The consequences of insufficient IGFs are dramatically illustrated by the 'lit/lit' strain of mouse, genetically deficient in IGFs. Here a lit/lit mouse (black) is seen next to a normal mouse of the same age.

The molecules of growth

'Eat up your food', we tell our youngsters, 'and it will make you grow big and strong'. But, no matter how much you eat, it is your body's hormones that really enable growth to occur, and also control the extent of it.

Undeniably, you cannot grow without food; equally, your body stops growing after adolescence and no amount of food will induce further growth — only further girth!

But apart from children 'growing up', other types of growth occur: in adulthood muscles can grow with use, and following a wound most tissues will grow to repair the damage. Normally, once the wound is closed the growth ceases, suggesting that an efficient control exists.

In humans and other mammals a very complex series of hormones regulates the growth of the whole body, following the instructions laid down in the genes to arrive at the optimum size for the individual. The body is no democracy — its unconscious regulation depends on a strict hierarchy, with a tiny part of the brain called the hypothalamus at the top of the pyramid of control.

Close to the hypothalamus, and under its direction, lies the pituitary. It is the main gland in the endocrine (or hormonal) system, and the role of many of its hormones is to cause other glands — such as the gonads, or the thyroid — to produce theirs. Following instructions from the hypothalamus, the pituitary itself produces growth hormone or somatotropin, which is responsible for the co-ordinated growth of the entire body.

In some children the gland makes little or no growth hormone, and these unfortunates used to remain as dwarfs. Nowadays, when their early lack of growth is noted, they can be treated with somatotropin, and so pituitary dwarfism is becoming a thing of the past. (Interestingly, an extremely rare class of individuals, called Laron dwarfs, do not respond to growth-hormone therapy, for reasons that will be revealed later.)

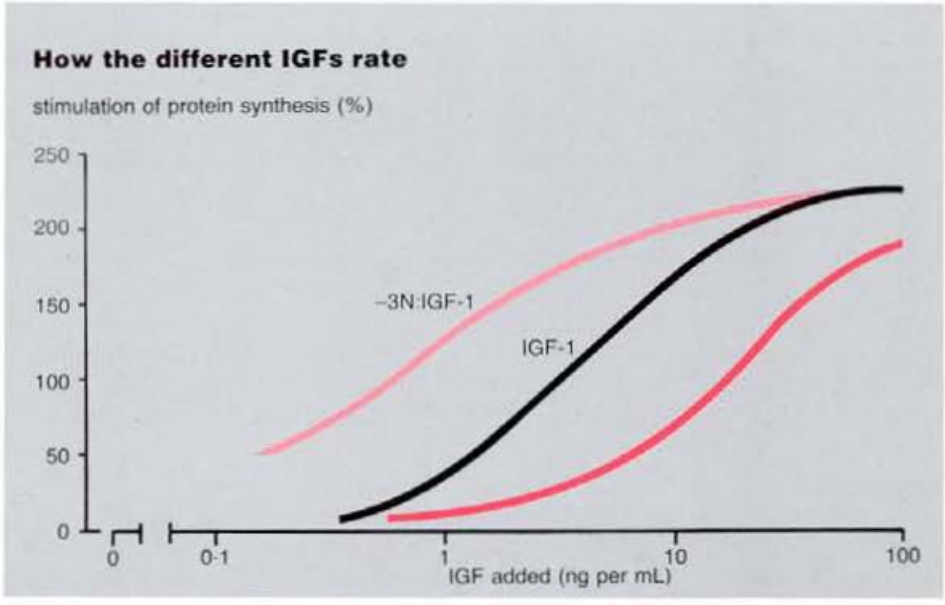
Wasting

In certain situations, we see almost the opposite of growth. Breakdown, or catabolism, of tissues occurs in various inherited diseases and under conditions of extreme physiological stress — for example, following car crashes, severe burns, or chronic infections such as AIDS. In hospitals throughout the world, sufferers from these conditions lie in intensive-care units, sometimes unconscious, literally wasting away. We instinctively feel that their thin frames, lack of strength, and sallow complexion signify a body in decline.

Despite the best efforts of the medical profession, the chronically sick or injured tend to lose weight, even if they are fed intravenously. Children in these situations don't grow as much as they should. It was well known last century that young adults

The start of the long road to IGF: CSIRO technician Kerrie McNeil with a bucket of fresh cow's colostrum. Later, chromatography is used to separate out about 100 micrograms of pure growth factor from the original bucket-full of colostrum.

IGFs 1 and 2 and the –3N truncated form stimulate protein synthesis in cells when added to culture medium in nanogram per mL quantities (a nanogram is one thousand-millionth of a gram).



with tuberculosis would slowly become thin and weak even if they ate plenty of good food.

This generalised atrophy of the body is called cachexia, and loss of muscle accounts for a large part of it. Doctors are still not quite sure how it occurs.

Cachexia is often just one aspect of an unusual state that the body may enter following severe, disruptive trauma (often called polytrauma) — be it occasioned by cancer, infection, burns, or multiple fractures. Other features include fever, a persistently high metabolic rate, and a vastly increased calorie requirement. Muscle wasting alone can be the primary problem in several conditions, such as the inherited muscular dystrophy or cystic fibrosis, although in the latter an inefficient distribution and use of food energy appears to be part of the problem as well.

Recent research by a team of about 30 scientists from the CSIRO Division of Human Nutrition and the University of Adelaide offers hope for dealing with the breakdown of muscle in the chronically sick and injured. The work may also be applied to animals. When under stress, their muscle mass may break down too. As muscle contains the bulk of protein in the body, the whole problem is connected with the regulation of the metabolism of amino acids (the building blocks of proteins), and anything that causes growth in cells — especially those of muscle, cartilage, and connective tissue — may help counteract the condition.

For any type of growth, cells need to divide or enlarge, and for this, they need to take in more nutrients from the bloodstream. Now, the uptake of food molecules across the membrane of a cell is very carefully controlled. One of the best-known and most intensively studied of all hormones — insulin — affects this ability of cells to take up nutrients.

Insulin and its family

Insulin is often called the hormone of plenty; produced by the pancreas in response to increased levels of glucose in the blood (as may result following a large meal), it gives cells the capacity to take up more glucose, and to a lesser extent amino acids and fats, from the circulation. This reduces the surfeit in the blood-stream, following which the release of insulin falls and thus the hormone accomplishes its primary function — the regulation of the blood-glucose level.

A deficiency of insulin — diabetes mellitus — can cause the body's cells to starve in the midst of plenty (as the glucose level rises) and, untreated, may be fatal. Insulin is a simple protein of 51 amino acids arranged as two chains (called polypeptides) that are joined together by links or bridges between sulfur-containing amino acids.

In the early 1970s researchers in diabetic clinics found that something else in the body could show mild insulin-like effects. This 'something' was definitely not insulin itself, as proved by the failure of antibodies to insulin to suppress its activity. Following further work, Swiss scientists isolated factors from human blood in 1976, which brought about this 'non-suppressible insulin-like activity', as it was first christened.

At a similar time came the discovery that the production of these substances depended on growth hormone. They were therefore named somatomedins, because they were the medium through which growth hormone worked. (So despite its name, growth hormone does not directly cause growth; it will bring it about only by stimulating the production of other factors.)

Finally, in the early 1980s, scientists demonstrated that these substances promoted growth in normal animals, and would also do so if given to animals that had no pituitary and therefore lacked any growth hormone. By that time, biochemists had worked out the precise nature of somatomedins, showing them to be polypeptides with a similarity to insulin, and since then they are usually referred to as insulin-like growth factors — IGFs — being classified (with a few other molecules) in the insulin family of proteins.

Despite their similarity to insulin (see the box on page 25), IGFs in naturally occurring concentrations have only a small effect on the regulation of blood glucose. Certainly, in general they do facilitate the transport of most nutrients (including glucose) into cells, which accounts for their slight insulin-like effect. However, they are most effective at increasing the accumulation of protein within cells, which in turn affects cell size and, indirectly, division.

Two types of factor were originally identified in humans: IGF-1 and IGF-2, of 70 and 67 amino acids respectively. Immediately, IGF-1 attracted the most interest because, of the two, smaller quantities of it stimulated growth in isolated cells. Most IGF-1 comes from the liver, which produces it in response to pituitary growth hormone, although scientists have recently shown that many other tissues can also release some, which may be important locally. However, the consensus is that the IGF-1 in blood mainly comes from the liver, and that this organ represents by far the most important source.

In contrast, IGF-2 seems to have no predominant source — many cell types produce it. Furthermore, it does not fall under the control of growth hormone. Although effective in cell culture (usually at higher levels than needed with IGF-1), when given to an animal it does not stimulate growth at doses that are successful with IGF-1.

The existence of insulin-like growth factors was of great interest to a group of scientists led by Dr John Ballard in the CSIRO Division of Human Nutrition. In the late 1970s, Dr Ballard and his colleagues were studying how hormones and growth factors regulate the metabolism of protein in cell cultures, while Dr Frank Tomas, in the same Division, was developing methods

suitable for measuring protein metabolism in experimental animals and human subjects.

The CSIRO scientists were especially interested in ways of inhibiting the major breakdown of protein that occurs in various states of stress, disease, or injury. They showed that IGFs and other growth factors had significant effects on protein metabolism and thus may have important applications in treating human diseases where 'wasting away' through muscle loss is important, such as with polytrauma, as well as in improving the growth of muscle (rather than fat) in farm animals.

An unexpected finding

In 1982 Dr Ballard teamed up with Dr John Wallace, of the Department of Biochemistry at the University of Adelaide, to purify growth factors that acted primarily on muscle. They chose as their starting point cow's colostrum — the protein-rich fluid that the mammary glands secrete before true milk. (Other researchers had used serum as their growth factor source, but Dr Ballard knew that colostrum supported the growth of cells *in vitro* more efficiently than did serum, so he suspected that it would yield a richer harvest of growth factors.)

Divisional biochemist Mr Geoff Francis and University colleague Mr Chris Bagley purified the two IGFs from bovine colostrum and determined the sequence of their amino acids. In the process, another peptide showed up, which upon analysis turned out to be almost exactly the same as IGF-1 except that the first three amino acids were missing. The scientists refer to this truncated form as –3N:IGF-1. To their astonishment this molecule, when tested for its effects on muscle cells in culture, stimulated the accumulation of protein about ten times more efficiently than either of the two previously known IGFs.

Using cell cultures, the team investigated exactly how IGFs exert their effects. By measuring the rates of protein synthesis and breakdown in cells exposed to IGFs in their culture fluid, the scientists found that the growth factors have a double action: they actively stimulate protein synthesis and the transport of nutrients into the cell, and at the same time inhibit the usual processes of protein catabolism or breakdown.

As with most chemical messengers, the IGFs attach to cells by binding to complementary-shaped receptor molecules on the membrane. Thus, IGF-1 and its shortened derivative bind to one receptor and IGF-2 to another. Surprisingly, IGF-2 only produces a noticeable growth when it binds to the IGF-1 receptor, something it does not always do as readily as IGF-1 itself (although it can with some cells), and this may account for its lower effectiveness.

Attachment to the receptors starts a chain of events that we don't yet fully understand, but that culminate in the effects on protein metabolism already outlined, as well as an increase in the synthesis of the both DNA (necessary before cell division can take place) and RNA (the messenger molecule that translates the DNA's instructions into the manufacture of enzymes and other proteins).

Together, these happenings bring about tissue growth. This mainly results from an increase in cell size, although the number of cells also increases, especially if other factors — such as the fibroblast growth factor (FGF) whose principal function is stimulating division — are present. While IGFs alone do not cause cell division as effectively as these other molecules, they have a far greater impact on protein metabolism and the entry of nutrients.

Most cells, including incidentally fat cells, have receptors for IGFs, but the factors do not work the same way on all tissues. We know that IGF-1 promotes growth most effectively in the musculoskeletal system; in animals it will promote the growth of muscle at the expense of fat, by enabling the body to channel amino acids into synthesis of protein and away from breakdown for energy release.

Binding and potency

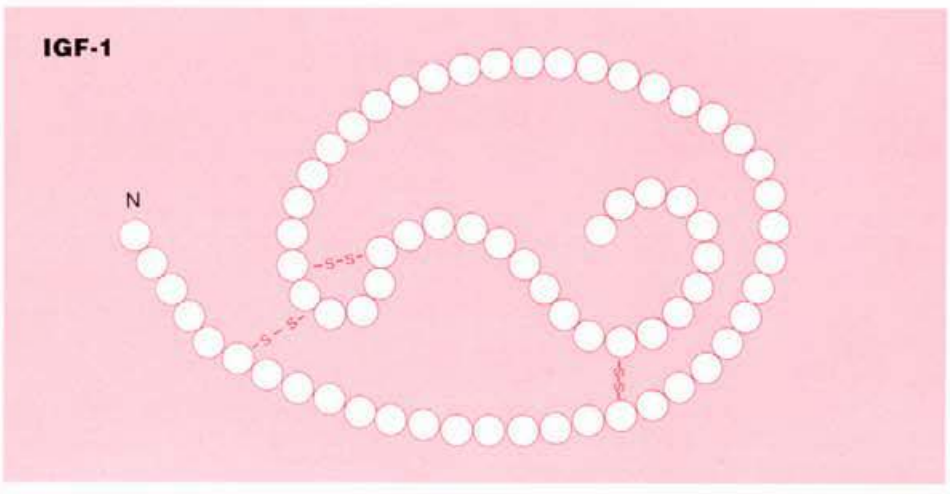
Having isolated IGFs from bovine colostrum, and determined their amino acid sequences, Dr Ballard and his team compared them with the sequence for human IGF-1 that had been discovered overseas. The results proved somewhat surprising: the IGF-1 of a cow is identical in every way to that of a human. As later work showed, pig IGF-1 is also the same, and that of the sheep differs by only one amino acid. Even the evolutionarily more distant rat and mouse have only three and four different amino acids respectively.

Many important molecules show similarities between species, but to find such a small variability usually implies that the molecule in question is so important that during the course of evolution any accidental changes to it have been selected out. Biologists speak of the molecule, somewhat reverently, as being 'highly conserved'.

Birds also have IGFs — Dr Ballard's team and the Adelaide University collaborators found that chicken IGF-1 differs in only four amino acids from the human — and probably fish, too. This suggests that IGFs were around before mammals evolved and have had an important role for a long time. They are certainly more highly conserved than insulin itself.

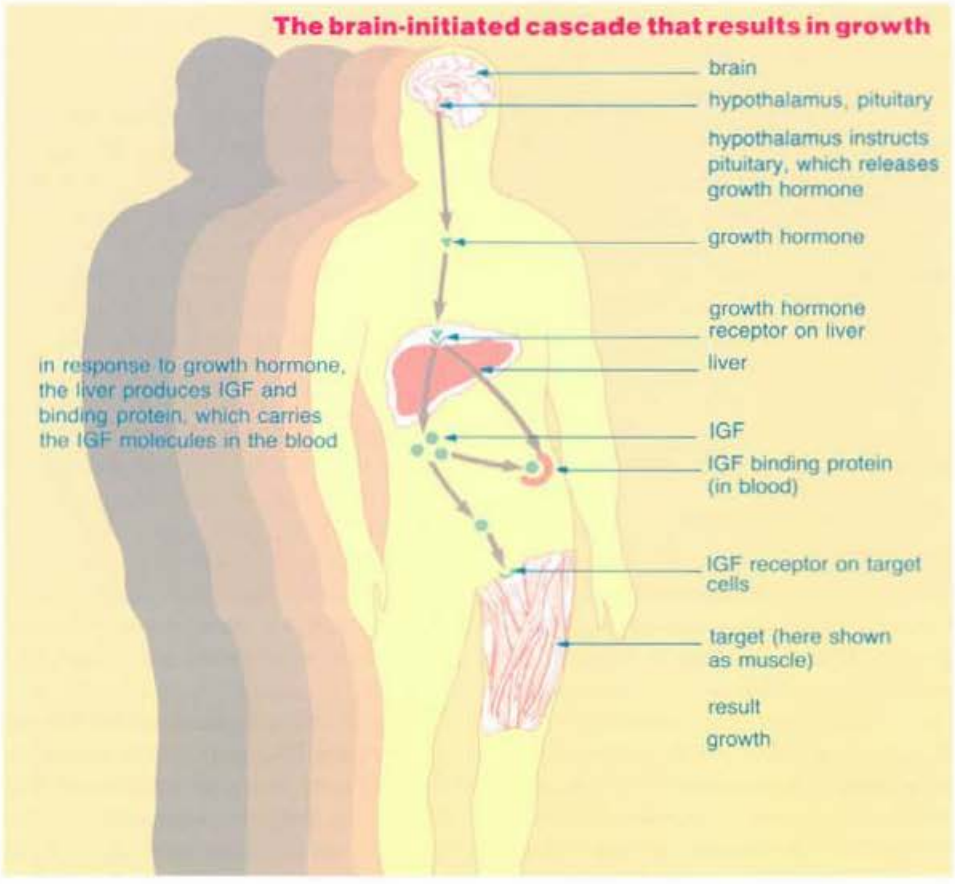
But why is the previously unknown form of IGF that Dr Ballard's team discovered so much more potent that the other two forms? And what useful role can the others play if –3N:IGF-1 is such a 'super-factor'?

Scientists already knew part of the answer to the first question, as it was well established that, like many important biological molecules, the IGFs do not float around freely, but rather are bound to special proteins. A high-molecular-weight binding protein (HMWBP), produced by the liver under the influence of growth hormone, is present only in blood. When attached to this protein IGF-1 has a far longer life than when it is free. (Its half-life when bound varies from 3 to 24 hours depending on the animal and the experi-



IGF-1 is a small protein of 70 amino acids (represented by circles). Disulfide bonds (shown as S–S) between pairs of sulfur-containing amino acids help to hold the chain into the configuration necessary for it to be effective. The potent –3N form has lost the last three amino acids from the end marked N.

This is a simplified view of what happens. In reality the target tissues may also produce IGFs and binding proteins, although not in the same quantities as the liver. (Also, the diagram does not distinguish between IGFs 1 and 2, or high- and low-molecular-weight binding proteins.)



mental conditions. When unbound the value is less than 1 hour.)

On the other hand, there's also a family of low-molecular-weight binding proteins (LMWBP) — produced by most tissues and found in extracellular fluid as well as blood — that produce the opposite result when attached to IGFs; they greatly reduce the factors' biological activity. One of the biochemical experiments, mixing radioactively labelled IGFs with one such LMWBP from bovine kidney cells, showed that the –3N form bound to the protein with far less affinity than did IGF-1 and IGF-2. It seems fairly clear, then, that the loss of three amino acids from one end of the IGF-1 peptide, by preventing effective binding to LMWBP, allows the factor a far greater biological activity. The lack of binding is the secret of its potency here.

However, when the scientists gave radioactively labelled –3N:IGF-1 to animals, they discovered that it remained in the blood nearly as long as the normal form. This result implies, of course, that it is being preserved by attachment to a binding protein, so it seems that it does attach to the HMWBP in blood. Mr Laszlo Szabo, in the Biochemistry Department at the University, and Dr Robert Baxter, of the Royal Prince Alfred Hospital in Sydney and a world leader in the area of IGF binding proteins, confirmed this idea in a series of experiments. The implication of this proof is that the tenfold increase in biological activity observed in tissue culture may not apply in the whole animal.

But the story doesn't end in the bloodstream. Once into the tissues — the realm of the LMWBPs — the –3N version may find itself unbound and thus able to be more active. At the moment, nobody knows for sure.

So will the substance be of clinical value? The latest results indicate that the –3N version will certainly stimulate the growth of animals, and potency comparisons between it and IGF-1 are still in progress. And exactly what is happening in the extracellular fluid awaits further research.

The less active — at least *in vitro* — IGF-1 and IGF-2 are probably not as redundant as the –3N form may make them seem. Dr Ballard feels it's likely that the latter is not naturally occurring. Although the team isolated it from a natural product, it is well known that cells and biological fluids contain plenty of protein-digesting enzymes that can cut peptides in various places. A number of such proteases could easily 'bite off' the three amino acids at the end of the IGF-1 peptide during the extraction process, so creating the truncated form.

The natural occurrence in blood of inhibitors of these protein-cleaving enzymes would explain why –3N:IGF-1 has not been isolated from that source, although scientists overseas have recently obtained the peptide from brain and uterus. Thus, IGF-1 and IGF-2 are quite likely to be of great importance in the normal running of the body.

Applications

The IGFs will not have a blanket use wherever growth is required. Growth hormone will remain in use in medicine and perhaps steroids in farming. For example, doctors will still continue to treat pituitary dwarfism with human growth hormone, the production of which is well established. IGFs are likely to cost more than growth hormone, the development of which — to increase milk production in cattle and improve the growth of pigs — is now proceeding rapidly. (Chickens, incidentally, don't respond very well to added growth hormone so there may be a role for the judicious use of IGFs in the poultry industry.)

Investigations have revealed that in animals stressed by parasites, physical trauma, high temperatures, or simply poor nutrition the quantity of IGF-1 in the blood falls. The level returns to normal once the stress has passed.

You might expect that administering growth hormone in these cases would, as usual, cause more IGF-1 to be produced and so help prevent loss of condition. Paradoxically, it seems that it would not. A stressed animal — or indeed person — has only a limited ability to produce IGF-1 in response to growth hormone. The normal link between the two is at least partly broken, due to a reduction in the number of growth hormone receptors. How that is brought about nobody really knows. Growth hormone is produced in greater than usual amounts under the stresses, but IGF levels decrease, and the result can be muscle wasting.

Although IGF treatment should help, therefore, administering it in the field would involve mustering the animals and, once that's done, it may be more appropriate to deal with the cause of the stress condition directly. But when you need to transport animals long distances, as is frequently the case in Australia, then an IGF injection before the trip could retard the muscle loss that the stress of the journey often entails.

But perhaps the main application of the team's research will be a faster, more

effective treatment of human polytrauma victims. Benefits will be economic as well as humane. In Australia, intensive-care treatment costs at least $1000 million every year. World-wide, the amount is likely to be 50 to 100 times more. Much of the expense is simply due to the fact that patients stay so long in hospital because they are too weak to go home. Any treatment that safely results in a shorter stay will reduce these costs. Of course, not all patients would be in the right sort of clinical situation to respond to therapy with a naturally occurring or modified IGF, but young, otherwise healthy, victims of multiple fractures or burns should benefit and so leave the wards sooner.

Following polytrauma, the level of growth hormone in the blood usually rises but that of IGF-1 falls — exactly as in animals. Furthermore, car-crash or burn victims suffer severe damage to tissues and this releases compounds that eventually bring about widespread changes in the metabolism of cells throughout the body. Protein from the body's now-unused muscles is broken down into amino acids that are wastefully consumed for energy.

Similarly, in chronic infections or cancer, cells of the immune system release a substance called cachectin or tumour necrosis factor that, if present for long enough, seems to be responsible for causing fever, tissue breakdown, and weight loss. The net result is that nutrients are removed from muscle and channelled to the liver. Presumably the 'point' of this is to use the protein from inessential muscle tissue to help in healing more vital parts of the body, or fighting an infection, at a time when the person would not be expected to be able to find or eat any food. In fact, these effects may be unhelpful and appear to be one example — allergy is another — of the body's response to something threatening being more injurious than the original stimulus.

In healthy people muscle is continually being broken down and synthesised at about equal rates; this accounts for the turnover of the body's protein pool. But the breakdown of muscle following polytrauma may rise by as much as five times the normal value and, to make matters worse, the rate of synthesis can also fall.

Because of their deranged and inefficient metabolism, and the need to heal major injuries, victims of multiple trauma and severe infection often have far higher caloric requirements than healthy, active individuals, even though they may be lying unconscious and doing nothing! (And if conscious they will certainly have lost their appetite and will not feel that they need many calories.)

Giving so much nourishment to such patients is difficult. Feeding by a tube into the stomach may not work when coma has drastically slowed the rate of gastric emptying and other digestive processes. And intravenous administration of such vast quantities of nutrient fluid upsets the normal concentration of nutrients in the blood. Moreover, it can put a tremendous strain on the kidneys, with the possibility of their eventual failure — a serious state that may endanger that patient as much as the original trauma.

On the other hand, if the doctors limit the quantity of 'food' to a level that would be 'normal', the patient has to cope with the added stress and metabolic changes of starvation. Feeding these severely ill patients is therefore — to use a cliche — something of a 'no-win' situation!

It is this state that Dr Ballard hopes IGF therapy can improve. Whether the –3N variant is used, or another even more suitable 'designer' version, the point is that IGFs are efficiency factors. They should allow the patients' cells to use nutrients more efficiently, and so cut down on the need to feed such large quantities, as well as reduce the breakdown of protein.

Premature babies, whose digestive systems are too immature to allow anything but intravenous feeding, also present a nutritional problem. If IGF therapy could increase their efficiency and cut down their loss of protein-derived nitrogen, it would speed their growth out of the critical phase.

Of course, clinical applications are still several years away, and studies on animals and human volunteers need to be done to test whether IGFs have any toxic side-effects when given for prolonged periods.

Although the cachexia associated with terminal cancer would also most likely be amenable to it, IGF treatment may not be sensible here. The problem is that the cancer cells may also respond to the growth factors — perhaps more so than the normal cells, because their basic characteristics include an over-enthusiastic desire to grow at all costs. Cancer and the control of cellular growth are inextricably linked, and we may well find that the biology of tumour cells incorporates an exaggerated response to the normal levels of IGFs; certainly, increased knowledge of IGFs could not but help in our understanding of cancer.

And what of those afflicted with a genetic growth deficiency? As noted above, human growth hormone should remain the treatment for those whose pituitary cannot produce adequate quantities. However, readers may congratulate themselves on their alertness if they have remembered the Laron dwarfs mentioned near the beginning

IGFs and similar molecules

Insulin consists of two polypeptide chains, joined by disulfide bonds and together comprising 51 amino acids. However, the *beta* cells within the pancreas (the main cells in the body that make it) produce it in the form of a larger molecule called proinsulin, which contains, in addition to the two chains, a third smaller peptide called the C-piece. The *beta* cells usually remove this — to give 'true' insulin — before they secrete the molecule, which is just as well as proinsulin has very little effect on the cellular uptake of glucose.

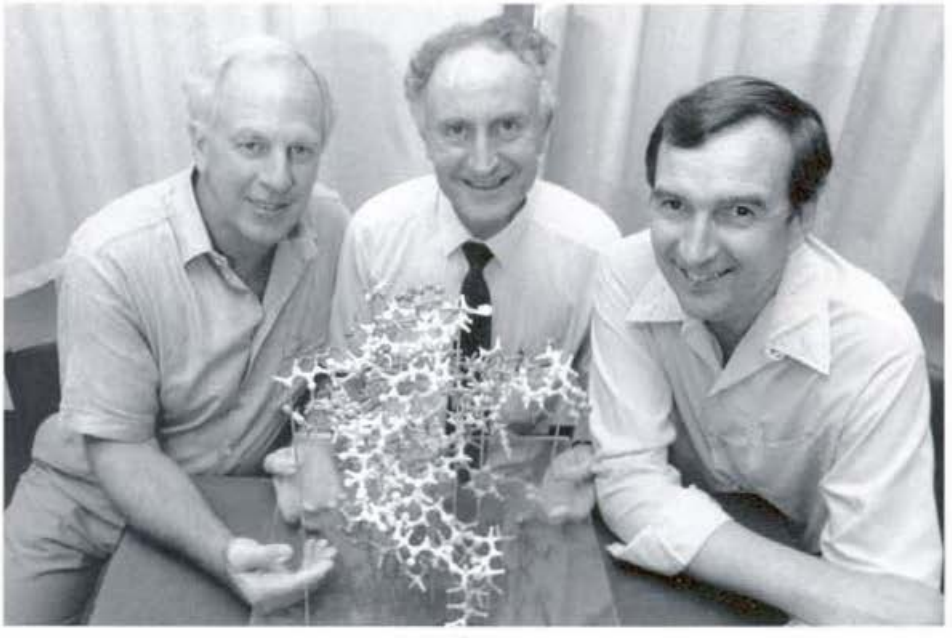
The IGFs are larger than insulin, but are made of just one peptide of about 70 amino acids. The chain folds on itself and disulfide bonds between sulfur-containing amino acids hold it in a particular configuration, necessary for its biological activity.

An important consideration in the commercial production of IGF by genetic engineering is to ensure that the molecules fold correctly after their synthesis by the 'expression system' — that is, the bacterial or other cells given the gene to produce the factors.

The region of amino acids in the C-piece of proinsulin also exists within IGF-1 and IGF-2. In fact, both growth factors have what biochemists call a 45–50% homology with insulin, meaning that about half of their amino acid sequences are the same.

Insulin does not have a binding protein, so its half-life in the blood is only a few minutes — much shorter than that of the IGFs. From a biological point of view this is fairly important, as insulin's function is to enable the body to respond quickly to short-term fluctuations in the level of glucose.

Also biochemically similar to insulin, although smaller, is the hormone relaxin. Secreted by the ovary during pregnancy it relaxes the muscle of the uterus, reducing its mobility and contractility, so helping to maintain pregnancy. Scientists think that deficiencies of it or lack of responsiveness to it may be responsible for some spontaneous abortions. It also helps prepare for birth by relaxing the connective tissue that holds the bones at the base of the pelvis together, so enlarging the birth canal.



The scientists and their molecule: Dr John Ballard (centre) with the University of Adelaide scientists Dr Julian Wells (left) and Dr John Wallace (right), and, in the foreground, a model of the IGF-1 molecule.

of the article. Investigations have shown that these extremely rare individuals, although dwarfs, can indeed produce their own growth hormone. Yet, paradoxically, this does not induce the usual production of IGFs. The problem is rather similar to that found in polytrauma victims, since the liver and other IGF-producing cells of Laron dwarfs also lack the receptors for growth hormone, and so are not receiving the signal to make IGF.

Finally, a further probable use for IGFs is in the world's biological and pharmaceutical laboratories, where growing cells and keeping tissues alive *in vitro* have become routine. The usual nutrients and elements and the correct pH and temperature are not enough to keep the cells dividing; to ensure division, scientists need to use fluids similar to those that bathe the cells *in vivo*, one of the most popular being foetal calf serum. This contains a lot more besides IGFs, and Dr Ballard believes that a cleaner and more accurate way of ensuring that cell cultures thrive would be the addition of known quantities of IGFs and other pure factors to the culture medium. Moreover, powdered IGF would be more easily transportable and more convenient than packs of chilled foetal calf serum.

The future

Adelaide University's Dr Wallace and Dr Julian Wells are using genetic engineering to produce various forms of IGF that Dr Ballard's group are evaluating. When commercial production goes ahead — for either cell culture or clinical applications — this is the means that will be used. Other members of the team are working on further modifications to the IGF molecule to change its binding properties, and are also investigating the family of binding proteins to see if any of them may actually enhance the potency of a factor by attaching to it.

GroPep, the company formed between CSIRO and the University of Adelaide (see the box), is sponsoring research by Dr Tomas of the Division and Dr Leanna Read at the University, and their associates, that will evaluate the abilities of the patented IGF peptides to reverse muscle wasting in rats. These animal trials are an essential step towards the eventual possible use of the –3N molecule as a new drug.

It may well be that the final product marketed for the treatment of polytrauma is not the –3N version, but another modification or the naturally occurring IGF-1, or both. Whatever happens, our understanding of the control of growth has already advanced considerably, which can only be to our benefit.

Roger Beckmann

The business end

To put it bluntly, the major scientific effort that the unravelling of IGF biology represents would not have been possible without money. As well as the support from CSIRO and the University of Adelaide, since 1981 Dr Ballard, Dr Wallace, and Dr Wells, with their colleagues, have attracted grants for this research of well over $1·5 million from a range of government-, business-, and privately funded organisations. But shortly the tables will be turned, and the discoveries should start to earn.

The CSIRO and Bresatec, the University of Adelaide's development company, have together formed GroPep Pty Ltd, which owns two patents on the IGF work, one covering the –3N:IGF-1 molecule and the second some developments from that. The scientists initially looked for a large company in Australia with the necessary expertise in biotechnology and marketing experience to commercialise their work, but were unsuccessful and in the end negotiated an agreement with the American-based Genentech, one of the largest biotechnology firms in the world.

The services of a large organisation are necessary because of the enormous cost of conducting clinical trials on humans and of steering any new product through complex legislation before it can be registered and put on the market. The licensing agreement negotiated with Genentech means that GroPep will receive royalties from any sales of a commercial product.

Perhaps more importantly, the technical information needed to manufacture the IGFs will be transferred to GroPep so that other recombinant proteins may be produced in Australia. Such information could underpin a future biotechnology industry here.

More about the topic

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