Animal Nutrition and Metabolism Group Symposium on 'Nutrient regulation of cell proliferation and death'

Nutritional and hormonal regulation of hair follicle growth and development

Hugh Galbraith

Department of Agriculture, University of Aberdeen, 581 King Street, Aberdeen AB24 5UA, UK

Hair follicles are complex and dynamic structures which are an important component of the integument in mammals. They vary in nature so that the hair they produce has a number of different functions. These include the formation of a physical barrier against the external environment, the provision of thermal insulation and sensory perception, the dispersal of scents from follicular glands and inter-animal recognition and display. The present review will focus principally on factors regulating development and growth of pelage hairs which form the coat of wool, hair or fur of animals. It will include information on the structure of the hair follicle and factors controlling (a) its development in the embryo and neonate and (b) postnatal follicular activity and the hair growth cycle. The review will conclude with a brief consideration of major nutritional influences on hair follicle activity and growth. A wide range of endocrine, paracrine and autocrine influences, in addition to those which are nutritional in origin, have been implicated in the control of hair follicle activity. Aspects of these have been the focus of a number of recent reviews (for example, see Rogers *et al.* 1989; Goldsmith, 1991; Messenger, 1993; van Neste & Randall, 1996).

Embryonic development

Follicle development and its control by extrinsic and intrinsic factors

The first hair follicles to form in the prenatal skin are the primary follicles, usually towards the end of the first trimester of pregnancy. The pattern of development frequently commences at the crown of the head and proceeds wave-like towards the caudal region. Secondary follicles develop thereafter, in close association with the primary follicles (Hardy, 1992). Hair follicles are formed from epidermal and dermal tissues which are derived from ectodermal and mesenchymal cells respectively (Holbrook, 1991). At the onset of folliculogenesis, mesenchymal cells condense beneath the epidermal hair germ and release a signal (the 'first dermal message') which stimulates the epidermal cells to form down-growths which develop to form the bulbous hair peg. A feature of this structure is the localization of the dermal papilla at the base of, and surrounded by, epidermal cells of the developing follicle, an event influenced by a class-specific epidermal message. Subsequent development in the primary follicle gives rise to the *arrector pili* muscle, the sebaceous and apocrine glands and the hair canal, and in the secondary follicle, the sebaceous gland and hair canal only. A second dermal signal is transmitted by the dermal papilla to the adjacent epidermal cells of the hair follicle matrix. This signal is considered to stimulate the production of a follicle which has region-specific function and properties (Messenger, 1993).

The close physical proximity of the cells of the dermal papilla and the epidermal cells of the 'hair matrix' is important in determining both physical size and subsequent growth characteristics of the follicle. The epidermal cells of the matrix region are arranged concentrically so that, on division, the daughter cells of those most centrally positioned differentiate and give rise to the medulla (where present), the cortex and cuticle layers, while those arranged peripherally produce the inner and outer root sheaths.

The developmental, mitotic and synthetic activities of hair follicles prepartum give rise to the hair fibres present at birth. Current evidence suggests that follicle numbers are essentially maintained throughout life with no production of new follicles in the adult animal.

The precise molecular signals and mechanisms associated with the control of embryonic hair follicle development are poorly understood. Previous studies have shown that thyroid hormones are essential for the development of

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secondary wool follicles of sheep (Ferguson *et al.* 1956). More recent interest has focused on measurements of the response of embryonic or neonatal tissue to the addition of growth factors and in determining the presence of growth factors and growth factor receptors by techniques such as *in situ* hybridization, competitive ligand-binding assays and immunohistochemistry (Messenger, 1993). For example, epidermal growth factor and transforming growth factor-α, which binds to the same receptor as epidermal growth factor, have been shown to inhibit hair follicle development in newborn mice. The presence of epidermal growth factor receptor expression has been demonstrated in developing rat and human skin and subsequently in the hair follicle bulb but not in the dermal papilla. Transcripts for members of the transforming growth factor-β family and bone morphogenic proteins-2 and -4 have also been identified in different locations in hair follicles. Retinol or retinyl acetate (see Hardy, 1992) when added to cultured embryonic mouse skin has also been shown to alter follicle development and expression of genes which influence differentiation at certain stages in follicle development. The extent to which regulators such as epidermal growth factor, retinoids or bone morphogenic protein-4 act as providers of essential dermal and epidermal messages remains to be confirmed.

The dermal papilla

The dermal papilla has an essential role in the control of activity in the established hair follicle. It is formed during embryonic development from a stable population of specialized fibroblasts. These do not display mitotic activity *in vivo* but undergo changes in cytoplasmic volume and components in the extracellular matrix. Associated with the dermal papilla are extracellular proteoglycan macromolecules including heparan sulfate and chondroitin sulfate proteoglycans (Goetinck & Winterbottom, 1991). These proteoglycans are major components of the basement membrane which separates the dermal papilla and epidermal matrix of the hair follicle. Certain growth factors may bind to proteoglycans which act as low-affinity receptors, preserving the growth factors from degradation and assisting binding to high-affinity receptors (Bond *et al.* 1996). The basement membrane has been considered to be largely continuous, although gaps have been identified by electron microscopy during development. It appears that direct contact between dermal and epidermal cells is not required thereafter, where the papilla interacts with an established follicular epidermis (Oliver & Johoda, 1989). Using cell and tissue recombination techniques, and the adult rat vibrissa follicle, these workers also demonstrated the essential role of the dermal papilla in regulating postnatal epidermal differentiation and hair follicle growth.

The hair follicle growth cycle

The follicle cycle and control by extrinsic factors

A major property of the postnatal follicle is the cyclical nature of hair growth, with every follicle proceeding from an active anagen phase through regression and shortening

(catagen) to the resting (telogen) phase. Important features of the anagen phase are the division of cells in the bulb and matrix, with daughter cells moving upwards towards the skin surface and differentiating to form the concentric layers of the hair shaft, the inner root sheath and the outer root sheath (Ebling *et al.* 1991). Mechanisms controlling the allocation of cells to the different structural components of the follicle have not been established, although a reaction–diffusion system involving the release of unidentified morphogens from the dermal papilla which interact with epidermal secretions, has been proposed (Nagorcka & Mooney, 1982). Orwin (1989), in contrast, has also suggested that specific regions of the bulb may give rise to specific cells lines and that cell division and differentiation are associated activities. The processes involved in hair production during anagen have been well characterized. In sheep wool, for example, seven zones have been identified (Fig. 1) which describe the changes occurring in hair follicle cells as they migrate from the bulb region to the skin surface (Orwin, 1989). Zone A describes
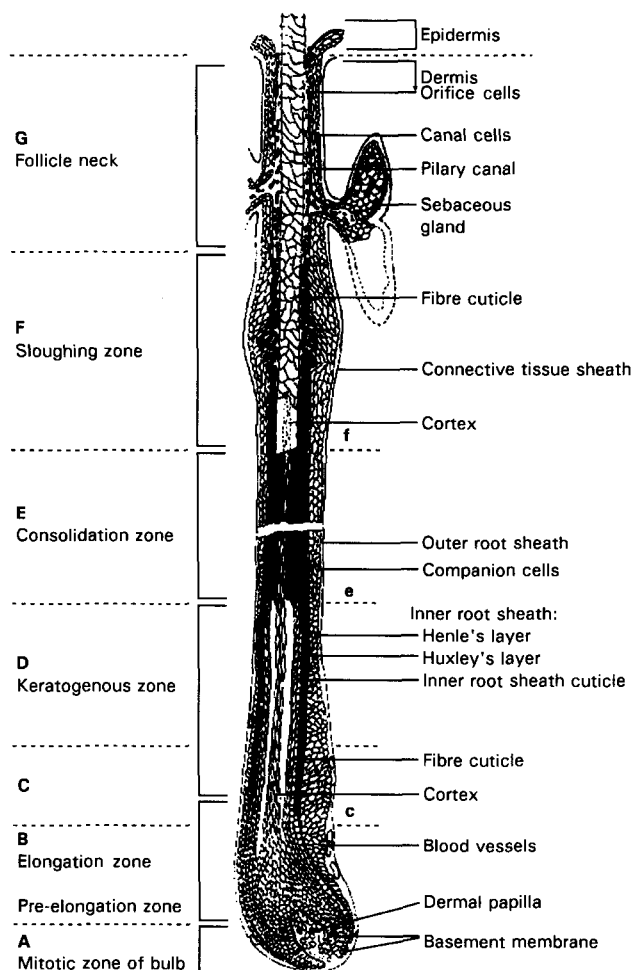

Fig. 1. Diagram of a non-medullated anagen wool follicle showing the changes occurring in follicle cells as they migrate from the bulb region to form the mature hair fibre at the skin surface. c, Henle's layer hardened; e, cortex histochemically keratinized; f, cortex ultrastructurally keratinized. Not all cortical cells are shown. The approximate dimensions are 2·5 mm long × 0·1 mm wide. (Adapted from Orwin, 1989; with permission from Chapman and Hall.)

the area of proliferation, above which cells undergo differentiation, elongation and keratinization (zones B, C and D). Zone E is characterized by cross-linking, stabilization and dehydration of the cortex. Degradation of the inner root sheath with sloughing into the piliary canal occurs in zone F. Zone G includes the piliary canal which terminates at the skin surface. The rate of growth of a wool fibre during anagen is a function of the total number of cells present in the bulb, their rate of division and the proportion and eventual size, after keratinization, of cells which produce fibre, or inner root sheath (Hynd, 1989).

Anagen–catagen–telogen changes and apoptosis

The duration of anagen is genetically determined for each hair type in a given species and is followed by a short catagen phase. This phase involves the cessation of mitosis of matrix cells and the elimination of the epidermal component in the lower transient portion of the hair follicle (Rosenquist & Martin, 1996). The process involves keratinization of the base of the hair to form the brush or club end, which rises to a level just below the sebaceous gland. The dermal papilla also moves higher in the dermis to remain in contact with epidermal cells of the hair germ. Epidermal cells are considered to undergo apoptosis in catagen, with changes in expression of apoptosis-associated genes. For example, expression of the product of the bcl-2 proto-oncogene which inhibits apoptosis has been shown to occur in bulb cells during anagen in Syngeneic C57 B6 adult female mice (Stenn et al. 1994). However, product expression decreased during catagen and disappeared in telogen. These workers also demonstrated continual expression in the dermal papilla which maintains its cell population throughout the complete cycle. Sieberg et al. (1995) have reported the expression of transforming growth factor-β immediately before, and tumour necrosis factor-β during, catagen in the skin of female mice, which may be involved in follicular apoptosis. These authors also suggested that altered levels of transcripts for the transcription factors c-myc, c-myb and c-jun observed in skin may be involved in the signalling or regulation of catagen. No appreciable changes in expression of the p53 gene were observed between anagen and catagen suggesting that p53 is not involved in programmed cell death in the follicle. Interestingly, Yamada et al. (1994) have described programmed cell death in three layers of the inner root sheath in anagen scalp follicles, which they associate with terminal differentiation and keratinization. The fate of these cells is degeneration and sloughing into the piliary canal. In contrast, evidence for apoptosis was not obtained in cells of the cortex and cuticle which require the maintenance of structural integrity to form the hair shaft.

Both epidermal and dermal cells remain essentially inactive in the resting (telogen) phase which persists until a new anagen begins. There is considerable interest in domesticated wool-bearing animals in the timing of shedding or moulting of the club hair, which may constitute a commercially valuable product. This event may occur during telogen, and is frequently associated with the reactivation of the follicle at the beginning of a new

anagen phase of the cycle (Dicks et al. 1995). Such shedding may be inefficiently synchronized and unless the fleece is combed or sheared with clippers, or the animals (e.g. Cashmere goats) are fitted with overcoats, losses of fibre may occur. In other species of animals such as guinea-pigs and man, there is a less orderly 'mosaic' pattern, with both anagen and telogen follicles being present at the same time (Ebling et al. 1991).

Development of new anagen and seasonal control

New anagen is characterized by regeneration of the hair matrix from stem cells resident in the upper permanent part of the follicle under the influence of the dermal papilla (Rosenquist & Martin, 1996). A new hair bulb is formed with epidermal cells once again surrounding the dermal papilla. This regenerated and elongated follicle structure now produces new hair, and the cycle progresses until the onset of the next catagen. Messenger (1993) has reviewed the possible role of stem cells in the renewal of the proliferative component of the hair follicle. Stem cells are normally slow cycling, but under the influence of certain stimuli may undergo cell division to produce transient amplifying cells. These cells have a finite mitotic potential which, when achieved, would be expected to cease division and the follicle to enter catagen.

It is well recognized that the hair growth cycle characteristics vary between species, between different body sites of the same species and between different follicle types on the same body site (Messenger, 1993). These characteristics are influenced by systemic and local control factors. There is particular interest in the development of follicles in hair-fibre-bearing sheep and goats. While uses are made of the coarser fibres produced by primary hair follicles, the fibres with smaller diameter produced by secondary hair follicles are of much greater commercial value. These include fine wools from breeds of sheep such as Merino, and mohair and cashmere by Angora and Cashmere goats respectively. Cashmere production is well recognized to be controlled by daylength, with major hair growth occurring in the time period between the summer and winter solstice and shedding of the fibre taking place in spring (McDonald et al. 1987; Dicks, 1994). Cashmere growth is associated with increasing exposure of individual hair follicles to endogenous melatonin and reductions in prolactin in blood, and moulting and preparation for subsequent anagen associated with increased prolactin concentration and reduced exposure to melatonin. Pinealectomy or administration of the dopaminergic antagonist pimozide maintains blood prolactin concentrations in animals changed to short daylength conditions, and has been shown to prevent or delay the development of the winter coat (Messenger, 1993). Implants of melatonin given in mid-spring to Cashmere goats in New Zealand were shown to stimulate the initiation of pro-anagen and growth of primary follicle in association with reduced blood prolactin concentrations. This result contrasted with the maintenance of predominantly quiescent (telogen) follicles and greater blood prolactin concentration in untreated controls (Nixon et al.

1993). The response in secondary hair follicle activity was variable; an effect attributed to the presence of active secondary follicles in a number of the goats at the beginning of the studies.

Endocrine factors which influence the timing of a spring moult in Cashmere goats were recently investigated by Dicks (1994) under Scottish conditions. Administration of slow-release implants of melatonin (18 mg) on 11 December, 1 February and 1 April advanced the timing of the rise in prolactin concentrations in association with an advanced spring moult and earlier activation of both primary and secondary hair follicles. Similarly, increases or decreases in prolactin concentrations following administration of prolactin or bromocryptine commencing on 5 January produced an earlier or delayed reactivation respectively of secondary hair follicles. Pearson et al. (1993) have also described bromocryptine-induced delays in sheep-wool follicle activity. They also subsequently demonstrated the presence of specific prolactin binding receptors in anagen wool follicles collected in autumn from Wiltshire sheep in New Zealand (Choy et al. 1995). Binding was localized most strongly, although not exclusively, in apocrine sweat glands and in the dermal papillae. These results support the hypothesis that prolactin may act directly on the hair follicle, and in particular the dermal papillae, to produce the effect on the hair growth cycle associated with increases or decreases in prolactin concentrations.

Dicks et al. (1996) recently reported the presence of receptors for insulin-like growth factor (IGF)-I on hair follicles at different stages of the hair growth cycle in both Cashmere and Angora goats, in samples collected between the winter and summer solstice. Specific binding was variously observed in both primary and secondary follicles in the sebaceous gland, inner root sheath, matrix, germinal matrix and dermal papilla. The presence of IGF-1 receptors in telogen follicles is a particularly interesting observation, given their suggested inactive state. These authors also reported the absence of specific receptors for melatonin in hair follicles of the two breeds of goat, which supported previous suggestions that the role of melatonin may be indirect and mediated by, for example, prolactin. Additional evidence to support the presence of direct effects of systemic morphogenic signals has been derived from studies in vitro using isolated hair follicles. For example,

positive growth responses of anagen cashmere (Table 1) and mohair follicles to physiological concentrations of prolactin have been reported under in vitro conditions, with no effects of treatment on follicle viability (Ibraheem et al. 1993, 1994; Galbraith, 1994). These authors also demonstrated a stimulation of hair shaft elongation by melatonin under similar in vitro conditions. This effect would normally require mediation by specific receptors which were not detected in the study of Dicks et al. (1996), and requires further investigation. Physiological concentrations of IGF-I have also been shown to stimulate hair shaft elongation in anagen cashmere follicles under in vitro conditions (Galbraith et al. 1997). This result also suggests that IGF-I may act directly on the hair follicle.

It is of interest to note that the previously described studies have not clarified the basic mechanisms involved in mediating the differences between Cashmere goats, which display a seasonally-regulated and synchronized hair growth cycle, and the genetically-distinct Angora goats, which grow hair continuously.

Rhind & McMillen (1995a,b) have investigated the relationship between the profiles of a number of systemic hormones and patterns of fibre growth and moulting in Cashmere goats of different genotype. They demonstrated the importance of a genetic component in hair growth patterns in that Siberian goats had greater growth rates, fibre yield and diameter and earlier initiation and later cessation of secondary fibre growth compared with Icelandic × Scottish feral crosses. They also showed that mean rates of secondary growth decreased in the period from mid-September to December in both genotypes, and that concentrations of insulin, cortisol, triiodothyronine and thyroxine were greater in winter and those of prolactin, somatotrophin and IGF-I were highest in summer. Growth of secondary fibre in Siberian goats between January and March was associated with higher plasma prolactin and lower insulin concentrations at this time than those in the Icelandic × Scottish feral goats in which there was no secondary fibre growth. Onset of moulting was associated with increasing daylength and concentrations of prolactin in both genotypes. Siberian Cashmere goats were also shown to have consistently greater circulating concentrations of thyroxine than Icelandic × Scottish feral goats. They have subsequently demonstrated that treatment of the

Table 1. Elongation (mm) and number of growing secondary hair follicles (V) over 120 h following exposure to prolactin in vitro (Data from Ibraheem et al. 1994)

(Mean values for five cashmere goats, sixty follicles examined per treatment; collected June–August)

Period of exposure (h)	Prolactin (μg/l)						SED
	0	50	200	400	800	4000	
24: Elongation	0·14[a]	0·15[ac]	0·20[b]	0·17[abc]	0·18[abc]	0·19[bc]	0·013
V	55	57	53	52	55	52	1·76
72: Elongation	0·12[a]	0·13[ab]	0·16[ab]	0·17[b]	0·13[ab]	0·12[a]	0·013
V	43	40	45	41	44	40	1·98
120: Elongation	0·14[ab]	0·14[ab]	0·14[ab]	0·17[b]	0·15[b]	0·10[a]	0·012
V	22	18	23	19	17	21	1·92
Cumulative total elongation	0·76[a]	0·72[ac]	0·84[b]	0·89[b]	0·78[bc]	0·72[ac]	0·024

[a,b,c] Mean values in the same horizontal row with unlike superscript letters were significantly different ($P < 0.05$).

Icelandic-cross goats with the deiodinase (thyroxine deiodinase; *EC* 3.8.1.4) inhibitor methyl-thiouracil reduced the proportion of active secondary follicles during March (Rhind & McMillen, 1996). This response was associated with a delayed moult, although there was no effect on the onset of, or cessation of, cashmere fibre growth. The authors suggested that the reduction in the activity of the hair follicle may have been produced by alterations in the local production of triiodothyronine, with associated secondary changes in profiles of insulin and IGF-I. In other species, thyroid hormones stimulate the onset of hair follicle activity, whereas their removal results in a delay (Messenger, 1993). Oestradiol-17β and thyroxine have also been shown to reduce the length of anagen in rats, although apparently acting differently, with the rate of hair growth being reduced by oestrogen and increased by thyroxine. Thyroid hormones have also been shown to stimulate growth of red deer (*Cervus elaphus*) hair follicles cultured *in vitro* (Thomas *et al.* 1993).

Local mechanisms are considered to control follicular activity of human hair, although there is some evidence of sensitivity to season. For example, Randall & Ebling (1991) in a study conducted at Sheffield, UK, showed that the number of anagen scalp follicles in human males peaked in March and was lowest in September, concomitant with maximum hair shedding loss. Courtois *et al.* (1996) have recently described the results of a long-term study in France in which a maximum number of telogen hairs in scalp hair of some of the adult men studied was present at the beginning of autumn. However, certain other individuals displayed two annual peaks, whereas others exhibited limited telogen and exhibited no recognizable annual cycle. Similarly, variations in the proportion of non-growing hairs have been described for the Angora goat, with values of up to 0·1 present in summer, contrasting with values of up to 0·4 or above in winter conditions, and increasing values recorded in older animals (Margolena, 1974).

Androgens, corticosteroids and the immune system

Androgens such as testosterone, and more importantly 5α-dihydrotestosterone, are well recognized to influence hair growth in man and other mammals (Ebling *et al.* 1991; Messenger, 1993). They may stimulate growth of the beard, but cause baldness of the scalp, indicating the importance of body site in determining response. There is particular interest in male pattern baldness, which is poorly understood, but may involve interactions of androgens with receptors in the dermal papilla in androgen-sensitive scalp follicles (Randall *et al.* 1992). Randall *et al.* (1996) have recently reported that dermal papillae derived from scalp follicles of non-balding men, were larger and produced cells which grew better in culture than those of balding men, an effect which emphasizes the likely importance of the dermal papilla as a site of androgen action. Corticosteroids are considered to inhibit the activity of hair follicles (Ebling *et al.* 1991), an effect which may be associated with hair loss in response to stress. Responses to corticosteroids in sheep were shown to be dose-dependent

in the study of Chapman & Bassett (1970). Cortisol plasma concentrations below 1 µg/ml stimulated the rate of wool growth, whereas concentrations of above 3 µg/ml were associated with almost complete inhibition. Topical dexamethasone treatment of mouse skin has been shown to induce a catagen-like state in depilation-induced anagen follicles, an effect inhibited by high intraperitoneal doses of cyclosporin A (Paus *et al.* 1994a). The mechanisms of action on the hair follicle of dexamethasone and cyclosporin A, which are both immunosuppressive drugs, are not understood, but may involve activation and inhibition respectively of apoptosis in follicle keratinocytes. Jiang *et al.* (1995) have demonstrated the induction of anagen in telogen mouse skin by topical application of the potent immunosuppressant FK506. It is apparent that the immune system, the presence or absence of major histocompatible antigens on the hair follicle and the involvement of cytokines may also be considered as important determinants of the regulation of the hair growth cycle (for example, see Westgate *et al.* 1991; König *et al.* 1996).

Intrinsic control and the role of growth factors

Investigation into the role of locally-produced activators or inhibitors of hair follicle activity have been facilitated by techniques of cell culture, whole-follicle culture, *in situ* methodology for the detection of morphogens or their binding receptors, and studies on animals with genetic mutations affecting hair growth (Hébert *et al.* 1994). Mechanisms which may be paracrine, autocrine or intracrine (Pittelkow *et al.* 1991) have been implicated in local control, although these may be affected by extrinsic factors such as endocrine influences and nutrient supply.

Philpott *et al.* (1994) reported positive responses of isolated human hair follicles to physiological concentrations (10–100 ng/ml) of IGF-I and -II which may be produced locally or systemically and which prevented premature entry into catagen. Insulin at pharmacological concentrations (10 µg/ml) had a similar effect. Similar responses to IGF-I and insulin have been demonstrated in isolated cashmere hair follicles *in vitro* (Galbraith *et al.* 1997); responses in keeping with the detection of the presence of IGF-I-binding receptors in follicles of Cashmere goats (Dicks *et al.* 1995). Philpott *et al.* (1990) also demonstrated the formation of a club-hair structure in isolated human hair follicles exposed to epidermal growth factor, indicating a possible role in the anagen–catagen transition of the hair growth cycle. This response is similar to that observed *in vivo* where epidermal growth factor has been shown to be an effective depilatory agent for wool in sheep (Orwin, 1989). Epidermal growth factor has also been shown to produce dose-dependent effects on elongation, DNA concentration and [U-^{14}C]leucine uptake by isolated mohair follicles *in vitro* (Souri *et al.* 1997a). The formation of the club-hair structure has recently been associated with a stimulation of mitosis of outer root sheath-like cells in the lower bulb matrix concomitant with inhibition of cell proliferation in the follicle bulb (Philpott *et al.* 1995). Bond *et al.* (1996) have recently demonstrated a similar maintenance of activity of outer root sheath cells

in cultured wool follicles exposed to epidermal growth factor and transforming growth factor-α.

Rosenquist & Martin (1996) have recently described expression of fibroblast growth factor (FGF) receptors (FGFR) and ligand genes in the hair follicle cycle of the mouse. During anagen, mRNA transcripts were identified for FGFR-1 in the dermal papilla, FGFR-2 in hair matrix cells, FGFR-3 in pre-cuticle cells and FGFR-4 in hair bulb cells, and in the inner and outer root sheath expression of FGF-7 only was detected in the dermal papillae in anagen, with down-regulation by the late anagen state. No mRNA expression of the genes for receptors was detected during late catagen or telogen. Expression of FGF-5 has been described in the outer root sheath of the follicle by Hébert et al. (1994). FGF-5 has also been implicated in the regulation of the transition from anagen to catagen in the Angora mouse, which has a null mutation of the FGF-5 gene. In this genotype, the transition to catagen is delayed and hair growth approximately 0·5-fold longer than normal occurs (Hébert et al. 1994). It is apparent that signalling factors in addition to FGF-5 are important in regulating the cycle, since the catagen state is eventually attained. The general role of the FGF gene family of intercellular signalling molecules has recently been reviewed (Mason, 1994). Other factors which have been implicated in the control of the hair follicle cycle include: vascular endothelial growth factor-I, receptors for which have been identified in the human papilla at the commencement of anagen (Lachgar et al. 1996); hepatocyte growth (scatter) factor (Jindo et al. 1996) which is shown to stimulate hair growth in mouse and human culture systems and on mRNA which is expressed in human follicular papilla cells; nerve growth factor which has been shown to modulate keratinocyte proliferation in mouse skin organ culture (Paus et al. 1994b).

Nutritional influences on hair follicle activity

Vitamins

Hair follicles are metabolically-active tissues which have complex requirements for both micro- and macronutrients to support structural and functional activities. Sherertz & Goldsmith (1991) have reviewed nutritional influences on skin, many of which include effects on hair follicle characteristics. In addition to consideration of the metabolic role of these nutrients, emphasis is placed on effects produced by deficiencies, including those due to vitamins and minerals. For example, riboflavin deficiency has been associated with epithelial atrophy and ragged fur in the rat, and a rough coat in the guinea-pig. Niacin deficiency has been shown to produce unkempt fur in the hamster. Inadequacy of pantothenic acid supply results in hair loss in rats and dogs and a rough coat in guinea-pigs. Folic acid deficiency has been associated with abnormal wool growth and alopecia in lambs fed entirely on synthetic liquid diets (Reis, 1989). Both folic acid and cyanocobalamin in its methylated form have important roles in the methylation of homocysteine to methionine. Pyridoxine may influence hair growth as a consequence of its role as a cofactor in the conversion of methionine to cysteine, which is frequently inadequately available for optimum synthesis of hair proteins. Biotin is an essential cofactor in the activities of many carboxylating enzymes, and has been shown to be important in maintaining normal function in integumental tissues, including wool and hoof horn, in ruminant animals. For example, we have recently observed significant reductions in the viability, although not the growth rate, of viable anagen sheep-wool follicles cultured in vitro in the absence of supplemental biotin (Tahmasbi et al. 1996). We have also noted a significantly greater combed hair loss in Angora, although not Cashmere, kids given liquid diets temporarily deficient in biotin, before development of rumination and supply of biotin by rumen microbes, which reversed this effect (Tahmasbi et al. 1997).

Minerals

Certain minerals are required for normal function in metabolically-active tissues. These include Mg which has a role in energy-providing phosphate transfer reactions and DNA degradation and synthesis. The increase in cytosolic concentrations of free Ca^{2+} is an important mechanism of signal transduction in keratinocytes and may mediate the response to epidermal growth factor, as suggested by the in vitro studies of Pruche et al. (1996). K deficiency in the rat causes hair loss and production of a lustreless coat in mice. It has been suggested that the opening of intracellular K channels in the follicle may be a hair growth-regulating mechanism and that responses to certain mitogens and stimulators of hair growth, such as minoxidil, may be mediated by their action as K^+-channel agonists (Sanders et al. 1996). Mn is essential as an activator of glycosyl transferase enzymes which incorporate pentose and hexose sugars into glycoproteins such as chondroitin, dermatan sulfate and collagen, which are important in the dermal component of the hair follicle. Se has recently been shown to be important in the enzyme involved in the deiodination of thyroxine to triiodothyronine, which has been shown to be important in the timing of the initiation of moult in, for example, Cashmere goats (Rhind & McMillen, 1996).

Zn is an essential component of a large number of metallo-enzymes with important functions in metabolic processes ranging from control of gene expression to protein, fat and carbohydrate metabolism (Neldner, 1991), and in the sheep cessation of wool growth and hair loss. Zn deprivation in the rat has been shown to produce dermatitis and hair loss (Reis, 1989). Cu is also an essential micronutrient required for the formation and activity of important enzymes in the skin and its appendages (Danks, 1991). It is required for (a) the production of cross-links necessary to maintain structural integrity in collagen and elastin fibres, which is catalysed by the Cu-dependent enzyme lysyl oxidase; (b) the maintenance of melanin pigment production in hair follicles which involves the enzyme tyrosinase (EC 1.14.18.1); (c) the post-translational formation of disulfide bonds between cysteine residues in structural proteins in the hair by an, as yet, unknown mechanism. Deficiency of Cu in sheep results in loss of crimp and reduction in the quantity and tensile strength of the wool produced.

Energy and protein

A ready supply of oxidizable substrate is required to provide energy for the synthesis of protein and other components of dividing cells in the follicle, and, following differentiation, the synthesis and deposition of protein in cells of the cortex and inner root sheath. A linear response to energy supplementation in diets increasing in energy supply from 0·5 to 2·0 × maintenance was recorded in sheep wool by Marston (1948). Approximately 0·25 of retained N was diverted to wool production at twice maintenance, indicating the high priority given to hair deposition in these animals. Protein–energy malnutrition has also been shown to result in reductions in hair diameter and in the number of anagen follicles present in the skin of human subjects (Sherertz & Goldsmith, 1991).

Protein and amino acids

The major product of the hair follicle, hair, is formed largely from cortical cells which contain large amounts of intermediate filaments (microfibrils) embedded in a non-filamentous matrix (Gillespie, 1991) and cells of the cuticle. The intermediate filaments are considered to be composed of partly α-helical proteins of relatively low cystine content (low-S proteins). The matrix is composed of two families of non-helical proteins designated intermediate filament-associated proteins, one cysteine-rich (high-S proteins) and the other rich in glycine and tyrosine. Gillespie (1991) has summarized information describing

differences in the amino acid composition of hair of different species and in different protein fractions. For example, the concentration of S amino acids in the low- and high-S and high-tyrosine protein fractions expressed as S-carboxymethylcysteine residues per 100 amino acid residues are given as 6·0 (Lincoln sheep wool) 18·9 (Merino sheep wool) and 6·0 (Merino sheep wool) respectively. Sheep wool, with an overall cysteine concentration of approximately nine residues/100 amino acid residues, has a much higher concentration of this amino acid than muscle. This concentration is also greater than that supplied by rumen microbial protein or that present in fishmeal or soyabean meal as typical protein supplements in ruminant diets (Table 2; Galbraith, 1995). The supply of cysteine and methionine at the small intestine, above that provided by microbial protein, depends on the digestibility of the rumen-undegraded fraction of each nutrient source. Positive responses to diets supplemented with white fishmeal and soyabean meal at two levels of metabolizable energy were recently obtained in yearling British Angora goats over a 16-week study period (Table 3; Shahjalal et al. 1992). While throughout the study period raw fibre yields and diameter were increased significantly by protein supplementation, significant effects due to energy were recorded only in the final 3 weeks. Examination of treatment means suggested that the latter effect was produced predominantly on the low-protein diet, although a significant interaction between protein and energy level was not attained. It was apparent that under the conditions of the study, mohair production was more sensitive to

Table 2. Relative composition of selected amino acids in tissues and dietary protein sources (Data from Galbraith, 1995)

Amino acid	Wool*	Muscle*	Ruminant microbial protein*	Extracted soyabean meal†	White fishmeal†
Threonine	5·5	3·9	5·2	4·2	4·2
Leucine	6·5	5·8	7·4	8·2	6·7
Phenylalanine	4·6	3·1	5·5	5·5	3·9
Lysine	3·5	5·9	8·1	6·8	5·7
Methionine	0·6	1·8	2·5	1·4	3·0
Cyst(e)ine	9·1	1·1	1·0	1·4	0·9

*g amino acid/16 g N; as cited by Harris & Lobley (1991).
† g amino acid/16 g N; adapted from Ministry of Agriculture, Fisheries and Food (1990).

Table 3. Raw yield and diameter of mohair fibre of Angora goats given diets containing (/kg DM) 10·MJ (LE) or 11·9 MJ (HE) and 108 g (LP) or 180 g (HP) crude protein (nitrogen × 6·25) (Data from Shahjalal et al. 1992)

Raw fibre yield (g/100 cm²)	Treatments					Statistical significance of contrasts		
	LE-LP	LE-HP	HE-LP	HE-HP	SED	P	E	I
Period of treatment (weeks):								
1–4	1·68	2·49	1·65	2·11	0·357	*	NS	NS
5–8	2·88	3·97	3·05	3·53	0·335	**	NS	NS
9–12	2·50	3·74	3·19	3·75	0·319	**	NS	NS
13–16	1·74	3·14	2·59	3·31	0·279	***	**	NS
1–16	8·91	13·3	10·5	12·7	1·08	***	NS	NS
Fibre diameter (μm):								
(day 112)	29·9	35·6	32·4	35·8	1·49	***	NS	NS

NS, $P > 0.05$; P, protein; E, energy, I, interaction.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 4. Fibre yields and diameter of cashmere and mohair produced by goats supplemented with (M) or without (O) rumen-protected methionine (Data from Souri *et al.* 1997*b*)

	Treatment groups					Statistical significance of contrasts		
	CO	CM	AO	AM	SEM	D	G	I
Days 31–58:								
Total raw fibre yield (mg/100 cm² per d)	46·0	54·0	87·0	156	7·0	***	***	**
Guard hair (mg/100 cm² per d)	34·0	35·0			2·9	NS	NS	NS
Cashmere (mg/100 cm² per d)	12·0	19·0			1·5	*	NS	NS
Day 58								
Diameter (μm)	18·9	19·7	28·3	32·6	1·7	***	***	***

NS, $P > 0·1$; C, Cashmere goats; A, Angora goats; D, diet; G, genotype; I, interaction.
*$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

changes in the supply of dietary protein, than changes in dietary energy.

Supplements of methionine and cysteine given in a form to bypass rumen protein degradation are recognized to stimulate wool growth in sheep and mohair by Angora goats but not cashmere by Cashmere goats (Russel, 1995). The absence of response in Cashmere goats suggests that S amino acid supply in the absence of supplementation was adequate to support the production of cashmere, which is produced in smaller quantities than mohair. However, more recent work in Angora and Cashmere goats (Souri *et al.* 1997*b*) did produce a significant response in cashmere, but not guard hair, to a supply of rumen-protected intestinally-available methionine (Table 4). It was interesting to note that increases were obtained in the diameter of mohair, but not cashmere, suggesting differences in response at the follicle level between the genotypes.

As indicated previously, the disproportionate concentration of cysteine residues in wool fibre in relation to amino acid supply has resulted in values for the efficiency of conversion of dietary protein of less than 0·3 (Agricultural and Food Research Council, 1993). Given the competition between wool and other body tissues, the question arises as to whether the partitioning of N towards the hair follicles is altered in the presence of an increasing supply of a limiting amino acid. This question was addressed in a recent study in which Angora goats responded to a supplement of rumen-protected intestinally-available methionine (Table 5) by increasing daily N retention and quantity of N retained as mohair (Souri *et al.* 1997*c*). However, the proportion of N retained in mohair fibre was not altered, suggesting the absence of change in the relative partitioning of N retention into fleece and non-fleece tissues. It was also

of interest to note, in this study, that supplementary methionine also stimulated growth of hoof horn tissue, which is produced by mechanisms similar to those of hair (Mengal *et al.* 1997).

Conversion of methionine to cysteine

The mechanism by which ruminant animals respond to dietary supply of rumen-protected methionine assumes, at least partly, a conversion to cysteine by tissues such as liver and skin (Reis, 1989). Recent studies (Souri *et al.* 1996) *in vitro* have confirmed the *in vivo* response of cashmere follicles to supplementation with rumen-protected dietary methionine. Methionine in the culture medium was shown to be essential to support hair shaft elongation and to maintain follicle viability, and when given alone produced a growth response approximately 0·8 that of methionine plus cysteine combined. Cysteine was not essential, provided methionine was present. The responses exhibited in the presence of methionine and absence of cysteine were compatible with the presence of a trans-sulfuration pathway within the cashmere secondary hair follicles. The presence of a such a trans-sulfuration system has been confirmed by the recent demonstration of the quantitative transfer of isotopically-labelled S from methionine to cysteine in the cashmere follicle (M Souri, H Galbraith and JR Scaife, unpublished results). It is apparent that a supply of methionine, but not cysteine, is essential for follicle growth, reflecting additional roles of methionine, including those as a precursor for polyamine synthesis, polypeptide chain initiation and as a methyl donor in biochemical reactions (Reis, 1989).

Table 5. The effect of protected methionine (M) supplementation (2·5 g/d; +M) on nitrogen balance and nitrogen partitioning between mohair and non-fleece body tissues (Data from Souri *et al.* 1997*c*)

	Treatments			Statistical significance of difference
	−M	+M	SEM	
N intake (g/d)	10·8	12·0	0·87	NS
N retention (g/d)	2·60	4·35	0·28	**
Clean mohair growth (g/d)	7·00	11·8	0·91	**
Mohair N retained (g/d)	0·97	1·64	0·098	***
Proportion of N retained as mohair	0·37	0·38	0·02	NS

NS, $P > 0·05$; −M, no supplement.
*$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.

The mechanisms by which supplements of protein or amino acids in the diet produce effects at the hair follicle level are not fully understood. For example, it is not clear whether the responses are purely those of substrate supply or whether there are alterations in the sensitivity of hair follicles arising from effects of the amino acids on, for example, cellular signal reception characteristics.

Cellular response to amino acid supply

In this context, the results from the study of Hynd (1989) are of particular interest, since sheep responded to increases in protein nutrition (from 0·09 to 0·3 crude protein ($N \times 6·25$) in dietary DM) as expected by producing a heavier weight and faster growth of fleece. However, one feature of the response was a faster rate of division of cells in the follicle bulb matrix. Thus, the improved supply of amino acids in the diet stimulated not only keratin gene expression and protein deposition in differentiated cells but also mitosis in proliferating epidermal cells by mechanisms which remain unclear.

Conclusions

The development of hair follicles in the embryo and neonate and the subsequent characteristics of hair production, as determined by the follicle growth cycle, are subject to a variety of extrinsic and intrinsic influences. A wide range of systemic hormones and systemic and local growth factors are known to influence follicle activity. Responses are determined by the sensitivity of individual follicles according to species, genotype within species, location in the body and stage of the follicle cycle. Successful dermal–epidermal interactions are essential for normal development and growth of the follicle. Although the precise nature of diffusible factors has not been established, receptors for various morphogens have been identified as present in both dermal and epidermal components. Mechanisms regulating the transition between the different stages of the follicle cycle are of major importance in elucidating developmental, growth and differentiative processes central to mammalian cellular biology. The role of epidermal apoptosis in the transition from anagen to catagen and the involvement of stem and transient amplifying cells in the regeneration of the follicle are of particular interest. Successful hair growth and optimal functioning of the hair follicle are dependent on an adequate supply of nutrients, including vitamins, minerals, oxidizable substrates and amino acids. The major proteins in hair contain cysteine in the range of six to twenty residues/100 amino acid residues and the requirement for this amino acid is disproportionate to that supplied by rumen microbial protein or major dietary protein sources for ruminants. Cysteine can be synthesized in the cashmere hair follicle from methionine which, because of its multi-functional role, is an amino acid essential for hair growth.

Improved protein nutrition has been shown to increase wool growth in sheep, not only by stimulating protein deposition in differentiating keratinocytes, but also by increasing their rate of initial mitosis. The question of whether amino acids have a role other than provision of substrate in stimulating mitosis and protein deposition in the hair follicle, remains to be answered.

References

Agricultural and Food Research Council (1993) *Energy and Protein Requirements of Ruminants. An Advisory Manual Prepared by the AFRC Technical Committee on Responses to Nutrients.* Wallingford: CAB International.

Bond JJ, Wynn PC & Moore GPM (1996) Effects of epidermal growth factor and transforming growth factor alpha on the function of wool follicles in culture. *Archives of Dermatology* **288**, 373–382.

Chapman RE & Bassett JM (1970) The effects of prolonged administration of cortisol on the skin of sheep on different planes of nutrition. *Journal of Endocrinology* **48**, 649–663.

Choy VJ, Nixon AJ & Pearson AJ (1995) Localisation of receptors of prolactin in ovine skin. *Journal of Endocrinology* **144**, 143–151.

Courtois M, Loussouarn G, Hourseau S & Grollier JF (1996) Periodicity in the growth and shedding of hair. *British Journal of Dermatology* **134**, 47–54.

Danks DM (1991) Copper deficiency and the skin. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 1351–1361 [LA Goldsmith, editor]. New York: Oxford University Press.

Dicks P (1994) The role of prolactin and melatonin in regulating the timing of the spring moult in the Cashmere goat. In *Hormonal Control of Fibre Growth and Shedding. European Fine Fibre Network Occasional Publication* no. 2, pp. 109–125 [JP Laker and D Allain, editors]. Aberdeen: Macaulay Land Use Research Institute.

Dicks P, Morgan CJ, Morgan PJ, Kelly D & Williams LM (1996) The localisation and characterisation of insulin-like growth factor-I receptors and the investigation of melatonin receptors on the hair follicles of seasonal and non-seasonal fibre producing goats. *Journal of Endocrinology* **151**, 55–61.

Dicks P, Russel AJF & Linoln GA (1995) The effect of melatonin implants given under different day length regimes on plasma prolactin concentrations and fibre growth and shedding in Cashmere goats. *Animal Science* **60**, 239–247.

Ebling FJG, Hale PA & Randall VA (1991) Hormone and hair growth. In *Physiology, Biochemistry and Molecular Biology in the Skin*, pp. 660–696 [LA Goldsmith, editor]. New York: Oxford University Press.

Ferguson KA, Schinkel PG, Carter HB & Clark WH (1956) The influence of the thyroid on wool follicle development in the lamb. *Australian Journal of Biological Science* **9**, 575–588.

Galbraith H (1994) Follicle culture. A new approach to explore seasonal control of fibre growth. In *Hormonal Control of Fibre Growth and Shedding. European Fine Fibre Network Occasional Publication* no. 2, pp. 129–145 [JP Laker and D Allain, editors]. Aberdeen: Macaulay Land Use Research Institute.

Galbraith H (1995) The effects of diet on nutrient partition in Scottish cashmere and Angora goats. In *Nutrition and Grazing Ecology of Speciality Fibre Producing Animals. European Fine Fibre Network Occasional Publication* no. 3, pp. 23–50 [JP Laker and AJF Russel, editors]. Aberdeen: Macaulay Land Use Research Institute.

Galbraith H, Sims D & Hazlerigg DH (1997) The effect of IGF-I on the growth of secondary hair follicles of the Cashmere goat *in vitro. Proceedings of the British Society of Animal Science*, p. 170 Abstr.

Gillespie JM (1991) The structural proteins of hair: isolation, characterization and regulation of biosynthesis. In *Physiology,*

Biochemistry and Molecular Biology of the Skin, pp. 625–659 [LA Goldsmith, editor]. New York: Oxford University Press.

Goetinck PF & Winterbottom N (1991) Proteoglycans: modular macromolecules of the extracellular matrix. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 558–575 [LA Goldsmith, editor]. New York: Oxford University Press.

Goldsmith LA (editor) (1991) In *Physiology, Biochemistry and Molecular Biology of the Skin*, 2nd ed. New York: Oxford University Press.

Hardy MH (1992) The secret life of the hair follicle. *Trends in Genetics* **8**, 55–61.

Harris P & Lobley GE (1991) Amino acid and energy metabolism in peripheral tissues of ruminants. In *Physiological Aspects of Digestion in Ruminants. Proceedings of the VII International Symposium on Ruminant Physiology*, pp. 201–230 [T Tsuda, Y Sasaki and R Kawashima, editors]. London: Academic Press.

Hébert JM, Rosenquist T, Gotz J & Martin GM (1994) FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. *Cell* **78**, 1017–1025.

Holbrook KA (1991) Structure and function of the developing human skin. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 63–110 [LA Goldsmith, editor]. New York: Oxford University Press.

Hynd PI (1989) Effects of nutrition on wool follicle cell kinetics in sheep differing in efficiency of wool production. *Australian Journal of Agricultural Research* **40**, 409–417.

Ibraheem J, Galbraith H, Scaife JR & Ewen SWB (1993) Growth and viability of secondary hair follicles of the Angora goat, cultured *in vitro. Journal of Anatomy* **182**, 231–238.

Ibraheem M, Galbraith H, Scaife JR & Ewen SWB (1994) Growth of secondary hair follicles of the Cashmere goat *in vitro* and their response to prolactin and melatonin. *Journal of Anatomy* **185**, 135–142.

Jiang H, Yamamoto S & Kato R (1995) Induction of anagen in telogen mouse skin by topical application of FK506, a potent immunosuppressant. *Journal of Investigative Dermatology* **104**, 523–525.

Jindo T, Tsuboi R, Takamori K & Ogawa A (1996) Local injection of hepatocyte growth factor/scatter factor (HGF/SF) promotes hair follicle growth *in vivo*. In *Hair Research for the Next Millennium*, pp. 433–435 [D van Neste and VA Randall, editors]. Amsterdam: Elsevier.

König A, Happle R & Hoffman R (1996) Cytokines characteristic of alopecia areata regulate the expression of ICAM-I and MHC class 1 and 11 molecules in cultured dermal papilla cells. In *Hair Research for the Next Millennium*, pp. 243–247 [D van Neste and VA Randall, editors]. Amsterdam: Elsevier.

Lachgar S, Charveron M, Ceruti I, Lagarde JM, Gall Y & Bonafe JL (1996) VEGF mRNA expression in different stages of the human hair cycle: analysis by confocal laser microcopy. In *Hair Research for the Next Millennium*, pp. 407–411 [D van Neste and VA Randall, editors]. Amsterdam: Elsevier.

McDonald BJ, Hoey A & Hopkins PS (1987) Cyclical growth in Cashmere goats. *Australian Journal of Agricultural Research* **38**, 597–609.

Margolena LA (1974) Mohair histogenesis, maturation and shedding in the Angora goat. *Technical Bulletin* no. 1495, Beltsville, MD: United States Department of Agriculture.

Marston HR (1948) Nutritional factors involved in wool production by Merino sheep. *Australian Journal of Scientific Research* **81**, 362–375.

Mason JJ (1994) The ins and outs of fibroblast growth factors. *Cell* **78**, 547–552.

Mengal MA, Galbraith H, Scaife JR & Souri M (1997) Effect of methionine supplementation of the diet on growth of hoof horn and mohair in Angora goats. *Proceedings of the British Society of Animal Science*, p. 168 Abstr.

Messenger AG (1993) The control of hair growth: an overview. *Journal of Investigative Dermatology* **101**, Suppl. 1, 4S–5S.

Ministry of Agriculture, Fisheries and Food (1990) *UK Tables of Nutritional Value and Chemical Compositions of Feedingstuffs. Ministry of Agriculture, Fisheries and Food, Standing Committee on Tables of Feed Composition*. Aberdeen: Rowett Research Services.

Nagorcka BN & Mooney JR (1982) The role of a reaction-diffusion system in the formation of hair fibres. *Journal of Theoretical Biology* **98**, 575–607.

Neldner KH (1991) The biochemistry and physiology of zinc metabolism. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 1329–1350 [LA Goldsmith, editor]. New York: Oxford University Press.

Nixon AJ, Choy VJ, Parry AL & Pearson AJ (1993) Fiber growth initiation in hair follicles of goats treated with melatonin. *Journal of Experimental Zoology* **267**, 47–56.

Oliver RF & Jahoda CAB (1989) The dermal papilla and maintenance of hair growth. In *The Biology of Wool and Hair*, pp. 51–68 [GE Rogers, PJ Reis, KA Ward and RC Marshall, editors]. Cambridge: Chapman and Hall Ltd.

Orwin DFG (1989) Variations in wool follicle morphology. In *The Biology of Wool and Hair*, pp. 227–242 [GE Rogers, PJ Reis, KA Ward and RC Marshall, editors]. Cambridge: Chapman and Hall Ltd.

Paus R, Handjiski B, Czarnetzki BM & Eichmuller S (1994a) A murine model for inducing and manipulating hair follicle regression (catagen): effects of dexamethasone and cyclosporin A. *Journal of Investigative Dermatology* **103**, 143–147.

Paus R, Luftl M & Czarnetzki BM (1994b) Nerve growth factor modulates keratinocyte proliferation in murine skin culture. *British Journal of Dermatology* **130**, 174–180.

Pearson AJ, Ashby MG, Choy VJ, Nixon AJ & Wildermoth JE (1993) The effects on wool growth of suppression of plasma prolactin surge following short to long day transition. *Journal of Endocrinology* **139**, Suppl., P 46.

Philpott MP, Green MR & Kealey T (1990) Human hair growth *in vitro. Journal of Cell Science* **97**, 463–471.

Philpott MP, Sanders DA & Kealey T (1994) Effects of insulin and insulin-like growth factors on cultured human hair follicles: IGF-I at physiologic concentrations is an important regulator of hair follicle growth *in vitro. Journal of Investigative Dermatology* **102**, 857–861.

Philpott MP, Sanders D & Kealey T (1995) Cultured human hair follicles and growth factors. *Journal of Investigative Dermatology* **104**, Suppl. 5, 44S–45S.

Pittelkow MR, Coffey RJ & Moses HL (1991) Transforming growth factor-β and other growth factors. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 351–384 [LA Goldsmith, editor]. New York: Oxford University Press.

Pruche F, Boyera N & Bernard BA (1996) K^+ATP channel openers inhibit the bradykinin-induced increase of intracellular calcium in hair follicle outer root sheath keratinocytes. In *Hair Research for the Next Millennium*, pp. 463–466 [D van Neste and VA Randall, editors]. Amsterdam: Elsevier.

Randall VA & Ebling FJG (1991) Seasonal changes in human hair growth. *British Journal of Dermatology* **124**, 146–151.

Randall VA, Hibberts NA & Hamada K (1996) A comparison of the culture and growth of dermal papilla cells from hair follicles from non-balding and balding (androgenetic alopecia) scalp. *British Journal of Dermatology* **134**, 437–444.

Randall VA, Thornton JM, Hamada K & Messenger AG (1992) Mechanism of androgen action in cultured dermal papilla cells derived from human hair follicles with varying responses to androgens *in vivo. Journal of Investigative Dermatology* **98**, 86S–91S.

Reis PJ (1989) The influence of absorbed nutrients on wool growth. In *The Biology of Wool and Hair*, pp. 185–204 [GE Rogers, PJ Reis, KA Ward and RC Marshall, editors]. Cambridge: Chapman and Hall Ltd.

Rhind SM & McMillen SR (1995a) Seasonal patterns of secondary fibre growth, moulting and hair follicle activity in Siberian and Icelandic × Scottish feral goats offered high and low levels of dietary protein. *Small Ruminant Research* **16**, 69–76.

Rhind SM & McMillen SR (1995b) Seasonal changes in systemic hormone profiles and their relationship to patterns of fibre growth and moulting in goats of contrasting genotypes. *Australian Journal of Agricultural Research* **46**, 1273–1283.

Rhind SM & McMillen SR (1996) Effects of methyl thiouracil treatment on the growth and moult of Cashmere fibre in goats. *Animal Science* **62**, 513–520.

Rogers GE, Reis PJ, Ward KA & Marshall RC (editors) (1989) *The Biology of Wool and Hair*, Cambridge: Chapman and Hall Ltd.

Rosenquist TA & Martin GR (1996) Fibroblast growth factor signalling in the hair growth cycle: expression of the fibroblast growth factor receptor and ligand genes in the murine hair follicle. *Developmental Dynamics* **205**, 379–386.

Russel AJF (1995) Current knowledge on the effects of nutrition on fibre production. In *The Nutrition and Grazing Ecology of Speciality Fibre Producing Animals. European Fine Fibre Network Occasional Publication* no. 3, pp. 3–21 [JP Laker and AJF Russel, editors]. Aberdeen: Macaulay Land Use Research Institute.

Sanders DA, Fiddes I, Thompson DM, Philpott MP, Westgate GE & Kealey T (1996) Minoxidil potentiates the mitogenic properties of growth factors *in vitro* in the absence of streptomycin. In *Hair Research for the Next Millennium*, pp. 467–469 [D van Neste and VA Randall, editors]. Amsterdam: Elsevier.

Shahjalal M, Galbraith H & Topps JH (1992) The effect of changes in dietary protein and energy on growth, body composition and mohair fibre characteristics of British Angora goats. *Animal Production* **54**, 405–412.

Sherertz EL & Goldsmith LA (1991) Nutritional influence on the skin. In *Physiology, Biochemistry and Molecular Biology of the Skin*, pp. 1315–1328 [LA Goldsmith, editor]. New York: Oxford University Press.

Sieberg M, Marthinus J & Stenn KS (1995) Changes in the expression of apoptosis-associated genes in skin mark early catagen. *Journal of Investigative Dermatology* **104**, 78–82.

Souri M, Galbraith H & Scaife JR (1996) The role of methionine and cystine in the growth and viability of secondary follicles of the Cashmere goat *in vitro*. *Animal Science* **62**, 669 Abstr.

Souri M, Galbraith H & Scaife JR (1997a) Response of isolated mohair secondary follicles to epidermal growth factor *in vitro*. *Proceedings of the Nutrition Society* **56**, 181A.

Souri M, Galbraith H & Scaife JR (1997b) Comparisons of the effect of genotype and protected methionine supplementation on growth, digestive characteristics and fibre yield in Cashmere and Angora goats. *Animal Science* **66**, 217–223.

Souri M, Galbraith H & Scaife JR (1997c) Effect of protected methionine supplementation of the diet on the partitioning of dietary nitrogen in the Angora goat. *Proceedings of the British Society of Animal Science*, p. 167 Abstr.

Stenn KS, Lawrence L, Veis D, Korsmeyer S & Sieberg M (1994) Expression of the bcl-2 protooncogene in the cycling adult mouse hair follicle. *Journal of Investigative Dermatology* **103**, 107–111.

Tahmasbi AM, Galbraith H & Scaife JR (1996) Development of an *in vitro* technique to investigate the role of biotin in regulating wool growth in sheep. *Animal Science* **62**, 670 Abstr.

Tahmasbi M, Galbraith H & Scaife JR (1997) The role of biotin in the pre-ruminant and immediately post-ruminant goat. *Proceedings of the British Society of Animal Science*, 169 Abstr.

Thomas DG, Brinklow BR, Randall VA & Loudon ASI (1993) Prolactin and triiodothyronine (T3) stimulate hair growth in cultured follicles of red deer summer coat. *Journal of Endocrinology* **139**, 50 Abstr.

van Neste D & Randall VA (editors) (1996) In *Hair Research for the Next Millennium*. Amsterdam: Elsevier.

Westgate GE, Craggs RI & Gibson WT (1991) Immune privilege in hair growth. *Journal of Investigative Dermatology* **97**, 417–420.

Yamada Y, Takama H, Kitamura T, Yokochi K, Nitta Y, Ikeya T & Matsumoto Y (1994) Intensification of programmed cell death in normal human skin tissues by using specific labelling of fragmented DNA. *British Journal of Dermatology* **131**, 521–524.