The monopoles are virtually eliminated because, over a region only one trillionth the size of a proton, the Higgs field is essentially constant. It is simply not unruly enough to tie itself into a lot of knots.

Meanwhile, as the inflation continues the slowly freezing Higgs field is converting its anomalous energy into a hot, dense plasma of elementary particles, much as freezing water gives off latent heat. The heat and entropy generated is enormous, says Guth, easily overwhelming any matter that the universe might have contained initially. Thus, there is the philosophically appealing possibility—although a difficult one to prove—that the Higgs transition is the origin of *all* matter and energy. "The universe," notes Guth, "could be the ultimate free lunch."

In any case, by the time the Higgs field solidifies and the inflation stops the universe has expanded by at least 25 orders of magnitude, and the patch that will one day surround Earth—the 10 billion light year sphere accessible to present-day telescopes—is at least 10 centimeters across. Smooth, flat, devoid of monopoles, filled with a brand-new plasma at some 10^{27} degrees Kelvin, it is ready to settle down into normal expansion as described by the standard model. Looking back, we call it the Big Bang.

Now in addition to all this, says Guth, the new inflationary model turns out to address yet another cosmic mystery: the large-scale "structure" of the universe. If the Big Bang plasma had been perfectly smooth, matter would never have been able to clump up into galaxies and clusters of galaxies. Cosmologists have simply had to assume that the density fluctuations were there at early times, without knowing where they came from.

But in the inflationary model, says Guth, the scale and magnitude of the fluctuations can be calculated. They arise from quantum and thermal fluctuations in the congealing Higgs field. These calculations were first made last summer at the Nuffield workshop in Cambridge, England, where a number of independent researchers obtained similar and very exciting results: the magnitude of the fluctuations is essentially independent of their linear size, which happens to be exactly what is required in the model of large-scale structure that is currently most favored by observation, the Zeldovitch "pancake" model (*Science*, 30 January 1981, p. 470).

True, the magnitude of the fluctuations calculated with the simplest GUT [the SU(5) model] are about 100,000 times too large, says Guth. But he regards this as an encouraging near-miss. Other GUT's do better, and anyway, no one has much faith in the details of any one GUT.

On the other hand, it must also be said that the all-important Higgs field is a weak link in the inflationary model. Linde, Albrecht, and Steinhardt had to make certain special assumptions about Higgs field dynamics before they could derive their model. And while the assumptions are not implausible, the fact remains that the Higgs is poorly understood in GUT's or in any other theory.

Nonetheless, the consensus now is that the basic idea of inflation is very good, a judgment echoed again and again by attendees at the Texas conference. "In its new form it is simple, it is natural, and it solves some fundamental cosmological problems," says Guth. It virtually eliminates the need to impose initial conditions on our theories and, assuming that the GUT's bear some relation to reality, it makes the universe as we know it seem almost inevitable.

—M. MITCHELL WALDROP

Is Tyrosine the Key to Growth Control?

Both tumor viruses, which cause uncontrolled growth, and growth factors, which stimulate controlled growth, phosphorylate tyrosines

The first tantalizing hints that an unusual chemical modification of proteins might have something to do with the way cells control growth were reported 3 years ago. Tony Hunter at the Salk Institute found, to his great surprise, that the transforming protein of Rous sarcoma virus, an RNA tumor virus, adds phosphate to tyrosines of certain proteins. "No one had ever detected tyrosine phosphorylation of proteins, and at first we thought it was an artifact."

But it was not an artifact and, 6 months after Hunter's discovery, Stanley Cohen of Vanderbilt University reported that when the cell-surface receptor for epidermal growth factor (EGF) binds EGF, the receptor starts phosphorylating tyrosines. Within a year, virologists learned that five different classes of RNA tumor viruses make transforming proteins that phosphorylate tyrosines (*Science*, 20 March 1981, p. 1336). These transforming proteins are essential for the conversion of normal cells into cancerous ones.

Now the connection between tyrosine phosphorylation and growth control looks even stronger. C. Ronald Kahn of the Joslin Clinic in Boston reports that when insulin binds to its receptor, the receptor starts phosphorylating tyrosines. One of the key actions of insulin is to stimulate cell growth. Carl-Henrik Heldin of the University of Uppsala in Sweden finds that when platelet-derived growth factor (PDGF) binds to its receptor, its receptor, too, phosphorylates tyrosines.

With these discoveries, investigators immediately began asking, Which cellular proteins are phosphorylated? Do the RNA tumor viruses, which cause uncontrolled growth, and the growth factors, which cause controlled growth, phosphorylate the same proteins? And how does tyrosine phosphorylation relate to growth control? The answers are not yet in, but researchers note that, with the data from both viruses and growth factors, they at least have a chance of answering the questions. Work with viruses has the advantage that the genetics is fairly well understood. With growth factors—particularly insulin—the biochemistry is well worked out.

Of course, just because no one had ever seen tyrosine phosphorylation before Hunter's discovery does not mean that it does not occur normally. Cells are known to contain enzymes, called kinases, that add phosphate groups to amino acids, although these kinases were thought to phosphorylate mainly serine and threonine—not tyrosine. In some cases, serine or threonine phosphorylations turn enzymes on or off.

One of the first things Hunter and his colleague Bartholomew Sefton did after finding that the sarcoma virus transforming protein phosphorylates tyrosines was to look in normal cells to see if somehow

tyrosine phosphorylation had been missed. "We found that indeed there was phosphorylation of tyrosine, although at very low levels. One out of every 3000 phosphorylations was a tyrosine—the rest were serines or threonines."

Next Hunter and Sefton looked in transformed cells. The original discovery was made in vitro and it was possible that the viral protein does not phosphorylate tryrosines in vivo. But Hunter and Sefton found that when cells are transformed by Rous sarcoma virus, the number of phosphorylated tyrosines increases 5- to 10-fold. "This presumably reflects the activity of the tyrosine kinase and it was the first evidence that tyrosine phosphorylation is important in transformation," Hunter says.

Following Hunter and Sefton's experiments and the subsequent discoveries that five classes of RNA tumor viruses direct the synthesis of tyrosine kinases, virologists began to ask how similar the viral kinases are. Already they knew one key fact. There are at least 17 different cellular genes that correspond to the transforming proteins of 17 different classes of RNA tumor viruses. Since five of these groups of viruses have tyrosine kinases as their transforming proteins, there are at least five different genes for tyrosine kinase in normal cells.

So far, molecular biologists have cloned and sequenced four of these five viral genes and found, says Hunter, that the genes "have striking structural similarities." In the sequences corresponding to the catalytically active parts of the kinases, there is greater than 50 percent homology. Moreover, there are indications that the EGF receptor protein could be structurally related to these viral proteins. Less is known about the structure of the insulin and PDGF receptors.

But studies of the growth hormones have led to another kind of information. For example, it is from studies of EGF and PDGF that investigators have learned the kinetics of the phosphorylation reaction. Hunter and his colleague Jonathan Cooper find that, within 1 minute of adding EGF to cells containing EGF receptors, there is an increase in the phosphorylation of tyrosine in cellular proteins. This includes phosphorylation of the EGF receptor itself and, in one human tumor cell line, phosphorylation of a 36,000-dalton protein that is also known to be phosphorylated by the Rous sarcoma virus transforming protein. No one knows what this protein is, although they do know that it is found on the inner surface of the cell membrane. The PDGF also causes tyrosine phosphorylation of cellular proteins within 1 to 5 minutes, Hunter and Russell Ross of the University of Washington report. But the phosphorylated tyrosines turn over fast. The half-life in transformed cells is less than 30 minutes, according to Hunter and Cooper.

The rapid rate of dephosphorylation is intriguing, however, because, Hunter explains, "It may be important that the phosphorylated tyrosines turn over fast. It may give a very sensitive signal and allow very fine tuning." One important difference between growth hormones and transforming viruses is that with growth hormones the signal that results in tyrosine phosphorylation is transient—it only persists as long as the hormones and their receptors are around. With transforming viruses, the signal is on all the time and the cells lose control of their proliferation.

Studies of tyrosine phosphorylation induced by insulin have just begun and there is still some question of whether the insulin receptor is itself a kinase or whether a kinase is closely associated with it. Ora Rosen of Albert Einstein College of Medicine in New York believes the receptor is a kinase because it retains its ability to phosphorylate tyrosines throughout the purification process. She concedes, however, that "there is always the very real possibility that we are copurifying the kinase along with the receptor."

Rosen believes that there are definite advantages to studying tyrosine phosphorylation induced when insulin binds to its receptor. "Many of the metabolic events are well defined for insulin. Many of the enzymes are well described and the work of many people has suggested that at least one thing that insulin has to do is to lead to the phosphorylation and dephosphorylation of a number of proteins."

But most of the phosphorylation or dephosphorylation induced when insulin binds to its receptor involves serines. How does this relate to tyrosine phosphorylation? And what connection, if any, is there between the action of insulin and the actions of tumor viruses, EGF, and PDGF?

Rosen proposes two possible connections. "First is that there is only a partial reaction in vitro. We may have swung the components of the reaction mixture in such a way that we only pick up tyrosine phosphorylation. My hunch is that that's not the answer. I think there is another enzyme—a serine kinase—that is activated when insulin binds to its receptor. We are trying to see whether there is a link between the activity of the tyrosine kinase to turn on or off other enzymes that phosphorylate or dephosphorylate serine."

One of the best-studied actions of insulin is its effects on carbohydrate metabolism. The carbohydrate-metabolizing enzymes, says Kahn, are an obvious place to start looking for direct or indirect effects of tyrosine phosphorylation and he and others have begun experiments to do just that. These enzymes also might provide a link between the insulin receptor and viral transforming proteins. Hunter and Cooper have been looking at the whole array of proteins in transformed cells to find those that contain phosphorylated tyrosines. Recently, they identified two such proteins as glycolytic enzymes, which is of interest, Hunter says, because, "glycolysis is perturbed in transformed cells. Most transformed cells show increased rates of glycolysis and lactate production. The reason why transformation leads to increased glycolysis is unclear."

So far, the insulin receptor is similar, in vitro, to the viral tyrosine kinases and to the kinase activities of the EGF and PDGF receptors. But, Rosen cautions, these actions in vitro "may all be fairly artificial. There may be major differences between these kinases when it comes to their actions in cells. They may look alike when you give them a particular substrate but they may in fact be different. Another possibility is that they are very similar and that what matters is where they are in the cell, how they are regulated and how much there is of them."

Hunter and Cooper have been looking for overlaps in vivo between proteins whose tyrosines are phosphorylated by viral proteins or hormone receptors. So far, they have had little luck. But the experiments are difficult, Hunter cautions. "We suspect there are proteins in common but the problem is that we are only looking at the most major substrates. What is most important is probably the minor substrates but we can't detect them because our methods are not sufficiently sensitive. The ones we detected may be proteins that are available for phosphorylations but on which phosphorylation has no effect."

Most researchers are convinced that there are links between the viral tyrosine kinases and the growth hormone receptors. And they are confident that it is within their ability to find those links. After all, says Rosen, "The fact that tyrosine phosphorylation is an early event in all those systems can't be an accident."—GINA KOLATA