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To: File

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Subject: Applications of human proteins.

It is as difficult to foresee all the applications of human proteins as it would have been to foretell the scope of usage of corticoid and estrogen activities in 1910. It is also prudent to recall that microbial production will be in competition with (a) organic synthesis, e.g. Merrifield-like automation and (b) human and hybrid somatic cell culture, and perhaps (c) cell-free ribosomal synthesis with contrived m-RNA. However, each of these options has its own peculiar difficulties and (b) and (c) also intersect with biophor technology and capability in many ways.

I will endeavor nevertheless to detail some of the most evident areas of application of the capability of producing specific human proteins in abundance.

I. The most attractive options that are visible today are the human antibody globulins. There are theoretical reasons to believe that this is more than a casual empiricism. The globulins are precisely the proteins that, according to present knowledge, have evolved to be variable in their primary specificity in accordance with the disease challenges experienced by individuals throughout their life history. Failures or errors in production of antibody globulin are therefore expected to be quite prevalent in the human population and are indeed known to play a major role in (1) defense against infectious disease and (2) autoimmune and allergic disease. In addition there is increasing evidence of an immunological factor in susceptibility to cancer and there is some evidence for a role of such factors in the most common forms of cardiovascular disease besides the well-established immunological component of rheumatic fever. Byron Waxman has given an excellent perspective on the emerging role of immunology in medicine and the artificial production of antibodies would certainly play a major part in the implementation of many forms of immunological therapy.

More specifically, the most obvious and perhaps the most comprehensive role of biosynthetic proteins would be in passive immunization against infectious diseases. Animal antiserum were once used but had to be abandoned because of the anti-animal antibody that they provoked in man: serum sickness. The following table indicates - with some vague implication of priority - some of the most important virus infections whose treatment and prophylaxis would benefit from biosynthetically available globulins:

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Asilomar Conference was Feb. '75
smallpox
rabies
herpes
influenza
hepatitis
encephalitis virus
"common cold"
rubella
trypanosomes
malaria (?)
schistosomes (?)
tuberculosis (?)
leprosy (?)

I believe there is reason for special urgency to develop a backup capability of passive immunization to prevent a global catastrophe that may result from our becoming too complacent about active immunization against diseases like smallpox and polio.

II. Polyvalent prophylaxis for infants. The principal medical argument for breast-feeding is the provision of colostrum and of a continuing supply of maternal mixed globulins in the milk. There would be a huge and valid market for polyvalent gamma globulin supplements to infant dietaries. Pediatricians are unanimous in the aim of deferring infant exposure to common virus infections like chickenpox, measles, rubella until at least one year of age. There is an analogous market for non-allergenic protein dietaries (see below).

This heading also encompasses prophylaxis against debilitating bacterial infections which are especially important in infants and the newborn: E. coli, special serotypes (and especially indicated for travelers); Salmonella; dysentery.

III. There is an important veterinary market analogous to II, for calves, lambs, kittens and pups. This opportunity would have the advantage of allowing potentially profitable test-runs of this principle of therapy.

The SYNTEX Veterinary Division is an outstanding prospect for participation in this arena of work; SYNTEX research also has a significant program of immunological research.

IV. Autoantibodies play a proven role in many life-threatening diseases (like lupus erythematosus; multiple sclerosis) which represent important markets for that reason even if they are quantitatively limited. They are also implicated in very prevalent diseases like rheumatoid arthritis and a wide range of other conditions for which the elderly are particularly vulnerable subjects. The role of autoimmunity in atherosclerosis is at this moment uncertain. It certainly plays a very large role in many life-threatening forms of kidney failure. It is generally believed that autoimmunity plays a vital positive role in surveillance against the development of cancer. In different ways our approaches to all of these fields would be substantially augmented by the availability of biosynthetic antibody. The now wide-spread use of "Rho gamma globulin" as a prophylaxis against the development of Rh disease in mothers who have already born one incompatible child, is a prototype of expected future developments.
V. Allergic disease manifested in hay fever and similar syndromes (including poison oak intoxication!) is extremely widespread as a medical nuisance problem and is life threatening to a smaller number of individuals who show symptoms like asthma. It should be possible to desensitize individuals against specific allergens if we could provide blocking antibodies biosynthetically.

VI. Specific antibodies are of course already very widely applicable as diagnostic reagents of high specificity and selectivity - as we already well know how valuable they might be for antibiotic assay.

Keep in mind that it may be possible to use bacterial cultures as prototypes of an immune-variable and responding system: that is to say that we could expect to develop the capability of selecting for specific antibodies that would show maximal affinity to particular antigens in experiments that involve the evolution of the microbial cultures themselves.

VII. Blocking antibodies may also be expected to play a useful role in protecting transplanted tissues and organs from more aggressive immunological attack by the new host. Conversely, tissues specific ligating antibodies although not necessarily themselves carrying cytotoxic capability may also be expected to be useful in enhancing the cell specific toxicity of cancer controlling compounds. Cell specific reagents will also be invaluable for diagnostic purposes and for the specific separation of human cell types to be used further for either diagnostic or therapeutic applications.

VIII. Anti-sperm immunity is also being very seriously proposed as an approach to durable male contraception. I have been quite uneasy about such proposals that involve the vaccination of men against their own sperm for fear of unwanted side-effects and also on account of probable difficulties in reversibility. Passive antibody directed against sperm flagella & demonstrably able to interfere with fertilization simply by the immobilization of the sperm and should have a minimum of other side-effects. Such immunizations would be reversible by the spontaneous decay of passive immunity over periods of from 3 to 6 months. Comparable possibilities exist for the immunization of women against sperm. (Unless this seems fantastic, WHO is sponsoring a very substantial effort of research in this area).

IX. Besides the specific antibody globulins, a number of important but less specific proteins play an important part in defense against infection. Research on the practical utility of components of the complement complex and of material like properdin has been impeded by difficulty in obtaining large amounts of material. Conversely, anti-complementary antibody may be important in other contexts.

X. Enzymes. Fibrinolysin (plasmin) and urokinase (plasminogen-activator) represent a group of enzymes that are experimentally promising for the control of embolism. They may also be important in wound surgery for debridement and prophylactically for the prevention of thrombi. Complement might also have been considered under this heading. Lysozyme is another human protein that has been isolated from urine (especially from patients with monocytic leukemia) which may be highly promising as a topical antibacterial antibiotic - lysozyme from eggs was the first antibiotic to be described and discovered by Flemming. For the same reasons mentioned under serum therapy, little progress in the use of these reagents will be made until abundant sources of the human protein are available. There are, of course,

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a considerable number of enzymes that are being used experimentally for the repair of genetic defects, including some of the mucopolysaccharide accumulation diseases of the central nervous system. Even glycogen storage disease might be amenable to intravenous enzyme therapy. The problem with most of these situations is that the enzyme has to be enabled to penetrate into the cells where abnormal products have accumulated. Microcapsulated forms of enzymes like phenylalanine hydroxylase might be useful in the treatment of phenylketonuria and it would be preferable to use the human protein because of the probable slow leakage of the microcapsules. Each of these diseases represents a small specialized market but one of vital importance to the few thousands or ten thousands of afflicted individuals.

XI. Factors in clotting disease - hemophilia. The provision of anti-hemophilia protein would be the most obvious application! This material is marginal available today, isolated from human blood, but the economics of supply are very far from satisfactory.

Protein transport factors, like that for cobalt, play an important part in disease syndromes like pernicious anemia; some individuals possess iron transport factors to excess. Copper transport proteins might be useful in the treatment of Wilson's disease which at least in part may reflect excessive copper deposits in the brain. This is an area we are just beginning to learn about and every month brings about new evidence of specific transport factors.

XII. Protein hormones, like gonadotropins, are now used, being isolated from urine. This area hardly need elaboration.

XIII. Structural components, like keratin, collagen, fibrin, elastin, are probably not in short supply at least as the final polymers since they can be obtained from cadaver material. However, the design of prostheses from such materials would undoubtedly be greatly enhanced if the unmodified, young, monomer components were available for more constructive modification in building tissue parts. There is every reason that surgical sutures should be made from non-allergic human proteins, least likely to elicit foreign body reactions, keloid, and some of the other side-effects of existing materials. If sponges were made from assimilable human proteins, there would be far less anxiety from surgical accidents. A good deal of structural bioengineering involving the cardiovascular system, various kinds of piping, heart valves, all would undoubtedly be enhanced by the ready available of such raw materials. There are obvious difficulties in any large-scale production of the counterparts from human cadaver sources. Keratin may have some role in cosmetic prostheses. And one might imagine using this kind of material even just for bandages.

XIV. Non-allergenic dietary proteins are an important area. For animal milk-sensitive infants there is no present substitute for mother's milk, and even for the routine feeding of babies, human milk still excels in digestibility although this may be confounded with the problems of withdrawal of antibody globulin. There is no really good reason why one could not design a complete digestible non-allergenic human protein for mass-production for special dietary purposes.
XV. Human cell antigens will undoubtedly play an important role as diagnostic reagents and as inocula for vaccination against cancer. (This point was already brushed upon earlier).

XVI. A considerable variety of protein factors bearing on regulation of cell growth and specific cytotoxicity (lymphotoxin); vascularization of tumors etc. have been described -- many of them surely will have important clinical applications once they can be characterized and produced in quantity. (Note attachment on tumor cell Recognition Factor as one of many examples.)