Commentary

Protein Drugs: A Revolution in Therapy?

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Miracle cures are just on the horizon—or so it seems if one follows the incessant news releases touting yet another breakthrough in the biomedical sciences. Much of the public attention focuses on novel proteins with powerful biological properties that mediate and regulate interactions among various tissues of the body. Sometimes referred to under the pretentious name “biological response modifiers”—I would prefer a simpler term, such as the cell signal proteins—these substances have several features in common: They act in exceedingly low concentrations to affect crucial functions of the body—hemostasis, the immune response, the endocrine system, neural development, among others. Further, they are transmitted from one cell to another with the active species, hence, circulating in the extracellular fluid that can also be reached by the exogenously administered substance. Once cloning of the corresponding gene has been accomplished through recombinant DNA technology, these signal proteins are instantly available in large quantities. As most of these factors are highly conserved and derived from cloned human genes, potential immunogenicity is minimized.

Expectations are high, the therapeutic potential staggering. But is it not premature to invoke a revolution in therapy? Revolution suggests profound and violent changes of an entire system, in this case the health care system, which consumes a shocking 10% of the entire gross national product in the USA. The formula, biotechnology plus cell biology yield novel therapies, indeed rocks the very fabric of the health care system, affecting medical, scientific, economic, legal, and public issues. Market analysts estimate the total investment into biotechnology ventures approaches $2.5 billion, spawning some 300 biotech companies in the USA alone. Among the three major thrusts of this biotechnology boom: (1) human diagnostics and therapeutic drugs, (2) process engineering and instrumentation, (3) agriculture/animal health, pharmaceutical developments take a prominent place. While the exceedingly long lag time and high expense of pushing a new therapeutic agent through the entire drug approval process have dried up some of the venture capital and an industry shakeout appears likely, at least the two frontrunners, Genentech and Cetus from California, have each set their course on growing into a full-fledged pharmaceutical company. If successful, they would be the first to break into the major pharmaceutical ranks since the success of Syntex Corporation, propelled by marketing the birth control pill more than 25 years ago. Meanwhile, nearly all major drug companies and industrial giants, such as Shell, Monsanto, and Dupont, are buying into small biotechnology firms to secure part of the expected benefits.

Next to economic upheaval, new legal problems emerge. Can living organisms or cells be patented? What would be the value of such patents if they can be readily circumvented with minor modifications of therapeutic proteins? A rather small but somewhat bizarre legal case comes to mind: A patient sues the University of California after medical researchers have transformed cells from his blood into an established line that produces valuable substances, such as interferon. The patient claims he should be a beneficiary of the University’s patent rights and licensing agreements with two companies. This legal dispute highlights the immediate tangible profit that can be gained with the help of biotechnology, and the ethical and legal challenges that we face. It also suggests the trust, or better distrust, between the public and the medical research community. Scientists must become accustomed to the fact that the public eye begins to scrutinize ongoing research closely and is less willing to wait for the final results. I was recently startled to see a news reporter monitor one of our otherwise tranquil research seminars that dealt with a potential drug against AIDS. After initial resentment over losing the scientific privacy of the collegium, I began to realize the importance of conveying scientific ideas and therapeutic developments in a fashion that can be understood by the general public. I have since learned that nonscientists are keen on hearing the inside stories on alleged medical breakthroughs, which can elicit confusion and anxiety among the less well informed. The advent of biotechnology and novel therapeutic agents provides the biomedical-pharmaceutical scientist with a unique opportunity to bridge the gap through better communication. While one should avoid premature announcements of cures (remember the public blitz with interferon?), silence will be equally damaging. At least, there does not appear to be any lack of public interest.

Few therapeutic agents have attracted as much attention as the interferons, initially hailed as the new magic bullets against cancer. Their turbulent recent history sets an example for the type of sensationalism that scientists, reporters, and the public should avoid. Early experiments were performed with rather impure interferon preparations until the cloned interferon products became available. During this initial time period, expectations were inflated to the point where the rather meager first clinical results inexorably led to disillusionment. Interferon actually represents a family of related glycoproteins (α, β, γ-interferon) that are secreted by fibroblasts and leukocytes. The fact that degly-

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cosylation does not affect interferon’s antiviral activity is important in view of the unglycosylated proteins obtained by genetic engineering. Nevertheless, the full significance of post-translational modification within the cell remains poorly understood and reflects one of the many complexities associated with proteins as drugs. It is now clear that interferon may play some role, possibly as an adjunct, in cancer therapy, but that it falls far short of a panacea. Most protein drugs possess multiple effects on tissues, with the interferons providing a good example. Being first discovered as an antiviral substance, α-interferon as a nasal spray was found to reduce significantly the incidence of common colds, according to Dr. F. Hayden and his colleagues from the University of Michigan. His study could mark the first significant progress against these pervasive infections. Further, Dr. L. Jacobs and colleagues from Buffalo reported a marked reduction in disease symptoms of multiple sclerosis patients treated intrathecally with β-interferon over a 4-year period, again a possible advance against this previously untreatable disease. γ-Interferon is being tested against rheumatoid arthritis in a Biogen (Cambridge, Massachusetts) directed study. Hence, many more years may be required to evaluate the full therapeutic potential of the interferons.

Another hot spot among the protein drugs are the interleukins, especially interleukin-2 (IL-2), a T-cell growth factor that stimulates killer cell activity. Together with α-interferon, IL-2 is one of the major products of Cetus Corporation with focus on cancer chemotherapy. Steven A. Rosenberg, Chief of Surgery at the NCI, and his colleagues recently reported good responses and even a complete remission in patients with melanoma, colorectal, kidney, and lung cancer, all difficult to treat. His novel approach includes treating lymphocytes extracted from the patient’s blood with IL-2, in the hope of stimulating killer cell activity against cancer cells, and reinjecting the cells together with additional IL-2 into the patients. While some have labeled these results as a “breakthrough against cancer,” the procedure is costly and complicated, and significant side effects are observed. In contrast to IL-2, interleukin-1 has only very recently been cloned in two varieties (α and β), but it also holds considerable clinical promise. IL-1 is released from monocytes in response to inflammatory challenge and activates IL-2 producing lymphocytes. It hence resides at an earlier link of the lymphokine chain. Potent growth-promoting properties for multiple hemopoietic cell lineages are attributed to the 140 amino acid peptide IL-3, a T-lymphocyte derived kinine. Its complete chemical synthesis with the solid-phase technique of Merrifield was recently reported by Clark-Lewis and colleagues from Cal Tech. The ability to synthesize peptides of this length opens countless possibilities of modification and definition of the active sites on the molecule, an undertaking that can also be accomplished with recombinant DNA methods (cloning of restriction fragments, site-specific mutations).

The known lymphokines, which include the interleukins, and tissue growth factors are rapidly increasing in number: erythropoietin, granulocyte-macrophage CSF (colony stimulating factor), hepatocyte stimulating factor, epidermal growth factor, nerve growth factor, tumor necrosis factor, and many more. All of these factors play key roles in hemopoiesis, regulation of the immune system, nerve growth, and the development of neural connections, and are likely to affect the course of diseases. I am most fascinated by recent discoveries how these proteins can serve as links between major endocrine, neural, and metabolic systems, thus providing a fresh glimpse of the body as a whole. Thus the body reacts to stress and disease. For example, the hepatocyte stimulating factor which is released by monocytes was shown to stimulate ACTH release in pituitary cells, thereby providing a new axis between monocytes and adrenal cortical cells. Further profound advance in our understanding of cell proliferation, differentiation, and neoplastic transformation could result from the newly discovered link between the tissue growth factors and some of the cellular oncogene products. The cytoplasmic oncogene encoded products may be essential in processing the information carried by growth factors to the cell and may thus mediate or facilitate the cell’s response. In some cases, oncogenes may represent altered protooncogenes that could make the cell independent of the growth factor. For example, the erbB oncogene is thought to represent an altered receptor for epidermal growth factor. Understanding of these fundamental processes could become crucial in the development of future cancer therapies.

Tumor necrosis factor (TNF) is currently being tested as an anti-neoplastic agent, with some encouraging results. TNF-α is produced by mitogen-stimulated macrophages, TNF-β by lymphocytes. However, the effect on tumor cells is rather selective, with some cells showing no response and normal fibroblasts even augmented growth. One realizes that factors such as TNF have multiple actions on many cells, and selective cancer chemotherapy may be feasible only in a select few cases. TNF-α has also been combined with γ-interferon, which gave synergistic kill against some cell lines, according to researchers at Genentech. The possibility or even necessity of combining two or more factors results in a quantum leap in the complexity of any therapeutical regimen that may arise from these studies.

Seven hundred fifty thousand patients suffering from heart attack in the USA alone could benefit from tissue plasminogen activator (TPA). Single out by Genentech as its product of greatest therapeutic and commercial value, close to FDA approval, and in large-scale production licensed to Boehringer Ingelheim, Activase (TPA) has shown superior ability to dissolve blood clots in vivo without noticeable side effects. Severe competition from other drug houses is assured, and one must now await the potential benefits in large-scale clinical application. Zivin and colleagues in a recent Science article noted that TPA also reduces neurological damage after cerebral embolism in experimental animals. Thus, TPA may also become useful in the treatment of embolic stroke. Of similar general importance could be angiogenin, which was painstakingly isolated from colon adenocarcinoma cells by B. L. Valleé and co-workers of Harvard University. It is thought to play a crucial role in the angiogenesis of coronary arteries, would healing, and embryonic development and may be useful in diabetic retinopathy. Possibly of even greater therapeutic importance, the inhibition of angiogenin’s function could halt the growth of solid tumors which are dependent on the development of new blood vessels.

Guided by morphological studies on atrial cardiocytes with secretory features, A. J. de Bold of Kingston, Ontario, Canada, characterized a novel hormone-like peptide that