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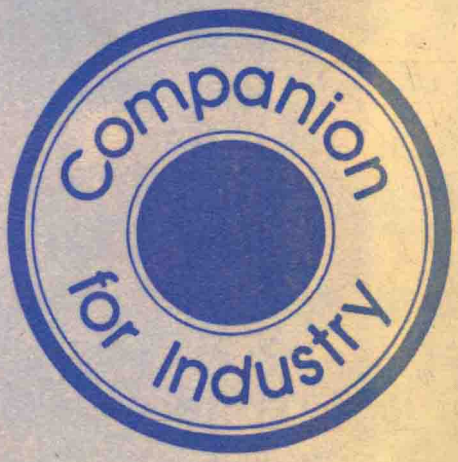
technology advances and corporate developments



Longman

Industrial Biotechnology International 1988/89

technology advances and corporate developments

LAURENCE H. SEENATH

Longman

INDUSTRIAL BIOTECHNOLOGY
INTERNATIONAL 1988/89

Published by Longman Group UK Limited,
Professional Reference and Information
Publishing Division, Longman House,
Burnt Mill, Harlow, Essex CM20 2JE, UK

British Library Cataloguing in Publication Data

Seenath, Laurence H.
Industrial biotechnology international –
1988/89-
1. Biotechnology industries
I. Title II. Series
338.4'76606

ISBN 0 582 02635 0

Typeset by Tradeset, Welwyn Garden City, Herts
Printed by Bell and Bain Ltd., Glasgow

INDUSTRIAL BIOTECHNOLOGY INTERNATIONAL 1988/89

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Dedication

This work is dedicated to:
The Venerable Bede
Jarrow and Wearmouth
672/673 – 735

Mission Statement

Biotech Link Consultants is a service organization to the biotechnology and allied industries. Our mission is to develop these industries and, in so doing, contribute to the development of mankind.

Acknowledgements

Biotech Link Consultants recognizes itself merely as an instrument through which the efforts of others have been channelled during the preparation of this volume. Most of the credit for this work should go to researchers who have worked tirelessly to find answers to persistent questions; to investors, entrepreneurs and intrapreneurs for taking the risks which have allowed scientists' answers to benefit the public; and to the governing bodies for their coordinating effort and watchful eye. Journalists, writers and publishers have also contributed in the form of some 350 references which comprise the foundation of this volume. We are grateful to the Industrial Biotechnology Association (IBA, Washington, DC) for permission to use their glossary of biotechnology terms. The IBA is in no way responsible for the content of this manuscript. Lisa Heddema at Biotech Link enriched the IBA's glossary with additional terms and explanations, which we hope will enhance the readership's appreciation of this volume.

We are deeply indebted to John Rutherford (Vancouver, BC), who provided us with the early guidance which gave rise to the concept for this volume. Mrs Hayes, who is also from Vancouver, was later consulted by us and she provided additional guidance, which is more than sufficient to carry us through to future volumes. My former lecturer, Dr Alan Wiseman, Biochemistry Department, University of Surrey, Guildford, England, was very considerate to have taken time from his busy schedule to review and offer valuable advice and support for our proposal. Dr Wiseman is also an author of several volumes in biochemistry and biotechnology. We are also grateful to Dr J. John Marshall, president, Consolidated Biotechnology, Elkhart, Indiana, and Dr Michael Gronow, joint-managing director, Cambridge Life Sciences, Cambridge, England, who also reviewed our proposal for this volume. Denise Bukowski, in Vancouver, has also generously contributed her expertise in many aspects of this project. She answered our calls for help even when they came at the most inconvenient times.

At Biotech Link, we are grateful for the support of Jeanne Jablonka, Debra Lem, Lynda Kingsley and Faye Xiao who worked on the manuscript for this volume. Deanna Fong, Lisa Heddema and Faye came to our rescue when our hired computer experts failed to meet our expectations for the graphs in Part II, Biotechnology and the Corporations. Lisa and Deanna were also responsible for making our manuscript both readable and ready, well in advance of the required date of delivery. My association with Dr Leonard Greenberg and Andrew McIntosh at Canadians for Health

Research (CHR, Montréal, Québec), publishers of *Future Health/Perspectives Santé*, first engendered my interest in writing and this volume would certainly not have been written if I did not have the privilege of learning from them. My family has been very supportive and understanding during the preparation of this work. In many ways they have been neglected while I pursued a very independent, rigid lifestyle. We are also grateful to our publishers who have given us much advice and encouragement throughout the development of this volume.

Above all our greatest acknowledgement must go to The Great Provider and Architect who assures us of all the tools we require to make our contribution to mankind.

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August 1987

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Therapeutics

1.1 Neurophysiological applications

Alzheimer's disease

In late 1986, there were reports in at least three journals of a drug, 1,2,3,4-tetrahydro-9-aminoacridine (THA) that might relieve some of the symptoms of Alzheimer's disease (*see also* Chapter 2, Diagnostics). THA, originally developed 80 years ago to kill intestinal parasites and subsequently used in the treatment of addicts of a street drug known as angel dust, has shown some promise in Alzheimer's patients. William Summers, a psychiatrist who worked with drug addicts and was familiar with THA's effect on the neurotransmitter acetylcholine (ACh), teamed up with another psychiatrist, Arthur King, at the University of California at Los Angeles and decided to test it on Alzheimer's patients. The connection between THA, ACh, and Alzheimer's disease is that brains of Alzheimer's patients have an abnormally low level of the neurotransmitter ACh, and THA tends to increase the level of ACh in the brain. The researchers suggested that THA does this by inhibition of the enzyme monoamine oxidase, which breaks down ACh in the brain. In a study of 17 patients with the disease, 12 showed significant improvement and for some, the result was dramatic. 'One patient identified her husband, which she hadn't been able to do. Another patient, a professional, went back to work,' said Summers[1]. The researchers conceded, however, that THA is not a cure but seemed to relieve the symptoms in intermediate patients in much the same way that L-dopa works on Parkinson's disease. Although Summers and King have produced some interesting results. Kenneth L. Davis, director of Alzheimer's Disease Research Center at Mt. Sinai Medical Center (New York City) remarked that THA had been used earlier at the National Institutes of Health with more modest outcomes.

Vice-president of Aldrich Irwin L. Klundt has been flooded with calls from doctors keen on trying THA on their patients. Aldrich, the manufacturer of THA, is a tiny subsidiary of Aldrich Chemical Co. (Milwaukee, WI). The $200 million a year subsidiary does not expect to reap a bounty, as THA is long out of patent. Another drug, Antilirium, made by Forest Pharmaceuticals Inc. is also used for Alzheimer's, but has more side effects than THA.

For some time, scientists have known about a protein called amyloid which is present in low concentrations in young people, but in higher concentrations in the elderly and highest in patients with degenerative brain diseases. Dmitry Goldgaber and his team at the National Institutes of Health (NIH, Bethesda, MD) reported at the November 1986 meeting of the Society for Neuroscience (Washington, D. C.) that they had cloned the gene for amyloid. The researchers used a complementary DNA probe (cDNA) to screen genes from brains of Alzheimer's and other senile patients and identified four matching clones. Chromosome 21, on which the identified gene is located, is also associated with Down's syndrome, a condition in which there are three chromosomes instead of a pair. The research does not itself lead to a cure, but rather, provides some insight into the pathogenesis of Alzheimer's disease.

Reginald Rhein Jr. suitably expressed the impact of the research news of THA as a 'promise of aid' for Alzheimer's patients[1]. 1987 and 1988 could prove to be exciting years for research into Alzheimer's disease.

Brain stroke

Roger P. Simon, neurologist at the University of California, San Francisco, reported in late 1986 that kynurenic acid reduced the amount of brain damage due to stroke by as much as 50 per cent in animal studies. Blood clots or constricted arteries can cause strokes which, in turn, result in death of brain cells. The mechanism by which this works begins to act when brain cells secrete large amounts of the neurotransmitter glutamic acid following a stroke. Large quantities of glutamic acid signal other brain cells to become hyperactive and therefore deplete the already low supply of oxygen. Cells without oxygen die, but kynurenic acid blocks the effect of glutamic acid and cells do not become overactive. The rapid onset of cell death due to anoxia would suggest that kynurenic acid should be administered as soon as possible following a stroke[6].

Parkinson's disease

Another topic discussed at the November 1986 meeting of the Society for Neuroscience (Washington, D.C.) was Parkinson's disease[7].

Researchers at the Centro Medico La Raza, Mexico, reported dramatic improvement in a Parkinson's patient following grafts of tissue from his own adrenal gland.

The disease, which is typified by trembling and rigidity of the limbs, is associated with low levels of the neurotransmitter dopamine in the brain; the adrenal gland was used because under suitable conditions it can produce dopamine. The researchers removed an adrenal gland from the patient, removed its medulla and inserted the graft into one of the brain's fluid-filled spaces, the lateral ventricle. The 35 year old patient, who had been unresponsive to therapy prior to the operation, began to regain control over his movements in two weeks. After two months, the researchers said, he could walk, eat and speak fluently. Three younger patients showed considerable improvement while those over 55 improved only slightly. In the early 1980s, Swedish scientists unsuccessfully attempted adrenal grafts in four Parkinson's patients, but in their approach grafts were inserted deep into the brain tissue where fewer nutrients and less oxygen were available[7].

1.2 Orthopaedic and dental applications

Polyhydroxybutyrate (PHB)

In spring 1986, the Materials Department of Queen Mary College, London, UK, announced the use of a natural, biodegradable polyester in the repair of broken bones[8]. The polyester, polyhydroxybutyrate (PHB) is made by bacteria and was previously exhibited by Imperial Chemical Industries (ICI), UK, as a scientific curiosity[9]. ICI's Biochemical Research Group (Billingham, UK) showed in early 1985 that PHB degraded in the human body at a controlled rate without causing inflammation or other toxic reactions. Marlborough Biopolymers, the company which leased the process from ICI initially, has conceived of low volume, high value applications of PHB in orthopaedics. Further market evaluation suggests that PHB could also be competitive with petroleum-based plastics in regions of the world where sugar is plentiful, since sugar is used as a bacterial feedstock and would increase the production of PHB.

Researchers at Queen Mary College have taken PHB one step further by mixing it with hydroxyapatite, a component of bone and teeth. Ray Smith and Christina Doyle have been conducting experiments on the resulting composite, working on the hypothesis that steel supports which are screwed into broken bones to hold them in place actually discourage mending. The reasoning behind this hypothesis is twofold. Firstly, stress on the bone activates bone growth, but steel implants tend to bear the stress themselves, leaving the bones stress-free. Secondly, a second operation is required to remove the steel supports. However, it is expected that the PHB–hydroxyapatite composite, when applied to the broken bone will gradually degrade, shifting stress to the bone.

Hydroxyapatite

In Japan at Toa Nenryo Kogyo K.K. an artificial bone material called fibrous hydroxyapatite was developed and reported in fall 1986. The company claims that existing hydroxyapatite materials have several shortcomings such as being too powdery, too granular or too porous, which make them difficult to handle in orthopaedic cases. The fibrous variation, however, has good machinability and can be applied to a wide range of cases. Experiments carried out on the shinbones of animals proved to be encouraging and further work is in progress to expand the application of the fibre[10].

Bone diseases

Another report was released from Japan in fall 1986, this time from the Sagami Chemical Research Center, Sagamihara City. In a joint effort of four private corporations, *E. coli* has been used in the mass biosynthesis of the precursor of salmon calcitonin. The precursor is used as a pain suppressant for patients with bone disease and malignant tumours. The researchers also reported a process for using the calcitonin precursor in conjunction with porcine pituitary amidating enzyme, in obtaining natural salmon calcitonin. The natural salmon calcitonin produced by C-terminal amidation had a high blood-calcium density-decreasing activity comparable to that of natural *calcitonin*[11].

Similar work on orthopaedic therapy was reported in late 1986 by Ciba-Geigy in the treatment of Paget's disease of the bone. Researchers reported the first synthesis of human calcitonin which was subsequently approved by the Food and Drug Administration (FDA). In Paget's disease, the equilibrium between the activity of osteoclasts and osteoblasts is disturbed. The former break down old bone while the latter rebuild bone mass. Disorderly formation results when osteoclasts become hyperactive and, in turn, osteoblasts over-respond to compensate for the loss of bone. The result is loosely constructed bone. Calcitonin reduces osteoclast activity[12]. In late 1986, researchers at Massachusetts General Hospital reported their findings on a preventative osteoporosis therapy. In their experiments, the researchers administered doses of Vitamin D and parathyroid hormone to a group of men and women with the disease. A year later bone density in treated men increased by 70 per cent, while in the women, who had lower densities before therapy, bone density only showed a 12 per cent increase. Parathyroid hormone's role is to regulate the use of calcium by the body, while vitamin D increases the uptake of calcium from the digestive system. These densities are still far below the bone density of young people but could prevent the incidence of some fractures. The researchers next planned to see how long the effect would last after treatment ceased[13].

In the treatment of another disease associated with bone, rheumatoid arthritis, the Arthritis Center (Wichita, KS) reported some success with gamma interferon made by Biogen (Cambridge, MA). Rheumatoid arthritis is characterized by tenderness and swelling of joints which, in turn, reduce mobility in patients. Symptoms of the disease, with a minimum of side effects, were reported in 23 of 30 patients. Another trial in West Germany showed an improvement in 24 of 40 patients. The company expected its interferon to be approved by West German regulators in late 1986[14].

Dental composites

The use of dental composites has grown considerably in the past few years and according to Richard Asa of the American Dental Association (ADA), patients are looking for more sophisticated restorative dental work. Indeed, director of technical services at Kerr Mfg. (Romulus, MI), James C. Hamilton, called the growth of the use of dental composites between 1983 and 1986 explosive[15].

In 1986, the market for restorative dentistry was estimated at $140 million, with growing segments for composites and ceramics. New products in 1986 included glass-filled tooth-coloured composites, all-ceramic crowns and a titanium–bioceramic tooth root. As early as the 1960s, composite resins had been used to restore front teeth, which are most visible and therefore cosmetically important, while at the same time not used for grinding. *Bis*-glycidyl methacrylate (*bis*-GMA) formed the basis of these composites according to Roy L. Smith, manager of composite research at L. D. Caulk (Milford, Del.), a division of Dentsply International (York, PA). More recently, resins and filler particles have been added to increase strength Van P. Thompson, director of the University of Maryland's Dental Materials and Chemical Research Unit admits that composites are still less reliable than amalgams but they are more attractive. Two other advantages are that composites are not harmful to patients who are allergic to mercury in amalgams and, secondly, there is no need to cut away good tooth structure and replace it with amalgams, according to Nicholas Hilt, a marketing manager at 3M (St. Paul, MN), the leading manufacturer of dental composites. The American Dental Association (ADA) has shown some recognition of the use of composites by granting provisional acceptance to four composites for use in rear

teeth. The association plans to review their durability in the long term. The first of these composites is L. D. Caulk's Ful-Fil, a composite of *bis*-GMA resin with barium glass and fumed silicone dioxide. The second was made by Imperial Chemical Industries' (ICI) Chicago-based Coe Laboratories. This is a light-cured barium aluminoborosilicate in a urethane dimethacrylate resin. The third is 3M's P-10, a self-cured resin-bonded ceramic with a high input of filler particles. The fourth, made by Kulzer & Co. (Friedrichsdorf, West Germany), is Estilux, a light-cured methacrylic ester filled in with silicone dioxide and other inorganic compounds.

Although more attractive, composites can require twice the time by dentist and staff compared with amalgams. This in turn, costs the patient more. Some companies, such as Kulzer, premixed tinted resins which reduced labour and time costs. Porosity and polymerization shrinkage are two common problems associated with composites that can be overcome by ensuring that dental technicians do not manipulate the material content of the composite and that dentists put the resin into the tooth in layers. Composites and adhesives, as they are continually improved, are increasing their share of the $70 million annual market for fillings and cosmetic bonding materials. The 1986 estimate of the market share for amalgams is about one half the total market. 3M's Nicholas Hilt believes composites will be increasingly used in rear teeth as this is a relatively new market which grew by 25 per cent in 1985 and is expected to continue as dentists and technicians become more familiar with the new materials and methods. Some very well established and diversified firms have also been attracted to the dental field in the replacement of porcelain-fused-to-metal (PFM) crowns by ceramics. A joint venture between Corning Glass (Corning, NY), as manufacturers, and Dentsply, as marketers, resulted in the development of Dicor, a glass–ceramic crown. Produced in 1984, Dicor was granted provisional acceptance by the ADA. Many ceramic products have a problem with shrinkage of as much as 20–30 per cent. Dicor, however, does not have this problem, according to Michael Karnas, a senior applications specialist at Corning. This problem is overcome by preparing Dicor by a centrifugation process in which molten glass is cast in a mould of the tooth. The glass is then heat treated, or 'cerammed', to allow mica crystals imbedded in the glass to grow so that a ceramic duplicate of the tooth is formed[15].

Japanese firms and institutions, not to be left out of these developments, are developing an artifical tooth root from titanium and a bioceramic made mainly of hydroxyapatite. The three organizations in Japan working on this are Matsumoto Dental College, Sumitomo Chemical and Tokyo Plastic Dental Society. Artificial roots currently on the market are made from apatite or single-crystal alumina rather than a combination of materials. The current annual market in Japan for artificial roots is $13 million according to Sumitomo and clinicial studies are expected to have been completed by late 1986. The Japanese artificial root is prepared by plasma jet coating of titanium by hydroxyapatite at temperatures of up to 15 000 °C. Even at these temperatures, hydroxapatite does not decompose. If this artificial root follows the path of many other Japanese products, Sumitomo may well look beyond the $13 million annual Japanese market.

A novel tooth filling developed jointly between MacroChem (Woburn, MA) and Essential Dental Systems (New York City) was announced in late 1986[16,17]. The new development is the use of a sodium fluoride salt based on a *bis*-GMA resin. This salt, which is absorbed by tooth enamel, confers protection on the tooth. Fluids in the mouth can also slowly dissolve the salt in a controlled fashion which liberates fluoride ions in the mouth. Barry Lee Musikant of Essential Dental Systems thinks that there is enough fluoride salt packed into each filling to last 15 years. Addi-

tionally, the filling glows under black light and therefore can be distinguished from healthy parts of the tooth. The developers intend to increase the filling's bond to teeth in two ways: firstly, by improving the adhesive and, secondly, by using a composite that would expand rather than shrink.

Alza Corp. (Palo Alto, CA) reported in January 1986 the use of a hollow polymer thread filled with tetracycline, an antibiotic, in the prevention of periodontal disease. This disease, which is caused by an accumulation of bacteria between teeth and below the gum line, can be prevented by vigorous flossing and brushing. Treatment up to now has been by surgery. Alza claims that if the thread is packed in spaces between gum and teeth and left for 10 days, high doses of tetracycline pass directly to the site of infection and should eliminate the need for surgery. This claim is supported by the promising results of five years of chemical tests[18].

1.3 Dermatological applications

In spring 1986, Abe Widra, professor of microbiology at the University of Illinois College of Medicine (Chicago, IL) announced a biodegradable dressing for skin ulcers, burns and lesions. Made from cow hide, sheep wool and crab shell, it may be applied like a bandage and keeps exposed tissue moist and free from invading bacteria[19].

Essentially, the bandage consists of three water-soluble biological polymers, collagen acetate, ammonium keratinate and chitosan acetate. Each polymer represents a layer of the bandage and as the keratinate is negatively charged, it binds together the two acetates, which are positively charged. When mixed with water, the bandage becomes water-soluble and hygroscopic. Additionally binding forces come into play which include steric fitting, chemical bonding and cross-linking. In this form, the dressing resembles a paste or putty and can be worked into patches. Prior to hydration, its form is crystallite-packed microfibrils. After sterilization with ultraviolet radiation or ethylene oxide, it may be applied in 1–7 mm thick patches. Glycerine may be used to soften and increase flexibility, while antibiotics, antifungals, cells, antibodies, enzymes and pigments may be used depending on the type of treatment, according to Widra. The dressing is permeable to oxygen, adheres to underlying tissue and is elastic, which allows limb mobility. Although the tri-layered polymer absorbs wound exudates it does not change its structural characteristics. As the wound heals, the dressing hardens into a protective scab which falls off without the need for stripping. In addition to wound management, Widra believes that the dressing may be used to cover sutures, as a sustained-release drug carrier, as a tube lining in bypass surgery and as a lining in prosthetic implants.

The dressing has been used with success in the treatment of skin ulcers in 36 patients by Abraham R. Koransky, dermatologist at Sidney Hillman Health Center (Chicago, IL). Patients reported reduced pain, quicker healing and no side effects, and the dressing outperformed competing products. Kendall (Boston, MA), a branch of Colgate-Palmolive, has been granted the option to license the technology responsible for the product worldwide. Animal tests have already been carried out, says Richard W. Johansen, director of new business development at Kendall, and an application for clinical trials was to have been sent to the FDA in 1986. Johansen is optimistic that the venture will be successful but cited rather dated statistics for injuries in the