are in progress.

i)   <u>Effects on milk yield</u>   Without exception, in both short- and long-term studies exogenous growth hormone has increased milk yields of treated cows. Most studies have been performed in cattle after peak lactation has been attained. In these studies responses varying from c 10-40% increases in yield have been recorded – the response being approximately linear between 0-60 IU hormone/day (see Eppard et al. 1985).

Reports of a limited number of studies in cows treated with exogenous growth hormone at or prior to peak lactation have shown a positive effect on milk yield but the increase, expressed as a proportion of milk yield for control observations, has been less (< 10%) than for cows treated after peak lactation (McDowell et al. 1983; Richard et al. 1985).

ii)   <u>Effects on milk composition</u>   The effects of exogenous growth hormone have varied. McCutcheon and Bauman (1985) expressed the view that where cows are in positive energy and nitrogen balance, protein and fat contents of milk are not influenced by treatment. On the other hand, when treated cows are in negative energy balance fat content increases and protein content decreases.

The latter response most commonly has been observed in short-term studies where rapid and often marked increased in milk production occur, after initiation of treatment, without adjustment in feed intake (see below). In this connection, McDowell et al. (1985a) recorded that lactose content, decreased significantly, protein content tended to decrease and fat content tended to increase in milk of cows treated with growth hormone at peak lactation. These cows were in negative energy balance which was exaggerated by growth hormone treatment.

There is evidence to show that plasma non-esterified fatty acids released in response to growth hormone are utilised for milk fat synthesis. In this connection Bitman et al. (1984) recorded decreased proportions of short (C6:0-10:0) and medium (C12:0-16:0) chain and increased proportions of

long chain (C18:1) fatty acids in milk fat of cows treated with growth hormone. Similar changes have been observed in other studies with cows and sheep (J.M. Gooden and P. Niumsup, personal communication). '

iii) Effects on feed intake   In short-term studies increased milk production, following treatment with growth hormone, has occurred in the absence of a measured or allowed increase in feed intake (McDowell et al. 1983, 1984; see also McCutcheon and Bauman 1985). Under these conditions treatment induces a loss of body weight and an accompanying alteration in the partition of nutrients (see below).

Effects of treatment with growth hormone on feed intakes of cows treated for long periods with growth hormone have only been reported from two studies. Both Bauman (1984) and Peel et al. (1985) reported that feed intakes of cows treated for long periods gradually increased such that body weights of treated cows were similar to those of control cows, in spite of maintenance of high milk yields by treated cows.

The latter is significant in view of concern over the effects of treatment with exogenous growth hormone on milk production in subsequent lactations. Although the data is extremely limited, McCutcheon and Bauman (1985) cited evidence which indicated no detrimental effects of long-term treatment with growth hormone on subsequent lactation. It can be expected that further information will become available on this aspect in the near future. Indeed such information must be obtained to satisfy concerns with regard to animal health aspects.

iv)   Metabolic actions of growth hormone   Bauman and Currie (1980) proposed that hormones such as growth hormone act to regulate metabolic adaptat ions such as those required to support nutrient requirements during for example pregnancy and lactation. They considered that these metabolic adaptations were the result of the actions of homeorhetic hormones (such as growth hormone) which act to effect partition of nutrients without interferring with homeostatic balance.

To date, evidence obtained from studies where exogenous growth hormone has been administered to farm animals generally and dairy cows specifically suggests that growth hormone acts as a metabolic regulator or homeorhetic hormone. Amongst the important actions of the hormone are the lipolytic and diabetogenic effects (see Hart 1983).

Results of short-term studies have indicated that growth hormone does not alter digestibility of dry matter energy or nitrogen and there are data to show that growth hormone does not change maintenance requirements or part ial efficiency of milk synthesis. Thus it appears that growth hormone improves efficiency of milk production by diluting maintenance costs (see McCutcheon and Bauman 1985).

Effects of growth hormone on fat metabolism in the dairy cow were reported by Williams et al. (1963) who showed that treatment of cows increased plasma concentrations of non-esterified fatty acids. Similarly Kronfeld (1965) reported increased plasma concentrations of non-esterified fatty acids in lactating cows treated with growth hormone. The latter worker also noted increased plasma ketone bodies and decreased incorporation of acetate into milk fat, similar to that observed in spontaneous ketosis,

leading to the suggestion that growth hormone may play a role in the patho-
genesis of bovine ketosis.

There are several recent reports which indicate that treatment of
lactating cows with exogenous growth hormone increases plasma concentrations
of non-esterified fatty acids (Peel et al. 1981, 1983; McDowell et al.
1983, 1984) and the whole body irreversible loss of non-esterified fatty
acids (Peel et al. 1982b; McDowell et al. 1983, 1985a). Recently,
McCutcheon and Bauman (1985) discussed this lipolytic effect of growth
hormone and considered that the lipolytic effects of the hormone are
expressed when cows are in negative but not positive energy balance.

It is of interest to note that plasma concentrations of and whole body
irreversible losses of non-esterified fatty acids were not increased in cows
treated with growth hormone at peak lactation (McDowell et al. 1983, 1985a).
This observation is difficult to explain in the light of other data but may
have been due to the fact that the cows in this study were losing body
weight at the time treatment commenced and were thus unable to respond to
the lipolytic effects of the hormone.

In general terms, it appears that lactating cows treated with growth
hormone respond by reducing accretion of fat to preserve supplies of glucose
(and probably amino acids) required to support increased milk synthesis.
This suggestion is supported by the recent observation in studies with mid-
lactating sheep that whole body oxidation of non-esterified fatty acids, but
not glucose, increased in response to exogenous growth hormone (McDowell et
al. 1985b).

Results of studies by McDowell et al. (1983, 1985a) indicate that the
metabolic actions of growth hormone differ depending on stage of lactation.
Whole body irreversible losses of key metabolites were measured in cows at
peak lactation and later during mid-lactation in cows treated with saline or
growth hormone. At peak lactation exogenous growth hormone significantly
increased irreversible loss of glucose, consistently but not significantly
increased irreversible losses of urea and acetate and in most cases (4/5)
substantially reduced the irreversible loss of non-esterified fatty acids.
Irreversible losses at mid-lactation were increased for non-esterified fatty
acids and acetate, decreased for urea and unchanged for glucose. These
differential effects of exogenous growth hormone presumably reflected
changes in energy balance, and body tissue mobilisation/accretion at the
different stages of lactation.

In a recent study with lactating ewes Niumsup et al. (1985) showed
that exogenous growth hormone had marked effects on arterial plasma tri-
glyceride concentrations. Total plasma concentrations of triglyceride and
concentrations of very low density lipoproteins were significantly reduced
during treatment with growth hormone. This suggests that growth hormone
exerts an effect on the synthesis and/or release of triglycerides from the
liver.

Although available evidence supports the concept that growth hormone
alters the partition of nutrients/nutrient utilisation in the lactating cow,
direct evidence was lacking until recently. McDowell et al. (1984) used
mid-lactating cows surgically-prepared to allow simultaneous collection of
arterial blood and venous blood draining leg muscle and mammary tissues to

study effects of growth hormone on nutrient partition. During treatment with growth hormone mammary arterio-venous concentration differences for non-esterified fatty acids increased dramatically and there was a marked decrease in arterio-venous difference of glucose across leg muscle tissue. These data confirm the effects of growth hormone on nutrient partition/ utilisation in the body.

In the above animals marked effects of growth hormone on exchanges of amino acids across muscle and mammary tissues were recorded by Jois et al. (1984, 1985b). Arterio-venous differences across both tissues for most plasma free amino acids were not affected by growth hormone. There were however large changes for exchanges of peptide-associated amino acids. Whereas most peptide-associated amino acids were released from muscle and mammary tissues during control periods, growth hormone either reduced the output or resulted in an uptake of peptide-associated amino acids. The significance of this observation remains unclear at present. Even so it appears that growth hormone may influence the rate of protein breakdown in tissues thereby affecting availability of amino acids for tissue metabolism.

v) <u>Effect of growth hormone on mammary growth</u>   Bauman (1984) discussed the limited data on the effects of exogenous growth hormone on mammary growth. In heifers treated with growth hormone for 14 weeks, commencing shortly before puberty, there was a substantial increase in the proportion of mammary parenchyma by comparison with untreated (control) heifers. Similar observations were made in a study performed with growing lambs (Johnsson 1984).

The above very encouraging results require extension to test effects of subsequent lactational performance of growth hormone treatment during the period around puberty. Several studies currently are in progress but results are pending.

Although it has been suggested that growth hormone exerts local effects on the mammary glands of lactating animals (Eppard and Bauman 1984) available data do not support this suggestion - at least in situations where the hormone is administered over short periods. In this connection, McDowell and Hart (1984) reported results of studies where continuous infusions of growth hormone into the mammary arteries of sheep and goats failed to increase milk production. The results of this <u>in</u> <u>vivo</u> study are consistent with the failure of growth hormone to stimulate synthesis of milk constituents by cultured mammary tissue of ruminants (Skarda et al. 1982; Gertler et al. 1983).

Notwithstanding the above results, it is possible that long-term treatment of lactating ruminants with growth hormone increases numbers of mammary cells and/or the activity of cells.

vi) <u>Implications of use of growth hormone in dairy cows</u>   Kalter (1984) discussed the commercial viability of using "genetically-engineered" growth hormone to improve milk yield in dairy herds in North America. It was concluded that, at current market prices for milk, growth hormone is a viable commercial proposition - even allowing for increased costs of rations and costs of purchase of the hormone.

More recently Mix (1985) presented an appraisal of the impact of the use of growth hormone to increase milk production in North American herds.

Amongst the predictions made were that the hormone would be available for use by 1988, rate of adoption would increase slowly at first then rapidly, improved production stemming from use of growth hormone would be slightly higher than that due to improved breeding/management (52:48) and numbers of farms and cows would decline steadily. Projected changes are shown in Table 6.

Table 6.   Some projected effects of using growth hormone in North American dairy herds (adapted from Mix 1985)

	Year				
	1984	1988	1990	1995	2000
Milk/cow/annum (kg x 10^{-3})					
– without GH*	5.67	6.06	6.29	6.86	7.43
– with GH	5.67	6.24	7.23	8.49	9.28
Proportion of herds using GH (%)	–	20	60	95	100
Dairy cow numbers (x 10^{-6})	11.1	–	9.1	–	7.8

*Assumes annual increase of 114 kg/annum due to improved breeding and management.

(d) Delivery systems for growth hormone

To date responses to exogenous growth hormone have been monitored in animals given the hormone on a daily basis by injection or infusion. Results of studies in lactating cows have shown that responses to subcutaneous injections are essentially the same as those to intermittent intravenous infusions and continuous subcutaneous infusion (Fronk et al. 1983). Similar observations have been made in lactating sheep given continuous intravenous infusions or daily subcutaneous injections of growth hormone (G.H. McDowell and I.C. Hart, unpublished data). In growing cattle, Moseley et al. (1982) recorded similar effects on nitrogen retention of steers given continuous or pulsatile intravenous infusions of growth hormone.

To date no details have been published of simple delivery systems capable of obviating the need for daily administration of growth hormone. It is understood that several groups are working to develop such a device.

III.   GROWTH HORMONE FRAGMENTS

Lewis et al. (1980, 1984) showed that human growth hormone is not a single molecular species but appears to comprise a heterogeneous group of peptides exerting different biological activities. This observation led Hart et al. (1984a) to fractionate bovine pituitary growth hormone on anion exchange resin. Four fractions obtained were examined for biological activities and the results of analyses are shown in Table 7.

Table 7. Biological and immunological activities of fractions of- bovine pituitary growth hormone obtained by separation on anion-exchange resin (adapted from Hart et al. 1984)

	Fraction			
	A	B	C	D
Immunological activity (U/mg)	0.25	0.97	1.00	0.29
Growth promotion (U/mg)*	low	0.86	1.29	1.51
Lipolytic activity[†]	+	+	+	+
Diabetogenic activity[§]	−	+	+	−

* rat tibia test;   † release of glycerol from rat epididymal fat; § rate of glucose transport into epididymal fat of hypophysectomised rats and intravenous insulin tolerance in goats.

These observations raise the possibility that modified forms or fractions of bovine pituitary growth hormone might be exploited commercially. Use of the recent recombinant DNA techniques may allow production of forms of growth hormone capable of for example promoting growth without exerting lipolytic or diabetogenic activity (see Hart and Johnsson 1985). To date there is no published data on use of modified forms or fractions of growth hormone to alter productivity of farm animals.

IV.   CONTROL OF GROWTH HORMONE RELEASE

It is now apparent that the principal neuro-endocrine factors controlling the release of growth hormone are somatocrinin or growth hormone releasing factor (GRF) and somatostatin or somatotrophin-release inhibiting factor (SRIF) - see Fig. 1.

(a) Growth hormone releasing factor

The presence of a specific releasing factor for growth hormone had been suspected for many years but it was only recently that such a factor was isolated from human tissue (Guillemin et al. 1982; Rivier et al. 1982). Subsequently GRF has been isolated from hypothalamic tissue of pigs (Bohlen et al. 1983) and cattle (Esch et al. 1983).

Growth hormone releasing factor specifically promotes secretion of growth hormone. Release of growth hormone following injection of synthetic human GRF' has been demonstrated in a range of species including cattle (Plouzek et al. 1983; Moseley et al. 1984, 1985), sheep (Baile et al. 1983, 1985; Hart et al. 1985a,1985b) and goats (Hart et al. 1984a).

Since isolation of the natural human GRF and demonstration that it contains 44 amino acid residues (Guillemin et al. 1982) the peptide has been synthesised artificially. The large molecular size, and thus the relative difficulty encountered in synthesizing the peptide, has led researchers to investigate the minimum amino acid sequence capable of eliciting an increase in plasma concentrations of growth hormone.

External/Internal Stimuli

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│  HYPOTHALAMUS   │
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Somatostatin   Growth hormone
   (SRIF)   releasing factor
        \   (GRF, Somatocrinin)
         - ve   /
                                    + ve

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┌──────────────────────┐      + ve    (oestrogen
│  ANTERIOR PITUITARY   │   ◄───────   (androgen
└──────────────────────┘
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Growth Hormone

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┌──────────────────────┐              (thyroxine
│ LIVER AND SOME OTHER  │   ◄───────   (insulin
│      TISSUES          │
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Somatomedins

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│ ADIPOSE TISSUE   │  │    MUSCLE TISSUE      │  │   SKELETAL TISSUE     │
│   (Glucose       │  │  Synthesis of RNA, DNA│  │ Synthesis of RNA, DNA │
│  utilisation)    │  │    and protein        │  │  bone and cartilage   │
│                  │  │                       │  │       growth          │
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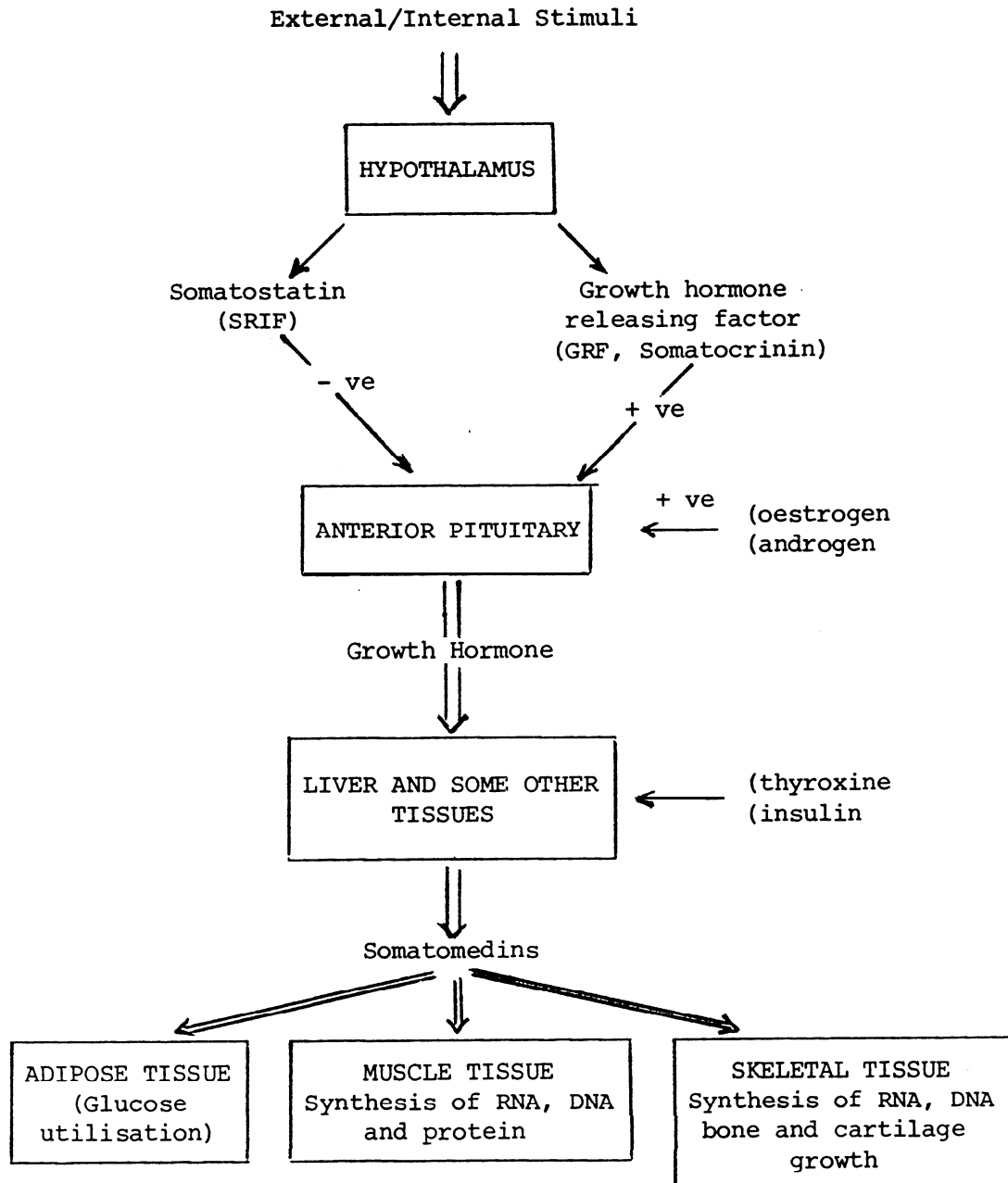
Fig. 1. Simplified scheme depicting control of release of growth
         hormone and interaction with some other hormones influencing
         growth in animals (adapted from Riis 1977; Spencer 1985a).

In fed and fasted sheep Hart et al. (1985a) found no differences in release of growth hormone following intravenous injection of synthetic human GRF containing either 29, **40** or **44** amino acid residues or rat hypothalamic GRF containing 29 amino acids. Similar results were obtained in cattle by McCutcheon et al. (1984) who showed that synthetic human GRF containing **24** or 29 amino acids elicited release of growth hormone. However, GRF 1-29 elicited a greater release of growth hormone than GRF 1-24.

The efficacy of using even smaller peptides to elicit release of growth hormone has been examined. Hart et al. (1984b) failed to measure release of growth hormone in vivo in goats injected intravenously with the synthetic penta-peptide Try-D-Trp-Ala-Trp-D-Phe-NH$_2$ but recorded release of growth hormone from cultured sheep pituitary cells. A synthetic hexapeptide (His-D-Trp-Ala-Trp-D-Phe-Lys-NH$_2$) was tested for effects on release of growth hormone in several species by Bowers et al. (1984). Intravenous injection of the hexapeptide increased plasma growth hormone in lambs and calves. In chickens given the hexapeptide by intra-peritoneal injection plasma growth hormone increased when plasma concentrations were low prior, to injection of the hexapeptide.

i)   Effect of GRF on animal production   There are few reports on the effects of GRF administration on productivity of animals (see Baile et al. 1985). In one of the few studies Hart et al. (1985b) found that synthetic human GRF 1-44 increased milk production and milk fat content in lactating ewes given intravenous injections of **0.6** g/kg GRF at intervals of two hours over four days. The changes in milk production and composition were similar to those obtained following intravenous injection of 15 µg/kg bovine growth hormone every two hours (see Table 8).

Table 8.   Effect of intravenous injection of vehicle, bovine growth hormone (bGH, 15 µg/kg) or human growth hormone releasing factor (hGRF44, **0.6** µg/kg) on milk yield and composition, plasma growth hormone and plasma metabolites in lactating ewes (adapted from Hart et al. 1985b)

	Injected intravenously with		
	vehicle	bGH	hGRF
Plasma growth hormone (ng/ml)	5.7	14.5*	12.3*
Plasma glucose (mM)	4.1	4.9*	4.6*
Plasma urea (mM)	5.2	4.5*	5.0
Milk production (relative)	100	131*	127*
Milk fat (g/kg)	286	34.8*	28.6*

*Significantly different from control value.

The above results suggest that GRF or active smaller peptides may be useful for improving animal productivity. Amongst the issues to be resolved is the delivery of the peptide (whether continuous release or pulsatile release) as it appears possible that continuous release of the peptide may deplete pituitary stores of growth hormone and/or induce a non-responsive state in the pituitary.

(b)   Somatostatin

Somatostatin was identified initially as growth hormone release inhibiting factor (SRIF) (Krulich et al. 1972). As well as inhibiting release of growth hormone, somatostatin inhibits release of at least insulin and thyroid stimulating hormone (see Spencer 1985b) thereby influencing release of somatomedins (see below) and growth.

i)   Effect of blocking the inhibitory effects of somatostatin on productivity of farm animals.   Active immunisation against somatostatin has been used to block the inhibitory effects of somatostatin on release of growth hormone and other hormones. Results of several studies on effects of active immunisation against somatostatin are summarised below.

The first report on effects of active immunisation against somatostatin on growth was that of Spencer and Williamson (1981). In this study twin lambs of the St. Kilda breed were paired such that one twin was immunised and the other served as a control. Lambs immunised against somatostatin grew at 176% of the rate of control lambs.

In a subsequent and more detailed study Spencer and colleagues (Spencer et al. 1983a, 1983b) immunised Dutch moorsheep, and observed increased weight gain and bone growth, improved efficiency of feed conversion but no change in the proportions of major carcase components.

Similar studies have been conducted with lambs of breeds used commercially for production of meat (Bass et al. 1983; Chaplin et al. 1984; Spencer 1985b). In most of these studies changes in growth rate and efficiency of feed utilisation were less marked than in the earlier studies with lambs of less conventional breeds. None-the-less there were indications of improved productivity following immunisation with somatostatin. The results of the study by Bass et al. (1983) suggest that nutrition should be adequate to support a growth response.

Spencer (1985b) discussed unpublished results on effects of immunisation against somatostatin on milk production in sheep and goats. Lambs of ewes immunised during pregnancy grew faster than control lambs and lambs actively immunised after birth, suggesting that immunisation of ewes may have increased milk yields. In goats immunised with somatostatin during pregnancy, milk yields during early lactation were higher than for non-immunised (control) goats.

From the above it appears from available information that immunisation against somatostatin may have application for improving productivity of sheep and goats. Spencer (1985b) cited data showing improved productivity cf poultry and pigs immunised against somatostatin.

In spite of the promising indications that performances of farm animals may be improved by immunisation against somatostatin there is sufficient variation in responsiveness to impose the need for further research. Amongst the factors which may be important are the magnitude of the immune response elicited by immunisation and environmental influences (such as nutrition and husbandry practices). In connection with the former it appears that there may be substantial within and between species variation in the nature of the immune response following immunisation (see Spencer

1985b).

ii) <u>Effect of immunisation against somatostatin on endocrine status of
animals</u>   Spencer (1985b) briefly reviewed evidence for changes in
hormone status of animals immunised against somatostatin. Although no
marked effects have been measured on plasma concentrations of growth hor-
mone, thyroid stimulating hormone, thyroid hormones or insulin, it appears
that there may be an effect on the action of insulin. Interestingly, in
many of the studies conducted to date there has been a consistent increase
in plasma somatomedin concentrations following immunisation. This observa-
t ion possibly explains, at least in part, the growth responses recorded
following active immunisation against somatomedin (see below).

Effects of somatostatin on gut hormones (and effects on gastric empty-
ing and duodenal motility) have been reported, and results of preliminary
data suggest increased retention time of digesta in the gastro-intestinal
tract after immunisation against somatostatin (see Spencer 1985b). The
latter observation may correlate with increased efficiency of feed utilisa-
tion in some studies with immunised animals.

(c) <u>Control of release of hypothalamic hormones</u>

Several neuropeptides and pharmacological agents affect the release of
the hypothalamic hormones GRF and somatostatin and so the release of growth
hormone. It appears that the balance between GRF and somatostatin is regu-
lated by interactions of several neuropeptides and biogenic amines. Baile
et al. (1985) outlined effects of a number of these compounds - see Table 9.

Although little is known of the overall control of growth hormone
secret ion at the hypothalamic level, much current research is directed at
understanding control mechanisms. In due course it appears possible that
compounds will be identified which may prove useful for use in animal
production systems.

Table 9.   Compounds found to stimulate or inhibit secretion of somatostatin
(SRIF) and growth hormone releasing factor (GRF) - see Baile et
al. 1985)

Hypothalamic Hormone	Action	Compound
SRIF	stimulation	dopamine, noradrenaline, glutamate, aspartate, picrotoxin[+], substance P, neurotensin
	inhibition	chlorpromazine[x], pimozide[x], gamma amino butyric acid, vasoactive intestinal peptide
GRF	stimulation	clonidine*, substance P, acetyl-choline, dynorphin 1-17, dopamine, noradrenaline, serotonin
	inhibition	phenoxybenzamine[ø], yohimbine[ø]

+ antagonist of gamma amino butyric acid; x blocks dopamine receptors;
ø α-adrenergic antagonist; * α-adrenergic agonist.

V. SOMATOMEDINS

The somatomedins (insulin like growth factors, lgF's) are produced in several body tissues of which the liver is the most important. There is now substantial evidence that the somatomedins lgF-I and lgF-II play important roles in regulating growth in a range of species including farm animals (see Riis 1977; Hart and Johnsson 1985; Spencer 1985a). Secretion of the somatomedins has a marked, but probably not absolute, dependence on growth hormone (see Fig. 1).

Partially-purified preparations of somatomedins have been found to increase growth in mutant dwarf mice (van Buul and van den Brande 1979). Recently, Schoenle et al. (1982) showed that purified lgF-I and lgF-II increased body weight, tibial epiphyseal width and incorporation of 3H-thymidine into DNA of costal cartilage in hypophysectomised rats. In this latter study lgF-I was much more potent, on a weight basis, than lgF-II.

Although there is now convincing evidence that many of the anabolic actions of growth hormone are mediated by the somatomedins, growth hormone apparently exerts some direct effects on tissues. Furthermore, interactions between growth hormone and somatomedins and effects on growth probably involve other hormones (see Hart and Johnsson 1985; Spencer 1985a).

(a) Somatomedins in farm animals

There are strong indications that growth rate in farm animals is correlated with plasma concentration of somatomedins. High plasma concentrations have been reported in rapidly-growing pigs (Lund-Larson and Bakke 1975). Similarly in young cattle (Lund-Larsen et al. 1977; Ringberg 1979; Falconer et al. 1980) and sheep (Olsen et al. 1981; Wangsness et al. 1981) growth rate is correlated positively with plasma somatomedins.

To date there are no data on effects of exogenous somatomedins on growth in farm animals. It is expected that recombinant-DNA techniques will allow production of sufficient "genetically-engineered" material to allow testing of effects of exogenous hormone in the near future.

VI. STEROIDS AND RELATED COMPOUNDS

Several sex steroids and related compounds are used as growth promoters (sometimes referred to as anabolics) in animal production systems throughout the World (see Table 10). Although most widely used in cattle production systems a number are known to exert beneficial effects on growth in sheep and goats (Buttery 1985; Roche and Quirke 1985) and evidence is available suggesting beneficial effects in pigs (Roche and Quirke 1985).

Often, combinations of active compounds are used. Generally, anabolics are administered as subcutaneous implants in the ear — trimmed from body of the animal at slaughter. Some anabolics are administered as compressed pellets and others as silastic implants impregnated with active compound (eg. "Compudose"). Compressed pellets have effective active periods of 90-120 days and give high release rates of compound for 30-50 days then release rates gradually decrease to negligible amounts. In contrast, silastic implants provide relatively continuous rates of release of hormone over prolonged periods (200-400 days) — the period depending on

Table 10. Brief details of a number of sex steroid and related compounds used as anabolic agents in cattle in various countries (adapted from Roche and Quirke 1985)

Active Compounds	For use with	Trade Name	Manufacturer
Oestradiol-17β	Steers	Compudose[†]	Elanco Ltd., U.K.
Oestradiol benzoate + progesterone	(Steers	(Synovex-S[†]	Syntex Ltd., U.S.A.
		(Torevex-S	Chanelle Ltd., Ireland
		(M-PO	Upjohn Ltd., U.S.A.
		(Steer-oid	Phillips Roxane, U.S.A.
	(Calves	Synovex-C	Syntex Ltd., U.S.A.
Oestradiol benzoate + testosterone propionate	Heifers and cows	(Synovex-H	Syntex Ltd., U.S.A.
		(Torevex-H	Chanelle Ltd., Ireland
		(F-TO	Upjohn Ltd., U.S.A.
Trenbolone acetate[§]	Steers, heifers, cows	Finaplix	Roussel-Uclaf Ltd., France
Resorcylic acid lactose[§] (zeranol)	Calves, steers	Ralgro[†]	I.M.C. Ltd., U.S.A.
Oestradiol-17β + trenbolone acetate[§]	Steers	Revalor	Roussel-Uclaf Ltd., France

† Registered for use in Australia; § compounds related to sex steroids.

amount of compound in the implant.

(d)   Responses to implantation with anabolics

i)   <u>Responses of cattle</u>   Responses in terms of growth vary depending on the   nature and dose of the anabolic,   the class of animal and environmental factors such as nutrition, husbandry practices, disease etc.   Average responses of 10-15% increases in growth rates have been recorded (Roche   and Quirke 1985) with   responses of as much as 50% under   some   circumstances (Buttery 1985).

Commonly,   improved efficiency of feed conversion for growth increased nitrogen   retention,   increased   proportion of lean meat and decreased   fat contents of carcases are observed in treated animals.   No adverse changes in meat   quality have resulted from implantation of cattle with anabolics   (see Roche and Quirke 1985).

It appears that different anabolics should be used for best results in di f ferent   classes of cattle.   Guidelines for appropriate preparations are provided   in Table 10.   Responses are often greater and more consistent   in yearling and older cattle than in calves.

A potential   problem with use of anabolics in steers is induction of mounting (bulling) behaviour (Heitzman 1985;   Roche and Quirke 1985).   The latter authors commented that the incidence of this behaviour varies from 2-5% in feed lots in North America.   Such behaviour reduces growth performance of both mounting and mounted steers and is undesirable.   It appears that the incidence of this undesirable side-effect of implantation with anabolics is higher when oestrogen-containing implants are used.

ii)   <u>Responses of sheep</u>   There is a limited amount of data to show that growth of sheep increases following implantation with anabolics (see Buttery 1985;   Roche   and Quirke 1985).   Available information suggests that sheep respond in much the same manner as cattle but the relevance of anabolics in sheep production systems appears to be less because of shorter growth phases and   extensive   husbandry   practices.   Optimum dose rates for sheep are not well defined.

iii)   <u>Responses of pigs</u>   Roche and Quirke (1985) reviewed the small amount of data on responses of pigs to anabolics.   Effects of growth and   carcase weights appear to be minimal but improvements in efficiency of feed ut ilisa-tion and lower fat contents (depth) of carcases have been reported.

iv)   <u>Contraindications</u>   Anabolics should not be used in animals which will be retained as breeding stock.   Amongst reported adverse effects are impaired   testicular   development in males,   delayed onset of puberty and reduced   ovulation   rates   in females and premature   closure of   epiphyseal plates of growing animals (see Heitzman 1985;   Roche and Quirke 1985).

(b) Endocrine changes in treated animals

Treatment of animals with anabolics induces complex changes in endo-crine status which presumably cause growth responses. Buttery (1985) and Heitzman (1985) summarised changes occurring in plasma concentrations of hormones in animals treated with anabolics.

Briefly, the androgenic steroids tend to increase oestradiol, decrease corticoids and may decrease thyroid hormones in plasma. These changes result in a relative increase in protein synthesis. Oestrogenic agents appear to exert effects by promoting secretion of growth hormone and possibly insulin.

(c) Residues of anabolics

The potential problem of residues of anabolics in carcases of treated animals is of substantial concern from a health viewpoint. Stringent registration procedures are imposed before anabolics can be used in the field but concern exists over failure to comply with regulations, for example, failure to withhold stock from slaughter for appropriate periods after treatment. Safety aspects of the use of anabolics to manipulate growth in farm animals have been discussed in some detail by Buttery (1985) and Heitzman (1985).

VII. β-AGONISTS

Buttery (1985) summarised the potential for use of β-agonists in animal production. Briefly, it is known that catecholamines regulate physiological processes by interacting with receptors (denoted $\alpha_1, \alpha_2, \beta_1$ and β_2) bound to cell membranes. Stimulation of B-receptors stimulates lipolysis and fractional synthetic rate of protein. The recent demonstration that compounds unrelated to the catecholamines stimulate B-receptors offers a means of controlling growth of animals using so-called B-agonists.

Two such compounds − clenbuterol and fenterol − both β_2-adrenergic agonists, increase liveweight gain and hypertrophy of muscle in rats, and apparently exert similar effects in sheep and cattle. Buttery (1985) cited evidence for: decreased fat and increased muscle tissue in cattle and increased efficiency of feed utilisation in sheep treated with clenbuterol.

Effects such as those above are of considerable interest. There is much research, but as yet little published information, on use of B-agonists for improving growth, feed conversion efficiency and carcase composition. In due course information relevant to public health aspects must be acquired as there is no information at present (Heitzman 1985).

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