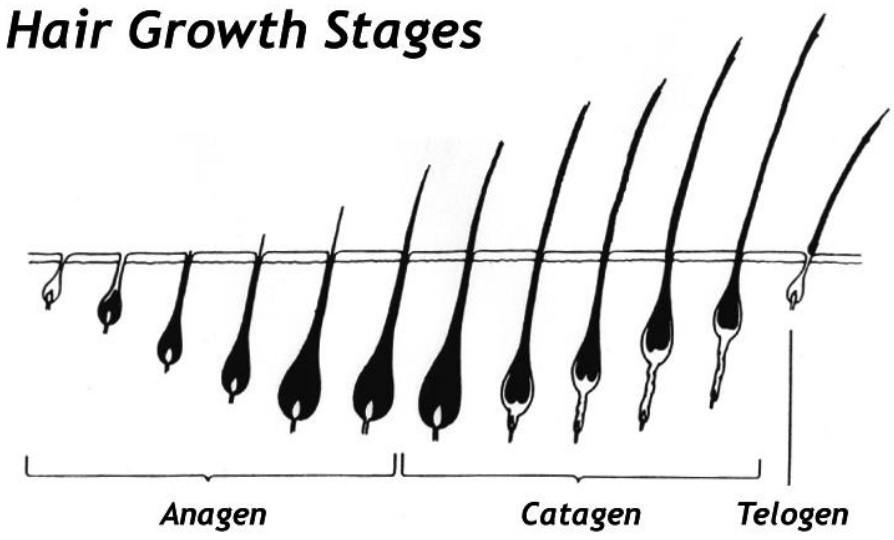
A Review of the issues in Historic and Current Hair Research, and an Overlooked Connection

This review is intended to describe in layperson friendly terms, the serious issues with historic and current hair research and a basic physical principle that has been overlooked in this context. Once this principle is factored into this context, it gives order and logic to the collective data. This connection goes on to shed light upon mammalian and human evolution, and raises an important testable question about some serious gender related diseases.

I suggest the current concentration upon molecular interactions in physiology, can overlook systems interactions at the functional level and this is a case in point. Because of this and to keeps it as simple as possible, i will not elaborate here upon the already recognised molecular mechanisms involved here. Further references can be provided in this respect if required. Most of the relevant information here is based upon text book physiology, and common observations.

Background

The basic issue in most changes in hair growth involve changes in hair follicle size. Hair follicles go through a cycle of regression then re-enlargement within the dermal tissue.



The amount of hair produced is directly related to the size reached by the follicle during anagen enlargement. Hair research looks for factors that could explain changes in the size of follicles produced by the hair cycle. For example in male pattern baldness, the follicles become smaller cycle by cycle producing less hair as illustrated here.

Figure #3 **Scalp Hair : Types**

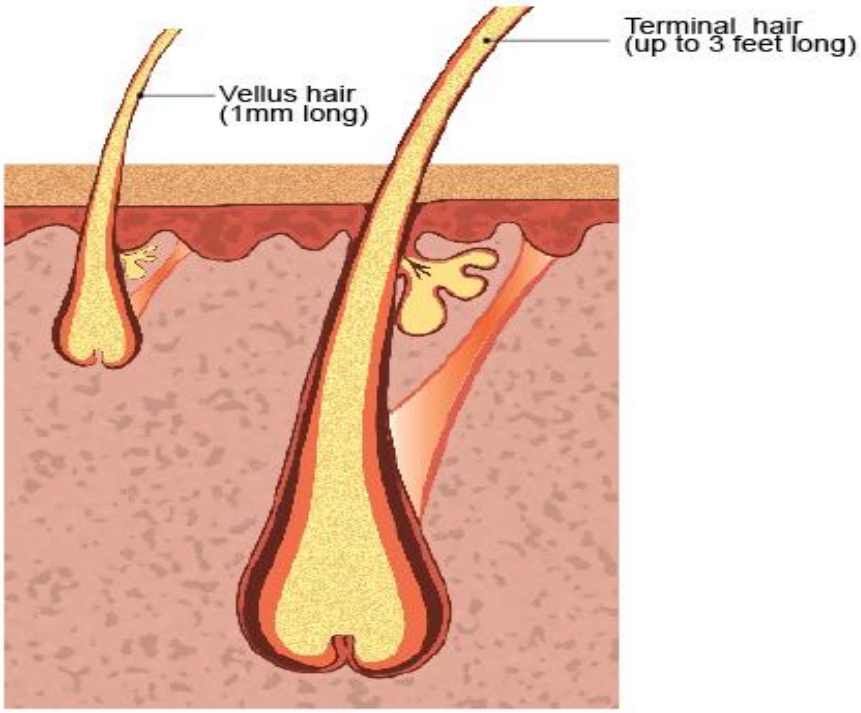
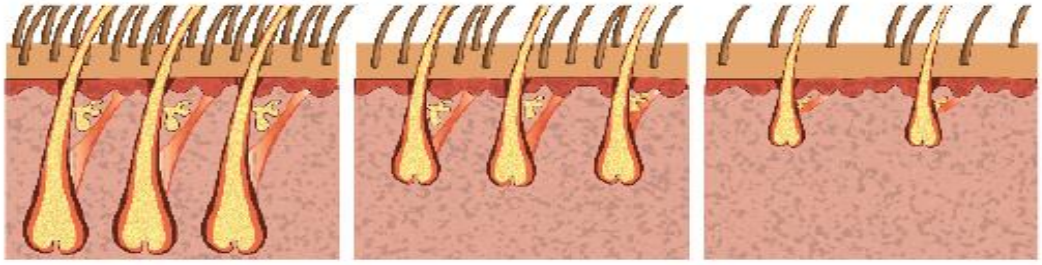


Figure #4 **Time-lapse : Miniturization of hair follicles in baldness**



Historic and Current Research

Historic and current hair growth research strategies, have failed to make any significant progress in understanding changes in follicle size in many years of trying. The public is aware of regular media articles about the latest discovery of a related factor in changes in hair growth. So far these associations have not

indicated the primary cause, or lead to any significant treatments. This ongoing situation continues to encourage quack hair loss treatments, and dangerous self medication with drugs untested in this context on humans. Potential treatments that show promise in mice and the test tube consistently fail in humans, clearly indicating something is being missed here.

In my opinion this failure to make progress continues, because most current research is based upon an untested assumption. This assumption relates to early hair transplantation studies in androgen related changes in hair growth.

In these early studies, hair transplanted into bald scalp areas seemed to retain its original growth characteristics. Transplanted large follicles did not miniaturise like the original follicles in this area. This effect became known as donor dominance. The authors of the early studies accepted that there were two possible reasons for this. Either the follicles were internally different in the way they directly responded to androgens, or this was because of a factor induced by the procedure itself. Whilst it has always been possible to perform experiments to establish which of these possibilities was responsible, such testing has not been done.

Instead early commercial hair transplantation made the sales claim that the transplanted follicles were “different” and so permanent, not being adversely directly affected by androgens. Over time however the early procedures based on this claim began to have issues. The early large grafts, scalp flap rotations and scalp stretching procedures initially hailed as breakthroughs, were discontinued. It has to be said that the explanations offered for this involved some very dubious science. Hair transplantation procedures evolved over time, and the only grafts that survive long term in the MPB area are very small containing only one to four follicles.

Later peer reviewed transplantation studies began to cast serious doubt upon the traditional explanation of donor dominance, and have demonstrated effects of the surrounding tissue upon follicle size and hair growth. One particular transplantation study that demonstrated re-enlargement of miniaturised MPB follicles in-vivo, effectively refuted any significant direct action of androgens in this situation. I will elaborate on this study later.

Everyone agrees that androgens in particular the male hormone Dihydrotestosterone (DHT), are responsible for significant hair growth changes in both sexes after puberty, and male pattern baldness. But again there are two possibilities here. This is either a direct action of androgens mediated through androgen receptors within follicle cells, the different growth effects being because of inherent differences within the follicles themselves. Or the alternative is some kind of external indirect effect induced by androgens.

The traditional claim based upon early transplantation, is that follicles are different in the way they respond to the direct action of androgens. However there are major issues with this claim based upon common observations. Such a direct hormonal action upon follicles to create MPB, goes against all we know about direct hormone actions. These are closely linked to hormone levels and exposure. Feedback loops exist to maintain hormone levels within the right range, and the cell reactions are very sensitive to hormone exposure levels.

In MPB it seems that the levels of androgens and exposure criteria are irrelevant. Future MPB follicles on average have to be exposed to androgens for periods up to many years after puberty, before there is any growth restricting effect. The levels of androgens can also apparently vary greatly in the individual, and have no direct relationship with the development of MPB. In this particular direct hormonal action it also seems that once the follicles do become sensitive to androgens, they become very sensitive indeed. This is because even though castration removes over 90% of circulating androgens, this has no effect upon reversing MPB.

The diehard supporters of this direct hormonal action in MPB, have many novel explanations for these anomalies. These include individual genetic "clocks" in each follicle, that dictate how long the follicle has to be exposed to androgens before it decides to react, and other such add on speculations. All of which go against basic scientific principles.

Exploring the Alternative

If we go back to basics, there is a fundamental principle in physiology that has been overlooked in changes in hair follicle size.

Basic physics dictate that in order for the follicle to enlarge during anagen, the surrounding dermal tissue has to move out of the way. This puts hair follicle enlargement, under the influence of the basic external pressure based control upon all normal tissue growth described here.

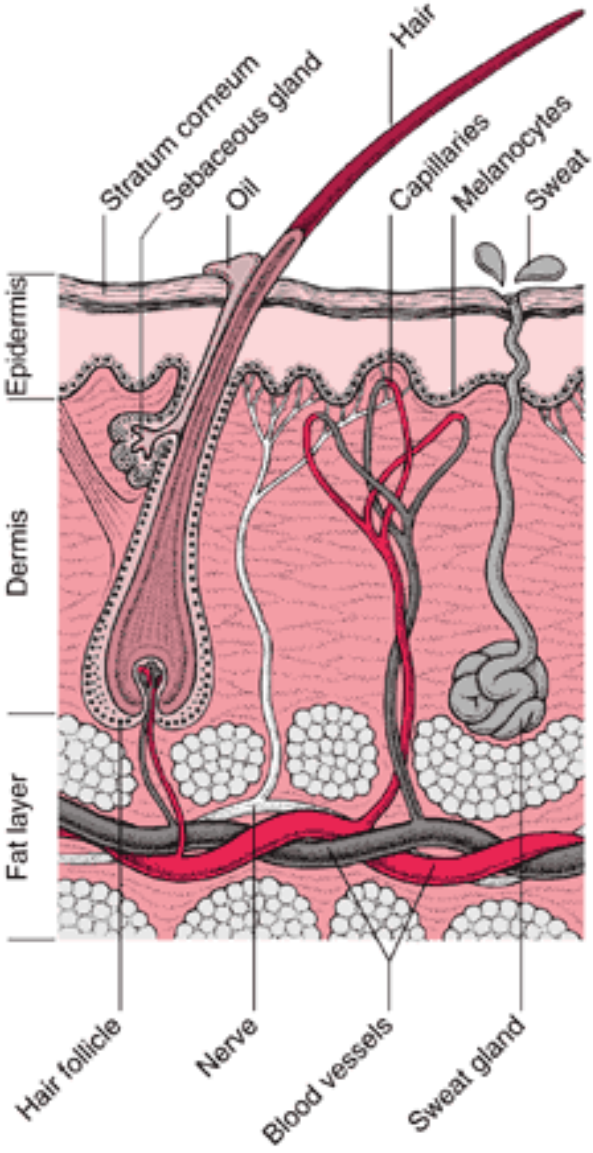
http://phys.org/news/2014-04-room-tissue-growth-cell-response.html

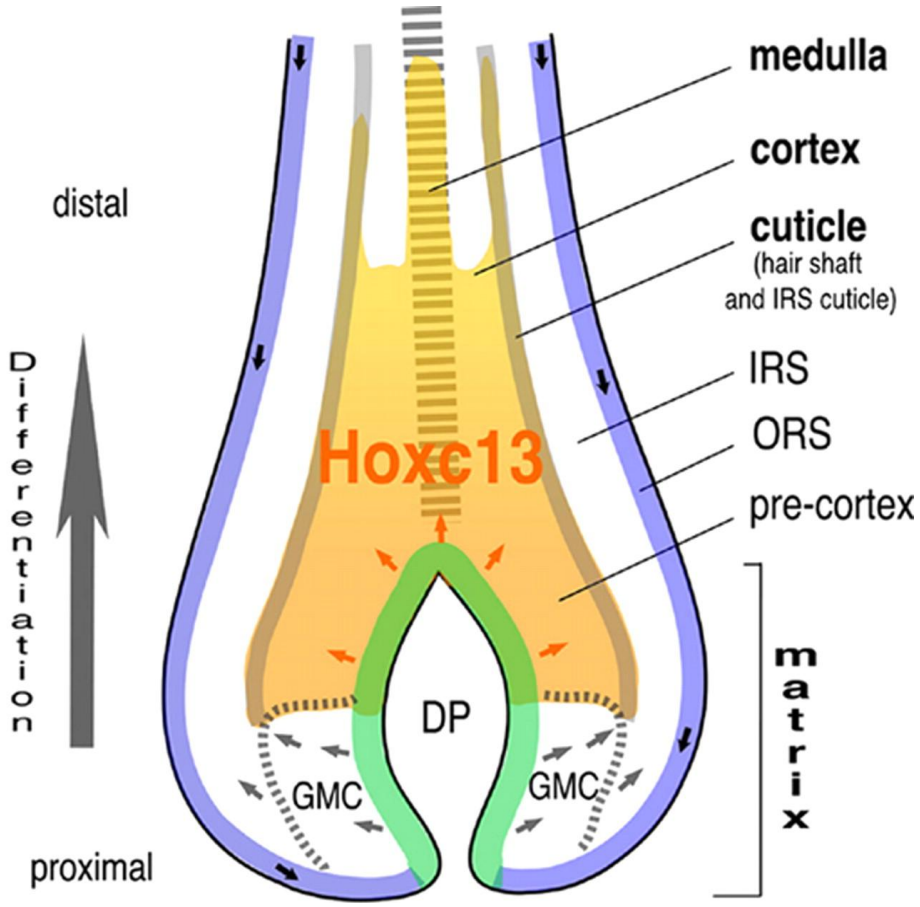
If you think about this, the hollow pocket based structure of hair follicles is particularly sensitive to changes in external pressure. This is because of the internal/external pressure differential of a hollow structure.

The external factors involved in this spatial tissue growth control, are the natural rigidity of external tissue, and in this case the prevailing tissue fluid pressure. The fluid pressure is important here because of the pocket based structure of hair follicles. Any increase in tissue fluid pressure will increase the resistance to the formation of a pocket in the tissue, by increasing the natural tendency of the surrounding tissue to move into this hollow space.

I think a good analogy here, is to think about this as trying to inflate a balloon under water with a fixed amount of air pressure. The size the balloon can reach is determined by the external water pressure. The external pressure control of normal tissue growth, must involve a particular level of external pressure as the cut off point to further tissue growth. So it is changes in the external pressure that change ultimate organ size, and in this case hair follicle size.

Given the known characteristics of the mammalian dermal system, this suggests that hair follicles and the hair cycle have evolved to use external pressure to adjust follicle size and so hair growth when necessary. The primary dermal response to changes in environmental temperature is to change the dermal blood flow characteristics through diverting flow either away from or close to the skin surface. The capillary loops involved are shown in this diagram, along with the hair follicle and sweat gland.


Hair
Stratum corneum
Sebaceous gland
Oil
Capillaries
Melanocytes
Sweat
Epidermis
Dermis
Fat layer
Hair follicle
Nerve
Blood vessels
Sweat gland



In hot conditions blood flow is increased in the surface tissue to dissipate heat, and diverted to deeper tissue in cold conditions to conserve heat. What this also does is increase local tissue fluid pressures in hot conditions, and reduce them in cold conditions. Sweat is essentially tissue fluid, and this enhances sweating capacity in hot conditions. According to this external pressure control on hair follicle size, these tissue fluid pressure changes will also reduce hair growth in hot conditions and increase it in cold conditions. The result is the winter coat and the summer moult. An examination of the hair follicle in cross section above, indicates that tissue expansion or shrinkage around follicles already in full anagen will also distort these follicles in such a way to reduce or increase the hair production area. Excessive tissue expansion as in inflammation caused by injury, will distort the follicles enough to create hair loss demonstrating the club hair shape.

The dynamics here involve the distance from the surface of the skin to the dermal papillae (DP). Hair is produced from the germinal matrix (GMC) wrapped around the DP. Tissue expansion around the follicle will move the surface of the skin away from the DP., pulling the body of the follicle with it.

This effectively moves the DP downwards from the base of the follicle, reducing the contact area of the GMC. This reduces hair production from the outside of the hair shaft inwards. In cases of significant tissue expansion as in the inflammatory response, this reduction in production area continues until the hair becomes detached and shed. The peripheral reduction of hair production inwards, creates the rounded end or so called club hair.

This “hydraulic” connection in evolution represents a very elegant dermal mechanism that integrates the dermal temperature control systems in the simplest way possible. It also provides for hair shedding when required, to reduce the chances of serious infection of wounds in hairy mammals.

The principle here is that hair growth is linked to the local tissue rigidity, modified by local changes in tissue fluid pressure. This means that any factor that affects tissue rigidity and tissue fluid pressures, will also affect hair growth. So can we identify any examples of this connection in humans?

Human Hair Patterns

On the face of it, human hair patterns don’t make much sense. We have hair follicles in most areas of the body, but before puberty most of these are in a miniaturised state producing small vellus hair shafts. The excessive scalp hair growth we have has no practical purpose, and in terms of survival in evolution has real disadvantages. I will discuss scalp hair later in connection with androgen related changes.

The first enigma answered by this dermal connection, concerns eyebrow hair growth. How do we get these small islands of increased hair growth?

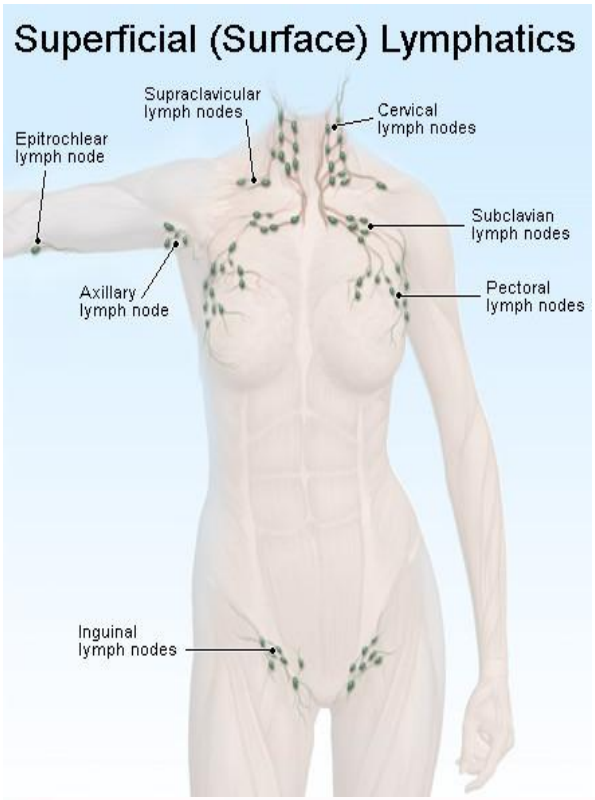
If you “raise” your eyebrows and run a finger from above into this hair, you can feel the change in tissue rigidity. Eyebrow hair grows from a strip of tissue noticeably softer than the surrounding tissue. Less resistance to follicle enlargement, larger hair follicles. Boxers can testify to how easily this soft tissue can be damaged.

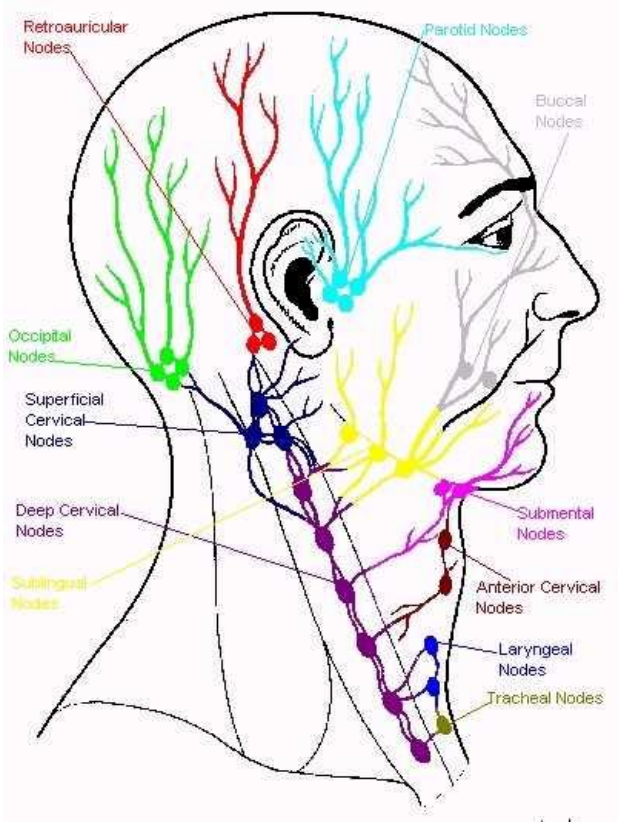
This raises an interesting question. Do eyebrows represent the last remnant of our original fur? If so what is the difference in composition of our generally

tougher tissue? In evolution what circumstances could have made this adaptation towards tougher tissue an advantage?

The principles of this external pressure control upon follicle size, require that significant changes in hair growth are linked to significant changes in local tissue fluid pressures. This means the areas involved must be privileged in some way towards significant changes in tissue fluid pressures. It is accepted that changes in hair growth at puberty are related to androgen action, in particular the action of DHT. We are all aware of the areas of increased hair growth.

They say a pictures worth a thousand words, and below are diagrams of the superficial lymphatic system. The lymphatic system plays a major role in the control of tissue fluid levels and pressures. These diagrams show concentrations of lymph vessels close to the surface tissue, that is close to hair follicles.





The implication is of course that DHT significantly increases lymphatic drainage efficiency, reducing local tissue fluid levels and pressures and increasing local hair growth. This action is physically possible through androgen receptors in

the muscle fibres that move fluid through lymph vessel contractions, and the one way valves. But why should DHT have such an action?

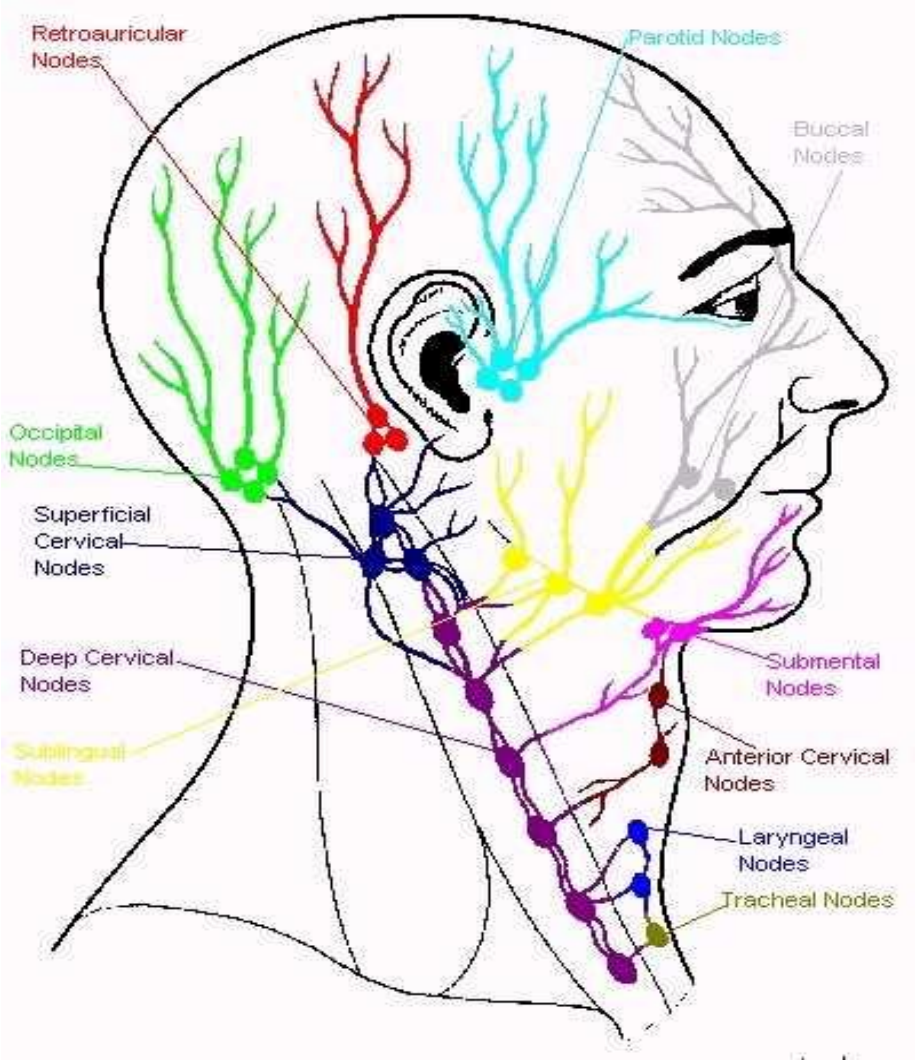
This makes perfect sense in terms of the tissue building and performance related characteristics of androgens. Increasing lymphatic drainage increases tissue fluid turnover in tissues, increasing nutrient supply and waste removal. The analogy here is to the high performance exhaust system, required to realise the full potential from a high performance engine.

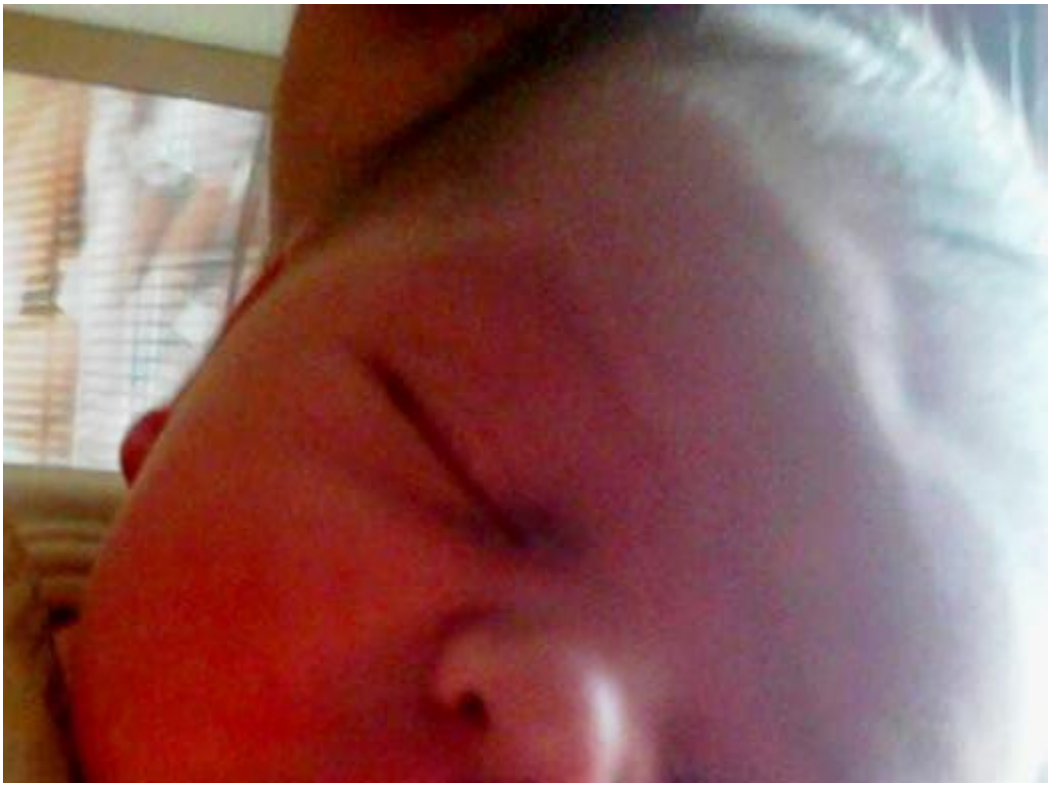
The link with hair growth and lymphatic function, puts the subject into the realm of complex fluid dynamics. The prevailing tissue fluid levels and pressures, result from the fluid feed and drainage equation. Arterial blood supply, venous return and lymphatic drainage all combine here. In any complex "plumbing" system, increasing the flow in one area can have the opposite effects of reducing flow from other areas. This is particularly relevant to systems having one way valves.

Given these fluid balance principles and human physiology it is perfectly feasible that the increased lymphatic drainage initiated by DHT, can have an opposite effect in vulnerable areas at the end of the system such as the scalp.

Modern Human Scalp Hair

There is evidence for the role of this external growth control in normal human scalp hair growth. Again, with reference to this diagram of the superficial lymphatic system of the head. There is a close relationship with the point at which the scalp superficial lymphatic's start to go deep, and the base of the hairline. Although not particularly obvious, a change in the characteristics of scalp tissue can be seen at the point of the frontal hair line. This is more obvious in babies under certain lighting conditions.


Retroauricular Nodes
Parotid Nodes
Buccal Nodes
Occipital Nodes
Superficial Cervical Nodes
Deep Cervical Nodes
Submental Nodes
Anterior Cervical Nodes
Laryngeal Nodes
Tracheal Nodes



It is accepted that the evolution of the human brain required a complex and efficient circulation system. Assisted by bipedalism and so gravity, the cranial lymphatic's have a short path to drain back into the main circulation. I suggest that Good circulation and lymphatic drainage combined with softer tissue in the area, combine to produce excess human scalp hair growth. It can also be seen from the lymphatic diagram, that the male baldness area lies at the end of the system, and so can be vulnerable to back pressure effects from below. The cranial fluid dynamics, and factors that affect these and lymphatic function and the timescale, are complex and beyond the scope of this article.

However, i would describe one particular principle relating to scalp tissue fluid levels. If lymphatic drainage is reduced in this area, this would not necessarily cause a significant increase in local tissue fluid pressures. Other factors are involved in individuals, most importantly the local blood pressure. Higher blood pressure feeding the area, would be more likely to create higher tissue fluid pressures where there is reduced drainage. Studies have confirmed a link with male baldness and coronary heart disease. http://www.medicalnewstoday.com/articles/258601.php Given this connection, the logical common factor here would be a high core blood pressure.

The Case for Increased Tissue Fluid Pressure as Directly Causal in Male Baldness

The scalp is a relatively thin tissue curving around the skull, and as such is well held together. It would take a considerable increase in tissue fluid pressure before any real swelling becomes obvious. Nevertheless, excess tissue fluid pressure in male baldness areas can be demonstrated by the clinical pitting edema test. The shiny bald head also offers a clue here. Once you know what to look for, you can actually see the point on the forehead were the swelling starts. Given that hair recedes from the front of the hairline rearwards, suggests that this forehead swelling is moving upwards over time. In contrast older men who retain a good thick hairline, show no sign of this forehead swelling.

All the recognised tissue changes in the bald scalp compared to hairy scalp, are also recognised in cases of increased tissue fluid pressure like lymphedema. This includes significant inflammatory changes, hypoxia and increased fibrotic tissue formation.

Hypoxia (a reduction in oxygen levels) is present in areas of male baldness. http://www.ncbi.nlm.nih.gov/pubmed/8628793 Some suggest hypoxia has a direct link to reduced hair growth. The paradox here however is that surgical induction of hypoxia in the scalp, significantly improves hair follicle condition and hair growth. http://www.ncbi.nlm.nih.gov/pubmed/157397 The only difference here is in the mechanism of how the hypoxia is generated.

Hypoxia in cases of increased tissue fluid pressures and levels like lymphedema, is due to the relative stagnation of the fluid. In the surgical procedure, hypoxia is induced by reducing the blood supply to the tissue. The difference here is that this also reduces local tissue fluid levels and pressures. This supports the causal mechanism in changes in hair growth, as the changes in tissue fluid pressures.

The same kind of immune changes and fibrosis recognised in MPB, are also known to be caused by tissue edema.
http://www.ncbi.nlm.nih.gov/pubmed/23185491

One of the most interesting studies of in-vivo androgen related hair growth in recent years, also supports this causal relationship. In my earlier description of the advantages of this mechanism in evolution, I discussed the link with sweating capacity. Increased fluid pressure equals reduced hair growth and increased sweating capacity and vice versa. This relationship was clearly confirmed in this study into androgen related hair growth/loss.
http://www.ncbi.nlm.nih.gov/pubmed/3203673

Apart from reducing the androgen stimulus, all treatments shown to improve hair growth in male baldness, have the common factor of reducing surface tissue fluid pressures by one action or another. These include Minoxidil, latanoprost, anti-inflammatories, and low level laser devices. Low level lasers are now licensed in the treatment of both male baldness, and lymphedema.
http://www.hairmax.com/

http://www.lymphedemapeople.com/thesite/lymphedema_laser_treatment.htm

In long term male baldness there is a formation of fibrotic scalp tissue around the miniaturised follicles. Some scientists have stated that this is a physical barrier to the re-enlargement of these follicles. So this already accepts this spatial growth control in this context, that when applied to follicle enlargement in general answers most of the outstanding questions. There is also evidence for the involvement of tissue fibrosis, in the effects of hair transplantation.

The Enigma of Hair Transplantation

The early hair transplantation studies date back to the 1950's, and used large punch grafts of around four millimetres in diameter. These were taken from areas of the scalp not affected by baldness, and transplanted into bald areas. In these studies of up to two years, the hair in these large grafts was reported as growing normally. However there were no longer term follow up studies of these large grafts.

It is now reported by those involved in the repair of early transplantation procedures, that these large grafts commonly loose most of the central hair. This effect known as "doughnutting" is regarded by some as inevitable in grafts of three millimetres diameter and over. The explanation for this from those with a commercial interest, is that this is caused by hypoxia induced by the initial procedure.

http://www.bernsteinmedical.com/research/art-of-repair-in-surgical-hair-restoration-part-i-general-aspects-of-repair-and-basic-repair-strategies/

However this and other claims made by commercial transplantation, have no real scientific basis. If this central hair loss in large grafts was due to hypoxia, this would have been seen within the timeframe of the early studies. What data is available here indicates the extended timeframe involved, as being consistent with the continuation of the male balding process in the larger area of these grafts. This is possibly the most important issue in historic hair growth research, as current research continues to be based on assumed internal differences in follicles. As i said earlier, it has always been possible to design

experiments to confirm what is really happening in these larger grafts and this could still be done.

In my opinion the question should be why does hair growth survive around the edges of these large grafts?

The early transplantation studies accepted the possible alternative explanation, that the effects could also be due to a factor induced by the procedure itself. If it is accepted that miniaturised follicles in MPB can be prevented from changing size by external fibrotic tissue, then the same principle must also apply to large follicles

Modern successful hair transplantation has evolved to use very small grafts, containing as little as one hair follicle. After these large follicles are transplanted, the healing process starts around them. This produces scar tissue, and a more rigid fibrotic shell around these large follicles.

This creates the same situation recognised in the long term development of fibrotic tissue around small follicles in MPB, only in reverse. In this case the tougher shell formed around the large follicles, resists pressure backed movement of the external tissue into the follicles space. This conserves the large follicles space.

This explains why the only hair to survive long term in the old large grafts, is that around the edges affected by scar tissue. This also explains why the smaller the grafts are, the better the results. This principle also explains very simply, the strange results of a transplantation study in 2002. To date this is the only in-vivo study that has demonstrated a complete re-enlargement of human miniaturised MPB follicles.

http://www.jaad.org/article/S0190-9622(02)61499-9/pdf

Here both balding (MPB) and non balding follicles from the same individuals, were transplanted into immune deficient mice. These mice had normal levels of androgens, and very small grafts dressed of original dermal tissue were used. According to the current claim of androgens directly causing miniaturisation of disposed follicles, all the conditions existed to maintain these follicles in the miniaturised state. All the necessary “machinery” was within the transplanted follicles, and the levels of androgens were more than

enough to maintain miniaturisation according to the necessary increased sensitivity aspect of this claim.

In reality these miniaturised human MPB follicles enlarged by around 400%. This completely contradicts the historical claims that never had any real scientific basis, but still manage to persist even today.

What is just as important in this study, is that the so called androgen neutral large follicles also changed their size. These follicles reduced in size by around 40%, resulting in all the transplanted follicles reaching the same size within very close limits.

I think we have to use the scientific rule of parsimony when considering the results of this study. To try to explain these reversed changes in follicle size by direct androgen action and other non androgenic direct effects, would require adding unnecessary complication upon complication. There is only one explanation for these results that demonstrates true scientific parsimony.

In immune deficient mice the healing process is affected, and scarless healing can result. http://www.ncbi.nlm.nih.gov/pubmed/16808805

The simple explanation for the results of this study is this. The follicles stripped of original tissue, are transplanted into tissue that does not develop any scarring upon healing. This allows all the transplanted follicles to directly respond to the prevailing external pressure in the mouse tissue. This results in all the follicles adjusting to the particular size allowed by this prevailing external pressure.

Other Examples of Changes in Hair Growth

The evidence strongly suggests that it is changes in the local tissue fluid pressures, that are causal in most cases of changes in hair growth. This is the consistant common factor.

Many hormonal changes are known to cause changes in fluid retention, and so tissue fluid pressures. Women can experience hair growth changes related to hormonal changes, especially with pregnancy.

Most other cases of hair loss are related to inflammatory reactions of one sort or another. Anti-inflammatory drugs are used to treat these conditions, often referred to as an autoimmune reaction against the follicle. The claim here is that the follicles are being attacked by the immune system. But it is a very strange attack that just miniaturises the follicles whilst leaving them still functional? In my opinion this is just another not very well thought out guess, that seems to be the traditional norm in hair research. The common factor here again, is an increase in the local tissue fluid pressures.

There are cases of rapid onset hair loss and shedding, for example radiation poisoning and chemotherapy. In radiation poisoning the widespread cell damage causes significant edema and tissue swelling. This is also true in chemotherapy.

Because chemotherapy destroys rapidly dividing cells, this is also claimed as the mechanism of hair loss. If this is true, it will be reflected in the shape of the base of the hair shaft being shed. Such an effect of these drugs would be quite immediate over the whole production area of the follicle. The shape of the shed hair with some shrinkage, should mirror the shape of the DP/germinal matrix of the follicle demonstrating a “dented” end.

Chemotherapy also causes significant edema and tissue swelling, because of the cell destruction. If the follicle distortion effect in mammalian evolution described above is valid, then both radiation sickness and chemotherapy related hair shedding should produce the club hair shape. So is it the dented end of hair shafts, or the rounded club shape in these cases of hair loss?

Examples of External Pressure Effects upon Full Anagen Follicles

The relative movement of follicle elements described in the shedding mechanism above, can be confirmed by undertakers. The old myth that hair continues to grow after death, has been refuted by science. It is now accepted that tissue shrinkage around the follicles after death, moves the hair production area upwards taking any hair stubble with it. This is why undertakers shave the beard area after the initial period of tissue shrinkage.

http://sciencefocus.com/qa/do-fingernails-and-hair-really-keep-growing-after-death

There is also a common example of how this relative movement of follicle elements, changes hair growth in life. In its evolved form it is changes in internal tissue fluid pressures, that distort follicles in full anagen to change hair growth. However external pressure on the skin for an extended period, will also mimic internal tissue shrinkage creating the same relative follicle movements. Here again the skin surface moves closer to the DP, increasing germinal matrix contact and so hair growth. This can be regularly seen after plaster casts are removed. http://www.independent.co.uk/life-style/health-and-families/health-az/hair-growth-why-is-my-leg-hairy-762704.html There is speculation about why this happens, but the common factor here again is external pressure.

Current Hair Loss Research

Any really effective medical treatment has to address the primary cause of the condition. What this external pressure mechanism means, is that the recognised changes in the male bald scalp are largely downstream from the actual cause of follicle miniaturisation. Tissue edema and inflammatory actions are closely linked, one can create the other and vice versa. It is important for effective treatments to target the initial cause of the increased fluid pressure.

According to this external follicle size control, there are no issues with the normal function of the hair cycle. The hair cycle is in effect being adjusted by external pressure, as it evolved to do.

This explains why mouse and in-vitro studies are just not representative of the human situation. Treatments that show some promise in mouse and in-vitro studies, have consistently failed to live up to this promise in humans for this reason.

One particular area of research has regularly appeared in the press over the last twenty years or so. Companies pursuing this have come and gone in this time, and still nothing significant has developed from this research to date.

This is the generation, and or re-generation of hair follicles through cell based treatments.

The idea here is based upon the traditional assumption of direct follicle sensitivity to miniaturisation by androgens. The claim here is that with the right procedure, cells from androgen "resistant" follicles can be made to create new follicles in the bald area. Some claim that local miniaturised follicles can also be made to enlarge using such procedures.

This overruling spatial control in physiology has an important role in the regulation of all normal tissue growth and regeneration. Only cancer cells fail to respond to this, and the molecular details of this control are of much interest in cancer research.

What this means in terms of cell based hair loss treatments is that these are doomed to failure in male baldness. Any manipulation of cells at the molecular level to get around this spatial control, would be far too dangerous and would not be licensed.

The only way forward in effective hair loss treatments becomes obvious in the light of this external control.

An Important Testable Link with Gender Related Disease

The indication here that the androgen DHT significantly increases lymphatic drainage has important implications. It is not currently thought that there is any significant gender difference in lymphatic efficiency. However such a difference would make a lot of sense of some serious gender related diseases, especially female susceptibility to autoimmune disease.

We know that lympedema has a pronounced effect upon the prevailing tissue immunology, increasing immune sensitivity and the chances of secondary immune reactions. Such a gender difference in lymphatic efficiency would in simple terms suggest that compared to men, women have low level tissue lymphedema. This is consistent with the recognised differences in gender immunology http://www.ncbi.nlm.nih.gov/pubmed/3907369

It has been accepted for a long time that sex hormones must be involved in female disposition to autoimmune disease, this connection indicates DHT as a

major player here. This important question would be quite easy to test by those in the position to do so.

There is an existing study of lymphatic efficiency that also supports this gender difference. This state's quote "Unexpectedly, three of the four parameters were significantly lower in women compared to men". http://www.ncbi.nlm.nih.gov/pubmed/9327386

This study tested lymphatic efficiency in the forearms of men and women. There are topical DHT creams and the prior use of these on women in such a study, could test if DHT is responsible for this gender difference. I can see no technical reason why this important question could not be tested, given the will to do so?

Discussion

This dermal interaction demonstrates a simple pathway from environmental conditions, to genetic expression involving tissue growth. This is mediated through hydraulics at the functional level, and not something that would come to light in molecular studies alone. The hydraulic characteristics of pressure and levels are also evident elsewhere as important at the functional level in biology.

Any secreting gland must have arrangements for an excess of local tissue fluid, as the raw material for the required secretion. It is also possible for a local fluid pressure increase, to be involved in signalling for the tissue development of a secreting gland. A number of sex hormones in particular demonstrate effects upon hydraulic changes in glands. Women are more aware of such regular glandular changes, with fluctuations in hormone levels.

In this dermal interaction, the male hormone DHT is implicated as significantly changing local tissue fluid pressures/levels through lymphatic changes. DHT plays a major recognised role in prostate gland development and enlargement. Drugs are available to reduce amounts of DHT in middle aged men with prostate enlargement, to shrink this gland. One side effect here is breast enlargement, demonstrating the kind of opposite effect common in complex fluid dynamics as indicated in DHT related male baldness.

There is also one other important example of significant hydraulic changes in tissue, that everyone experiences on occasion. No real functional significance is given to this particular hydraulic change, it just being regarded as a painful inconvenience. However i think it is a very important part of the immune response.

As referred to above any tissue injury for whatever reason, creates local tissue swelling. When tissues are injured it is important that the various immune components can penetrate the site, to clear up and address any infection. These components all have a physical size, and dense tissue presents a significant barrier to the penetration of these components into the tissue from the bloodstream.

Tissue swelling opens up the tissue moving the tissue cells apart. This allows easy access into the tissue for these immune components, and space to do their job. The increased local fluid pressure also speeds up the flow into the local lymphatic's to initiate further immune responses.

This suggest this hydraulic influence at the functional level, plays a significant role in increased immune sensitivity linked to lymphedema. This is yet another reason why, it is important that the indicated action of DHT upon lymphatic efficiency be tested by those in a position to do so.
