BIOTECHNOLOGY : HUMAN WELFARE

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Prospects of Biotechnology Industry in India in the Area of Human and Animal Health Care

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India has been practicing old biotechnology in producing alcohol for more than 100 years. The feed stock is cane sugar molasses. The modern alcohol industry began in this century only. Other than ethanol from molasses, the old biotechnology industry in the country would include acetic acid, several antibiotics,some vitamins, edible yeasts, sera and vaccines, biofertilizers, etc.

The country has just started setting up factories in the area of new biology. Increased interest to go in for manufacture of various new-biotechnology products among entrepreneurs is certainly visible. Thus, more than a dozen companies have taken permission for setting up of hybrid high yielding seeds and tissue-cultured plants including flowering plants, vegetables and horticultural plants. A production unit for producing tissue cultured crop plants,fruit plants, flowering and ornamental plants is already in operation in Cochin. Several proposals for the manufacture of biofertilizers have been cleared and about a dozen factories have been established. Many pharmaceutical companies have started marketing imported immunodiagnostic kits for early detection of various physiological conditions in human bodies, and several communicable as well as non-communicable diseases. Kits for blood grouping sera are also available.Genetically engineered vaccine for Hepatitis-B is also being marketed by a company based on imported vials; similarly imported r-DNA human insulin is also being marketed by another company.

Realising that modern biology and biotechnology hold great potential for improving certain existing products and for developing newer products and processes in the diverse areas of human healthcare, agriculture,animal husbandry,aquatic life forms, fuel, fodder and biomass production as well as energy and environmental protection, biotechnology has already been put to use in the several spheres of production including drugs and pharmaceuticals,fermentation-based fine chemicals, agricultural practices and effluent management. The Government of India has specifically created the Department of Biotechnology to serve as the focal department for planning, promotion and co-ordination of biotech-industries and academic programmes in February,1986. During 1988, after the department assumed the administrative responsibility of promoting biotechnology industries under the Industries (Development and Regulation) Act,1951.Themain aim of the department was to harness the benefits of modern biotechnology by catalysing the setting up of high-tech. industries based on the use of modern biology. The products, *inter alia*, would include the modern vaccines and the diagnostics related to human and animal health; therapeutic bioactive molecules produced by fermentation or by recombinant DNA technology; various metabolities produced by using micro-organisms in the fermentors; hybrid high-yielding seeds; artificial seeds; tissue-cultured propagules of agricultural, horticultural and forest plants; biofertilizers; biopesticides, etc. The products would also include developing animals of high milk producing capacity as well as robust drought animals by the use of modern animal husbandry practices based on embryo transfer technology and artificial insemination. This also includes the methods of preservation of embryos and gametes for longer periods. Increasing the productivity of fish and other aquatic life forms by biotechnological inputs is also a potential area of industrialisation. Finally microbial conversion of agricultural and other wastes into value-added products or into harmless effluents are also considered potential areas for the setting up of industries. An illustrative list of current and future potential biotechnology industries is placed at table I.

Table - 1 : Illustrative list of Biotechnology Industries

A. Agriculture, Horticulture and Flowering plants:

- Hybrid high yielding seeds.
- Artificial seeds.
- Tissue culture propagation of plant materials.

- Artificially modified plants by plant cloning vectors.
- Diagonstic kits or probes for plant diseases.

B. Fertilizers :

- Biofertilizers using natural or modified micro-organisms like:
- Rhizobium, Azotobacter etc.
- Compost fertilizers produced by treatment of biological wastes with micro-organisms or by vermi culture.

C. Pesticides/Insecticides :

- Biopesticides and insecticides using various natural or modified micro-organisms. (dead or alive).
- Secondary metabolites produced by fermentation using desired micro-organisms.

D. Products and Processes by use of Micro-organisms (other than drugs) :

- Large molecules such as enzymes, proteins, carbohydrates, fats and oils etc.,
- Primary and secondary metabolites having industrial use other than drugs.

E. Drugs and Pharmaceuticals :

- Drugs and pharmaceuticals by use of micro-organisms.
- Products produced by use of r-DNA technology including genetically engineered vaccines.
- Enzymes, amino acids, vaccines, monoclonal antibodies.
- vaccines produced by convential processes such as anti viral vaccines, antibacterial vaccines, antiparasitic vaccines.
- Diagnostics such as diagnostic kits for diagnosis of diseases, diagnostic kits for determination of physiological conditions of human and animals, production of monoclonal and polyclonal antibodies, DNA probes, oligonucleotide probes, molecular finger printing assay's and human leukocyte antigen system.

F. Animal Husbandry and Aquatic Life Forms

- Products and processes based on ETT and artifical insemination.
- Development of transgenic aquatic life forms by hormonal and other treatment.
- Development of monosex and sterile life forms by various techniques.
- Development of feed and other supplements for fast growth of poultry animals as well as aquatic life forms.

G. Biogas:

- Development of microbial strains for over production of methane.
- Design, fabrication and supply of efficient digestors for biogas plant.

H. Miscellaneous items :

Oligonucleotides, restriction enzymes, gels/modified polymers etc., required for bio-processes.

The focus of this paper is to discuss the prospects of biotechnology industry in India in the area of human and animal health care and the role of the department in promoting and developing this industry in the country. ,Modern biology and biotechnology shall play a major role in the following main areas of human and animal health care industry in the country:-

- Production of vaccines
- Diagnostics for the detection of diseases and various physiological conditions of the body.
- Production of bioactive molecules, including bioregulatory proteins, blood products , thrombolytic and fibrinolytic enzymes.
- Increase in the production of bulk antibiotic drugs by microbial methods.
- Improved drug delivery systems.

Vaccines

In human health care , the country has been producing several vaccines required for treating childhood and other diseases such as tetanus, diptheria, pertussis (whooping cough), tuberculosis, rabies, cholera, typhoid fever, yellow fever etc. The vaccines against certain childhood diseases like polio, measles, mumps, rubella, viral influenza as well as other diseases like viral hepatitis, etc., are not being produced in the country, but part of the requirements are met through imports. For certain other diseases like leprosy,filariasis,diarrhoeal diseases, etc.,no effective vaccine is yet available in the world.

Realizing the importance of mass immunization against the communicable diseases, including the childhood diseases, the department had taken up the task of setting up of two vaccine producing units in the recent past. An R and D-cum-manufacturing unit with an annual production capacity of 100 million doses of oral polio vaccine is being set up at Bulandshahr,U.P., through technology consultancy co-operation with the USSR under the integrated long-term of co-operation between the two countries. Another R and D-cum-manufacturing unit for the production of viral vaccines including injectable polio vaccine (10 million doses per annum) , hyper-attenuated Measles vaccines (20 million doses per annum) and quardruple diptheria-tetanus-pertussis-polio injectable vaccine (40 million doses per annum) is being set up at Gurgaon by the Department in the Joint Sector using the technology of the Institute Merieux, France (Now named as Pasteur Merieux). The expanded program of Immunization of the Government of India requires immunizing children against six childhood diseases namely, tetanus, diptheria, pertussis, polio, tuberculosis and measles. Abundant capacities have already been created in the country for the production of DPT vaccine (to protect against diptheria, pertussis and tetanus) and BCG (to protect against tuberculosis). After the above mentioned two units come into production, there would be complete self-sufficiency within the country for these six vaccines.

The setting up of these two units is a part of the mission of achieving 85-100 percent immunization coverage of all the eligible infants against

the childhood diseases and hundred percent coverage of the pregnant women against tetanus by 1990. The estimated annual requirements for fulfilling the tasks would require these vaccines as under during 1990 : (ARDB 1990)

Vaccines		Million Doses
DPT	-	110.4
Polio	-	110.4
BCG	-	26.6
T.T	-	117.1
D.T	-	38.3
Measles	-	33.1

Genetically engineered Hepatitis-B vaccine is being marketed in the country through imports. The improved vaccines against mumps, rubella and influenza as well as viral encephalitis are also being imported and used. The current imports of these vaccines are low and may be individually placed between 50,000 and 1,50,000 doses per annum.

Several diseases like viral hepatitis, rabies,malaria leprosy, filaria, tuberculosis, certain diarrhoeal diseases, etc., are creating enormous national problem. The research activities for the development; of vaccines required for protection against many of these diseases has been intensified on many fronts and some progress has also been achieved. A genetically engineered vaccine virus which imparts protection against rabies has been developed which has given hundred percent protection to dogs in one infection; further trials are in progress. Work is being done to control fertility in women by immunological approaches. A HCG vaccine for conferring infertility to women on reversible basis has completed phase-I clinical trials. A FSH- Vaccine for conferring sterility in men is also being developed and the vaccine has shown good protection in primates. Work is progressing satisfactorily on developing leprosy vaccines in 3 institutes in the country; one of the leprosy vaccines under trial has shown protection against tuberculosis also and would be used extensively for examining its efficiency in protecting human. A r-DNA vaccine, expressed in vaccinia virus for protection against hepatitis-B

virus has been developed and is being tested in primates. An animal birth control injection called "Talsur" has been developed for the sterilization of male animals (mammals). The product has been found to induce complete sterility in bulls and dogs with or without loss of libido. The product is at the final stage of evaluation for its introduction into the market.

Besides in-country efforts, highly focused and product- oriented research for the development of new and improved vaccines is being promoted by the department with USA under a bilateral programme called " the Indo- US Vaccine Action Programme(VAP)" which was initiated in 1987. The VAP has recognized several diseases as priority areas such as viral hepatitis, rota virus, cholera, E.coli, pertussis,pneumonia, haemophillus, canine rabies,respiratory syncytial virus, poliomyelitis,tuberculosis and meningococcal diseases.

It is anticipated that the indigenous as well as the bilateral efforts would enable the country to develop strong knowledge-base in the years to come and would help in combating many of these diseases by immunological methods.

In the field of veterinary biological(s), at present, there are 17 state-run production centers in addition to the Indian Veterinary Research Institute and some private-companies, which as catering to the needs of the country. Based on 1987 figures, the total population of domestic animals in the country were cattle -199.3 millions, buffaloes -74.3 millions, sheep-55.5 millions, goats - 105.0 millions, and dogs 8.8 millions. In order to cater to their need of vaccines, the country has been producing nearly 66 million quadruple-valent FMD vaccines (Capacity Installed (I.C) 57), 3.4 million anthrax spore vaccine (I.C. 4.1 million doses), 46.1 million doses of H.S. adjuvant vaccines (55 million doses I.C.), 25.7 million doses of B.Q. vaccines, 13.8 million doses of M.C.C. and enterotoxemia vaccines (I.C. 17.00 million doses), 72.00 million doses of rinderpest vaccines (76.7 million doses I.C.) and 3.6 million of sheep pox vaccines.Currently there are nearly 150 million commercial broilers,100 million layers and about 3 million parent breeders. The production is on the increase. To cope up with the demand of this country for the

poultryvaccines, substantial expansion in the production of several life-saving poultry vaccines like lasota, infectious bronchitis, fowl pox, new castle disease vaccine, ranikhet vaccine, marek's disease, etc. have been permitted in the two private sector companies in addition to the several of the 17 state-run veterinary biologicals production centers. However, the indigeneous production of vaccines for animals as well as the poultry industry is inadequate compared to the demand. Moreover, many of the vaccines produced are not very effective.

The recent developments in biotechnology have demonstrated considerable application in the preparation of modern vaccines for animal diseases, including poultry. Therefore strengthening of existing facilities and developing expertise for virus genecloning and expression, with the objective of developing genetically engineered vaccines has been taken up within the country to develop modern vaccines against foot and mouth disease, rinderpest, rabies, goat pox, IBD, and Marek's Disease. Considerable work needs to be done to have success in these fields.

Diagnostics

Accurate, speedy and timely detection of diseases is vital for the correct therapy. India has a large incidence of communicable diseases and the occurrence of non- communicable ones is on the increase. Compounded to this is the rapid growth of population. Realizing the value of early diagnosis, several companies in India have started marketing diagnostic kits by importing these from out side the country. Some quantities of biologicals; blood grouping sera and blood chemistry reagents are being made to develop marketable reagents and kits within the country. Public funded institutions as well as the industry have contributed towards this development. Application of immunotechnology in research and diagnosis is growing rapidly. This is being realized among all the practicing biotechnologists. However the antigens and the antibodies as well as their derivatives are largely being imported at this moment even though indigeneous capabilities exist. This area of immunobiologicals needs more attention. Only recently one unit in Bhopal (Lupin Diagnostics) has been established in this area which has just gone into production.

The Government of India had entrusted the task of developing Immunodiagnostic kits to the Department of Biotechnology. The communicable diseases that have been targeted for developing diagnostic kits include tuberculosis, leprosy, filariasis, typhoid fever, viral hepatitis, giardiasis, diarrhoeal diseases, malaria, leishmaniasis, toxoplasmosis, brucellosis, amoebiasis, schistosomiasis, encephalitis and AIDS. A country wide review was made by the department on the status of work done in disease diagnosis on the various laboratories, and the institutions in India vis-a-vis the commercialisability of the techniques as developed in certain laboratories, through the industries . It emerged that on the early diagnosis of filaria, amoebiasis, malaria, viral-hepatitis,brucellosis, typhoid fever and toxoplasmosis as well as the early detection of pregnancy the techniques developed in certain institutes were ripe for producing near commercial kits. The industries were contacted by the department for bringing in a dialogue with them and the institutes for transferring the techniques to the industry. By this process, 3 Memoranda of Understanding (MOUs) have already been signed, two kits have been inaugurated for commercialisation (filaria detection kits and early pregnancy detection kits) and more MOUs are in the offing Besides the above, several institutes are being supported by the department for perfecting their techniques to bring them to the level of near commercialisation. One pilot plant facility has been established in New Delhi for enabling the production of prototypes. In certain areas like the detection of AIDS where no in-country expertise exists, efforts are being made to bring in foreign companies for the setting up of basic manufacturing facilities in India.

The annual diagnostics market during 1989 rose to around Rs. 320 millions; most of the products were, however, imported. Based on the estimates made by the Department of Biotechnology,it is anticipated that there would be a substantial growth of the market for diagnostics, in general; and immunodiagnostics (including nucleic acid probes) in particular. The current market of Rs.320 millions will approach over Rs.1,000 millions by 1994-95. While the market would still be dominated

by the products based on the imported technology, it is anticipated that a large number of testing kits based totally on the indigenous research would also emerge and be available in the market .

Bioactive Molecules

Biotechnology would be used as a substitute for the conventional methods, for production of bioactive molecules in unlimited quantities.Already several molecules like human insulin, interferon, human growth hormone, interleukins, streptokinase, urokinase, etc., have been produced on a commercial scale by microbial methods by incorporating the required genes into the various expression systems like E.coli, yeast etc., (Walker and Gingold 1985; Ghosh and Biswas 1988) Human insulin was produced by r-DNA technology by Genetech corporation of USA and this was further licensed by genetech for marketing to Eli Lilly of USA. The product was available commercially since 1982. Subsequently, besides Eli Lilly, Novo of Denmark and Hoechest of Germany had also developed the technology. It is understood that currently the human insulin sold as Humulin by Eli Lilly is as expensive as the pork pancreas derived pure insulin produced by transpeptidation of pork insulin, and accounts for about 50 percent of the total insulin market world over. The success of r-DNA insulin has stimulated the introduction of further biological innovations in the pharmaceutical industry. Human and animal growth hormones used for growth promotions,healing burns and fractures, had been produced by r-DNA technology and was introduced in the market in 1985. Although human growth hormone has not yet been accepted for a large-scale consumption world over, it is premature to judge its success at this stage as it is anticipated that this will also have applications in various other fields. As regards Bovine Growth Hormone, a project for cattle herd Improvement for increasing productivity of milching cows and buffaloes and also for raising improved draught animals is being vigorously pursued by the Government of India through the department of Biotechnology . It is anticipated that this programme would require 50 to 100 kgs, animals of growth hormones when it becomes fully operational within the next 5 years. Interferons which are a class of immune

regulators also called as lymphokines and which regulate the response of cells to viral infections and cancer proliferations were introduced in 1986 in a bigger way world over by producing them through r-DNA technology. Hepatitis- B vaccine was also genetically engineered in 1986 and introduced by Smith Kline-RIT, Belgium. In the year 1987, several other r- DNA derived bioactive molecules , including tissue plasminogen activators, Protein-A, Immunocytotoxic agents,Beta Interferon and Gamma Interferon were introduced for the first time. In the following year(1988) epidermal growth factor, erythropoietin, Interlukin-2, superoxide dismutase and calcitonin were introduced.

The race for producing bioactive molecules by r-DNA technology has just started world over and this will soon be manifested by the production of many more numbers shortly in the years to come. These would include broadly the neuroactive peptides, lymphokines and other regulatory proteins and hormones.

The development in India in this field is far behind the world standard. In fact, very little is being done, except some R and D work in certain premier Indian Institutes. As yet, there is no worthwhile expression system available or developed in the country, although some R and D level work is being done at certain institutes on hGH,bGH,hCG,Insulin, etc.

The work on downstream processing for isolating the bioactive molecules from recombinant micro-organisms on a large scale has not yet even started. This calls for developing expertise for recovering milligram or microgram quantities (or even less) of materials from complex cell debri or cell soup; the techniques also require isolating the active materials from contaminated and unwanted biologicals. Obviously these are complex technologies. Considering the international developments in this field, it is high time that speacilized R and D programmes are developed in the competent Indian institutes, either alone or in collaboration with the other developed countries.

Blood Products

The main fractions derived from the blood that are extensively used by

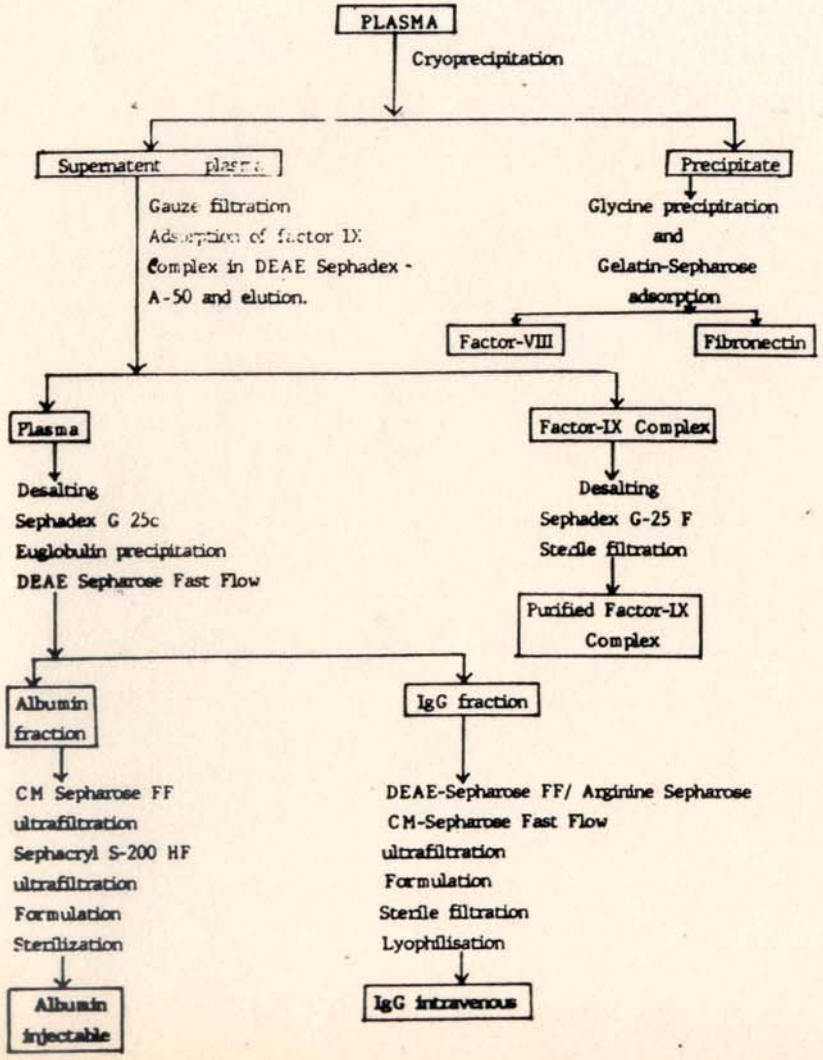
the medical profession are serum albumin, gamma globulin and antihemophilic factors . These account for 41%, 25% and 14% respectively of the global blood products market (Reasor 1980). The production of various blood products calls for superior technological innovations specially on separation techniques. Of the many methods, the modern chromatographic techniques have played the leading role in the separation and purification of various products from the plasma. Any method in use has to satisfy the stability of the finished products; the yield must be reasonable to justify the processing costs, the processing time and its practicability ; ultimately the cost of processing must be carefully examined for deciding about its commercial applicability. Chromatograpic methods have been found to be satisfactory when judged from the above mentioned criteria. The schemes generally applied for the separation of blood products from plasma are summarized in table 2.

Currently, 2 processing plants are operating in the country in the private sector, namely, M/s Serum institute, Pune, M/s Biogenetics India Limited, Lonawalla. Besides, a processing plant for the production of albumin, IgG and Factor IX has been set up recently at K.E.M. Medical College, Bombay. Although, the production of these facilities is not precisely known, it is anticipated that human albumin and immunoglobulins which are estimated to be consumed to the extent of 5000 Kgs and 100 Kgs. respectively per annum would be available from these producing units, once these go in for full production.

The antihemophilic factors are of considerable interest to the medical profession as these are used for the treatment of a set of hereditary disorders that prevent blood clotting. Type-A hemophilia is caused by the deficiency of factor-VIII and type-B of factor IX. These factors are very expensive and were selling at the rate of over US $ one million per gram a few years ago, as pure materials were very difficult to be obtained. Besides, quantities available from blood are very small. Realizing the importance of these factors, methods have been devised for the production of the factor VIII and IX by r-DNA technology and the process is being

Table - 2

(Schematic flowsheet for fractionation of blood plasma)



perfected elsewhere. In India no work has yet started on these lines. The facilities available at K.E.M medical college are, perhaps, the only one which could attempt to purify these factors from blood. This college along with the other institutes capable of handling genetic engineering methods in the country may perhaps be induced to take up research projects for producing these factors by the recombinant methods.

Thrombolytic and Fibrinolytic Enzymes

Thrombosis is the leading cause of death in many countries. Thrombosis is the blockage of blood vessels. Blood clots occurring in vessels that supply blood to heart, brain and lungs usually cause death of the patient if substances that dissolve blood clot are not injected immediately. At present, thrombolytic and fibrinolytic enzymes are utilized for the treatment of such disorders.

Urokinase and streptokinase are the two most widely used thrombolytic enzymes. Urokinase is recovered from human urine or from the cultures of human kidney tissues. The quantities available are usually small. Streptokinase is manufactured from colonies of streptomyces bacteria. While both urokinase and streptokinase are produced from the above mentioned conventional methods, due to their high costs alternative techniques for their production by r-DNA technology are also being explored.

Both, urokinase and streptokinase have non-specific interactions too and thus, their usage run the risk of internal hemorrhages. The tissue plasminogen activators were, thus, thought as the alternative, and the extensive work led to the introduction of the enzymes in 1987 by Genetech of USA. Several other companies were also working on this project like Biogen SA(Switzerland), Integrated Genetics (USA), etc. Currently the product is extremely expensive and it is reported that one treatment costs more than US $ 2200/-per patient.

Some R and D work for the isolation of urokinase from the human urine and streptokinase from colonies of streptomyces bacteria has been done in one national institute at Chandigarh. It is possible that by pursuing the work further on a large-scale by the industry, it might be possible to convert the work into the commercially usable products. At the same institute, the work on the method of production of these enzymes by the recombinant methods could also be pursued.

Antibiotics

In the area of antibiotic production, India has made a considerable progress. The first antibiotic plant was set up at Hindustan Antibiotics Limited, Pimpri, in early 1950s. Currently,the country consumes about 30 bulk antibiotics and produces more than eleven. The basic manufacturing plants have been set up for the production of Penicillins, Streptomycin , Erythromycin, Tetracycline, Oxytetracycline, Dimethylchlorotetracyline, Chlorotetracycline, Ampicillin Amoxycillin, Cephalexin and Gentamycin. Large quantities of certain antibiotics like Rifampicin and Chloramphenicol are being produced from the imported intermediates.

Over the years, substantial developments had taken place to make the antibiotics production technologies economically competitive. In this process, both public sector and private sector units worked hard to remain mutually competitive ones. Yet, the development in India could not keep space with the international standards .

Table - 3 Comparative Productivity Scenario, of Some Antibiotic Products in India and Abroad.

Antibiotics	Productivity of strains in g/litre (in hrs)			
	India		International	
Penicillin	12-24	(130 - 200)	30-40	(200-250)
Tetracycline	18-20	(150 -200)	28-50	(180-250)
Gentamycin	0.6-0.8	(100-120)	1.5-2.5	(120-150)
Erythromycin	4-8	(150-170)	8-12	(170-200)

Consequently, R & D efforts need to be strengthened substantially and, if necessary, the latest contemporary techniques may be purchased and research efforts continued there upon so that the Indian technology remains internationally competitive.

The consumption as well as demand of antibiotics in the country is increasing fast as it would be seen from the following table-4.

Table-4 Consumption and Demand of Antibiotics in India

Antibiotics	Unit	Consumption during 1986-87	1987-88	Estimated demand during 1990-91	1994-95
Penicillins by fermentatoin	MMU	715	1050	1880	3040
Tetracycline	MT	185	215	255	310
Oxytetracycline	MT	91	153	165	200
Gentamycin	Kg	2341	4365	6050	8860
Erythromycin	MT	42	43	75	100
Rifampicin	MT	100	120	180	300
Cephalexin	MT	25	30	80	140
Injectable Cephalosporins	MT	6	10	15	25
Ampicilin (oral and injectables)	MT	326	429	480	840

Realising the importance of antibiotic strain improvement and downstream processing, the department has constituted an antibiotic development (Improvement) consortium with four members (to start with) namely Hindustan Antibiotics Ltd, pune (HAL), Indian Drugs and Pharmaceuticals Ltd, Rishikesh (IDPL), Institute of Microbial Technology Chandigarh (IMTECH) and Biochemical Engineering Research Center of I.I.T., Delhi. The consortium is being funded by the department to carry out a high-class R and D to develop contemporary technologies. To start with, the concerted efforts would be put in for the strain improvement by conventional as well as recombinant methods for Rifampicin, Tetracycline, Griseofulvin, Gentamycin, and Penicillin acylase besides optimisation of fermentation parameters and scale up studies would also be initiated. The fermentation as well as processing equipment required for such purposes, are being provided by the department to HAL and IDPL.

Formulated antibiotics production in the country is currently estimated at Rs. 4610 million. A substantial part of this compromise of betalactam antibiotic formulations based on 6-APA, 7-ADCA, and 7ACA; besides, formulations of Rifampicin also account for a large part. As production

of 6-APA and 7-ADCA requires penicillins as the starting material, the installed capacity of penicillin which is currently , slightly over 800 MMU per annum in the country has to be increased to about 3000 MMU by 1994-95 and to about 5000-6000 MMU by 2000 A.D. A 1000 MMU plant at a new site requires an investment of about Rs. 900-1000 million and the gestation period is about 36 to 48 months. This has been realized by the manufacturers in the country and some are inititating steps for the setting up of newer capacities although the speed is slower. As the investmentt is very large and as the contemporary technologies are usually expensive for purchase and are often not available,it is not very clear if industrialists would hurry up in the investment decisions. On the other hand if undue delays take place in the setting up of capacities within the country, then the foreign suppliers who have been exporting the penicillin 1st crystals to India would continue to gain and there would be substantial drain of foreign exchange in the coming years. As regards 7-ACA derived injectable cephalosporins, the current demand is low. Moreover, the formulated products are extremely expensive. It is therefore to be seen how fast investment for the setting up of bulk cephalosporin C by fermentation takes place in this country.

Regarding rifampicin it is mentioned that the drug is consumed in substantial quantities in the country; about 30-35% of the world production is consumed in India (Ghosh 1985). It finds use in combating tuberculosis mainly, and partly for the leprosy control; very small quantities are also used for treating gonorrhoea. The contemporary technology can be procured. However, investments have not yet taken place for the basic manufacturing in the country on several counts. The investment for a 100 MT per annum plant is over Rs. 500 million. The cost of the bulk drug would work out to over Rs. 4000 per kg, against the imported bulk cost of US $ 170-200 per kg. Indigenous production of the bulk will no doubt bring in self sufficiency; this will however lead to a marginal increase in the cost of formulations to the consumer. If these situations are accepted and the bulk cost of manufactures are protected by the authority, there is no reason why investment for producing this vital drug from the basic stage would not take place. In fact the incremental difference in the price of finished formulations using imported bulk vis-a-vis indigenous bulk, which may amount to about Rs. 30-50 million annually for the whole country could even be considered for subsidy to the industry as the benefits of setting up bulk drug manufacturing facilities far offset the costs.

Improved Drug Delivery System

Encapsulation of oral active ingredients introduced in fifties was perhaps the beginning of improved drug delivery technology. Film coating of tablets, spray coating of solid medicaments on inert granular materials, etc., were the subsequent developments.

All these methods are extensively used in India. Since that time substantial progress has been made world over in this area. Transdermal methods of applying medicaments discovered more than a decade ago was another major innovation in this direction. Nitroglycerine for treating angina and Scopalamine for combating motion sickness has been used through transdermal drug delivery system outside India.

Various bioerodable non-toxic synthetic polymers have been introduced in recent years to encase drugs. Anticancer drugs have been used as slow-release pellets of such polymers by certain companies outside the country: such formulations are implanted directly at the site of infection and the drug is released on controlled way at much higher concentration than what is possible by conventional therapy. The polymers get eroded over time.

Microsponges made by using synthetic polymer spheres of diameter ranging from 5 to 300 microns have been used to deliver drugs transdermally. The microspheres remain on the skin surface as they are too large to penetrate, but release the drugs which get into the body through the epidermis. The pore volume of the sponge determines the amount of drug that can be trapped. These sponges deliver the drug over time and can be modified to vary the rate of release to the change in pressure or temperature.

Liposomes are used for delivery of drugs by oral route, ocular application and injection. Liposome formulations are single or multiple phospholipid bilayers, entrapping the drug within the layer. Liposmes are synthetic as well as natural. Liposome intercalated drug formulations have been made using Amphotericin - B (for treating fungal infections like aspergillosis), doxorubicin hydrochloride (anti-tumor anticancer drug), rifampicin (for treating tuberculosis) etc., and many of these formulations are undergoing clinical evaluation worldover. A formulation of Amphotericin-B has been developed in India also which is under evaluation. Liposomes tend to accumulate at the sites of inflammation and therefore liposome - intercalated drugs can be delivered at the sites of infection. By modifying the outer surface of the liposome by incorporating, say certain sugar molecules, the formulation can be made to be more site-specific. Moreover, Liposomes reduce the toxicity of the drug substantially and therefore more quantities of the drug can be applied for treatment.

Research in the production of improved delivery system, using contemporary techniques like bioerodable non-toxic polymers, transdermal methods of applications, microsponges, liposomes, immunological approaches, etc. are at a lower level of development in this country. There are a few small groups however, who are carrying out research in certain areas on their own. There is a need to develop an active group which should be linked up with the pharmaceutical Industry also. Such a group could from time to time meet and identify specific areas commensurate with the requirement of the country. Several setups could also be identified where active work could be persued. It is important that a national effort on a bigger canvas is put up to develop this important area.

Conclusions

Indian efforts in the modern biology and biotechnology are about a decade-and-a-half old. Only a few relevant areas are being worked upon within the country and some areas are being vigorously pursued. The setting up of two R and D-cum- manufacturing Units for the production of viral vaccines would bring in contemporary technologies in the

country, and the complete hardware for the prevention of a wide range of childhood diseases shall be available in India. Several other vaccines would however continue to be imported. R and D efforts within the country hold promise for the introduction of novel vaccines against human and animal contraception. The leprosy vaccine may also be developed and introduced in the country within a couple of years. The animal birth control vaccine, "Talsur" for the sterilization of male animals would be introduced shortly in the market. In the area of diagnostics which is developing pretty fast here, a large number of totally indigenously developed products would be introduced in the market; already two products- one for early detection of filaria and the other for the early pregnancy detection in human, have been introduced. However the majority of the current and future market shall be based on imported kits and technologies, and several factories shall be set up based on imported products and technologies. Interests of many large companies like Pharmacia United Limited, Bangalore; Cadila Laboratory, Ahmedabad; Lupin Diagnostics, Bhopal; Hoechst India,Bombay; etc., are already high. Several other companies like either Limited (Ortho Diagnostics), Bombay; Span Diagnostics, Surat; Boehringer Knoll, Bombay; Miles India Limited, Bombay; Infar India Limited, Calcutta; etc;, who are already in business would substantially expand their activities. In the areas of bioactive molecules by genetic engineering methods, the progress in research within the country is far from satisfactory. Only recently work has been initiated in some institutes. The need of the time is to have a mastery over developing highly potent expression systems and develop intricate knowledge of handling micro-organisms for enabling the separation of the required active principles from a cell-debri or cell-soup or fermented broth by sophisticated methods which include solvent partitioning, solvent precipitation, heavy-duty chromatography with high resolution, membrane separation techniques, gel filtration etc. In India, there is yet no good expression system either in E.coli or Bacillus subtilis or streptomyces or yeast organism for the production of bioactive molecules related to eukaryotic genes. The race for the production of bioactive molecules elsewhere in the world has picked up speed and this has been manifested by the introduction of several newer bioactive

molecules in the commerce during the last one decade. It is anticipated that many of these molecules will be responsible for the saving of precious human lives which hitherto was impossible due to the non-availability of the required active molecules. India must take recourse to these happenings and intensify research efforts in these directions so that atleast such important molecules as insulin, bovine growth hormone, hCG, streptokinase, urokinase, human growth hormone, erythropoietin, anti hemophilic factors etc., are produced in abundant quantities at a reasonable cost within the country itself. If these are not done, the country would continue to import these at exhorbitantly high prices and yet the availability would often be limited.

With regard to the recovery of value-added products from plasma such as albumin and immunoglobulins, substantial efforts have already gone in for the setting up of industries and these would show results within a couple of years. Substantial quantities of plasma derived albumin and immunoglobulins would be available in the country.

In the field of antibiotics, several units would be set up for the production of penicillins by fermentation. Such units would also convert major part of their production into 6-APA and 7-ADCA for their eventual transformation into ampicillin, amoxycillin, cephalexin, etc. While majority of the technological inputs would flow in from outside India, there would be strong need to sustain the highly intricate technology by indigenous efforts. Therefore, there would be need to strengthen the R and D base specially in the understanding of microbial strain maintenance, development and improvement; optimisation of fermentation parameters ; and mastery over downstream processing techniques. The country has already a base of trained personnel. The technology level is however low. This has been realized and two public sector units are being strengthened in their R and D inputs by the Dept. of Biotechnology. A strong RandD base in the public sector units would automatically foster the further strengthening of R and D capabilities in the private sector units, as the production area is becoming highly competitive.

In the area of improved drug delivery, Indian research is behind. No doubt that there has been introduction of several sustained release

formulations in the market; however there is no formulation yet available which works on immunological principles or through transdermal delivery system. Some work has been started using liposomes as the vehicle for transferring effective drugs in large quantities at an affected site. Liposome intercalated Amphotericin-B formulations have been found to clear aspergillosis in mouse model. Similar formulations have also shown similar effects of clearing leishmaniasis in mouse model. It is anticipated that it would be possible to develop liposome intercalated formulations using toxic drugs for treating fungal infections as well as certain types of cancer. For reaping the benefits of such research the department is making efforts to create facilities for enabling to conduct appropriate trials on human. However, the whole area of drug delivery needs a thorough review at the national level so as to put more efforts at multicentres for attacking several areas of the problems simultaneously.

It could be concluded from the above that Biotechnology in the Health care area would emerge as a strong Industry in the country soon. While major part of the technological inputs would come from abroad, there would be substantial developments based on purely Indian research. It is anticipated that the R and D efforts promoted by the Department of Biotechnology and others will have a profound impact. It is true that many of the efforts would be unproductive and futile. Even, if some of these are successful for which already positive indications have been obtained and if these are nurtured effectively and transferred to the industry as products and processes, then many novel products and some improved processes would emerge in the national scenario purely from Indian efforts in years to come in the Indian Biotechnology Industry.

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