BIOMEDICAL DISCOVERIES ADOPTED BY INDUSTRY FOR PURPOSES OTHER THAN HEALTH SERVICES

DEVELOPED FOR
THE DIRECTOR
NATIONAL INSTITUTES OF HEALTH

by

The Office for Medical Applications of Research
Office of the Director, National Institutes of Health

DRAFT REPORT
MARCH 2, 1981

FOREWORD

This report summarizes the findings of a study undertaken on behalf of the Director, National Institutes of Health (NIH), by the Office for Medical Applications of Research (OMAR), OD, NIH.

The objective was to identify discoveries in biomedical research that have been adopted by industry for commercial application outside the health care sector. The report concerns only technology transferred from the biomedical sector to fields outside the domain of human health and the mitigation of disease, and is confined by these constraints.

Methods

The report is intended to be neither comprehensive nor conclusive. Rather, it is a pilot study and represents an initial attempt to determine whether, within a limited period of time, evidence could be gathered that technologies had been transferred from biomedicine and applied by industry. In addition, we attempted at the same time to support the hypothesis that biomedical research and knowledge generation have provided important industrial applications and, as a result, generated substantial income for private-sector industry. A decision was made to limit the study to a two-month period, and to develop a list of candidate biomedical discoveries that could be thoroughly analyzed and reported within this period.

Only rarely does invention spring forth independent of antecedent scientific relatives, and knowledgeable people will, within reason, argue about "who was first?" In selecting the items studied, judgments were made in determining the critical observation that launched the technology; if this occurred in a biomedical research setting, only then was it accepted for analysis. The bibliographic citation for the biomedical discovery generally identifies the one or several scientists who documented the first and critical application of the innovation. In some instances, however, a constellation of scientists or observations contributed to the scientific advance, and so credit must be given to the general increase in biomedical knowledge rather than to an identified investigator. Both formulations of discovery, the flash of intuitive invention or the cumulative increase of knowledge, were deemed proper for inclusion in this pilot study. Each is consistent with our knowledge of the flow of discovery and both have been amply documented in the literature of science.

In keeping with our objective to trace the role of biomedical research, the discoveries identified encompass several different research sectors. They include: 1) those that flowed directly from a biomedical laboratory and 2) those in which there was a tradition of empirical practice, but which biomedical research served to explain and which eventually led to a controlled industrial process. In one instance alone did the biomedical research and the industrial application occur in the same institution and, in this instance, it was a commercial organization.

With equal discrimination, we have endeavored to be as precise as possible in justifying the conclusion that a biomedical research discovery selected for analysis had utility in fields with which it was not commonly associated and, when possible, confirmed this transfer by bibliographic reference or discussion with knowledgeable industrialists.

In all cases, the fiscal data have been documented and, as presented, are conservative. The major data sources -- Federal agencies having responsibility in the affected industrial area (e.g., the Department of Agriculture, Environmental Protection Agency), trade associations representing the identified manufacturers (e.g., Corn Refiners Association, Tanners Council of America), and/or the prime manufacturers themselves -- have all been identified in the References and Notes section. The data included are precise within the range that these organizations report as to retail sales in rounded numbers. When we received data from several sources and had no clear rationale for selecting either the higher or lower number reported, we have always chosen the lower figure. When the practice of a source organization was to report a range of figures, we have chosen the midpoint. Dollar totals represent retail sales and do not include industrial and economic impact of transfer funds generated by American industry operating overseas.

The study was conducted from December 1980 through January 1981, during which time OMAR utilized the technical support services of CDP Associates, Inc., of Rockville, Maryland, and Battelle Columbus Laboratories of Columbus, Ohio. The initial phase involved identifying examples of technology transfer that could be considered as candidates for inclusion in the study. These were traced in both directions -- i.e., by identifying biomedical discoveries that were thought to have had commercial applications, as well as industrial products or procedures with an apparent biomedical genesis. Publicly funded research formed the major emphasis, and, where applicable, NIH support is indicated by identifying the grant or contract number. Telephone interviews were conducted to elicit candidate technologies from approximately 100 opinion leaders representing industry, the research community, private foundations, and the Federal government, including knowledgeable individuals with a breadth of imagination such as recent Presidential Science Advisors and distinguished science award winners. These interviews were conducted in concert by OMAR, CDP, and Battelle, with the resultant list of 50 to 60 suggestions reduced to the most promising two dozen candidates for detailed investigation. Final selection of the discoveries to pursue was made by OMAR, following which Battelle traced and summarized the biomedical contributions and industrial applications of the discoveries, while CDP identified and analyzed the financial impact of each.

Findings

The report focuses on technology transfer as exemplified by 10 biomedical discoveries that are currently being applied by industry and continue to have a significant impact on the U.S. economy. A number of disciplines contributed significantly to several of the innovations studied. In many

cases, the industries identified in this study would not exist without the identified biomedical contributions; others have been greatly augmented or refined by such discoveries. In several of the latter instances, we were dealing with technologies based on empiricism dating back into prehistory (e.g., ale and beer brewing and skin and hide tanning). As indicated above, the contribution of biomedical research was to give a scientific base to the empirical practice, thus converting what had started as "cottage industries" into major industrial enterprises.

In all the cases selected, biomedical research furnished a critical element in bringing about technological advancement and industrial growth. As the representative of the Tanner's Council of America told us, "In the process of bating leather, it is the use of pancreatic enzymes that distinguishes the United States from primitive societies."

These 10 selected examples are estimated to contribute approximately $37 billion annually to the Gross National Product (see Summary Table), a figure that exceeds the total combined appropriations for the NIH since its inception in 1937. This amount is 10 times greater than the NIH budget for FY 1980.

Conclusion

Technology transfer is a well-documented phenomenon but, to our knowledge, no systematic study of economic impact of this process exists. The striking findings in this study of transfer of biomedical technology to other fields suggests that this may be a productive area for further evaluation. Of equal importance is the observation that an activity which is normally carried on the debit side of the Federal ledger has proven to make a striking contribution to the Gross National Product. If viewed in the light of the data obtained in this pilot study, Federal investment in biomedical research has not only yielded major contributions to the health of the nation, but has concomitantly proven to be a remarkably profitable investment. In addition, the explosion in biomedical invention characteristic of this past decade would make credible the speculation that the return on this investment will increase strikingly in the immediate future.

Charles U. Lowe, M.D.
Acting Associate Director
for Medical Applications
of Research

BIOMEDICAL DISCOVERIES ADOPTED
BY INDUSTRY
FOR PURPOSES OTHER THAN
HEALTH SERVICES

Table of Contents

SUMMARY TABLE

Estimated Retail Dollar Value of Selected
Biomedical Discoveries Adopted by Industry
for Purposes Other Than Health Services

Biomedical Discovery	Industrial Application	Estimated Annual Dollar Value* ($ in millions)
• Freeze-Drying	Food Preservation	3,800.0
• Immobilized Enzymes	High Fructose Corn Syrup, Sugar Beet Molasses	2,100.0
• Keratin Biochemistry	Home Hair Permanents	122.7
• Laboratory Instrument Computer (LINC)	Minicomputers	2,500.0
• Virology/Oncology	Vaccine for Marek's Disease	48.0
• Chlorotetracycline	Animal Feed	3,422.0
• Warfarin	Rodenticide	75.0
• Fiber Optics	Telecommunications	100.0
• Steroid Hormones	Animal Feed	1,515.3
• Enzyme Biochemistry	Chillproofing of Beer, Leather Bating, Enzyme Detergents	23,300.0
	TOTAL - 10 BIOMEDICAL DISCOVERIES	$36,983.0 ($37 billion)

*When a range is given (as detailed in the individual descriptions which follow), the midpoint is used for the purposes of this summary table.

INDIVIDUAL DESCRIPTIONS OF 10 SELECTED BIOMEDICAL DISCOVERIES

FREEZE-DRYING

First developed in biomedical laboratories for preserving protein solutions without refrigeration, freeze-drying has been adopted as a principal method of food preservation.

Biomedical Contribution

Under the proper conditions of temperature and pressure, frozen water will change directly from ice to water vapor without melting to a liquid. The slow disappearance of snow at below freezing temperatures is a common illustration of this sublimation process.

Preserving food materials by sublimation, also known as lyophilization or freeze-drying, has been practiced empirically for centuries in the northern climates, where fisherman hang their catch out in the cold, dry air so that the fish freeze to a solid and then slowly dry to a stable form. Under these conditions, the process is slow and several months may be required to remove the necessary water.

Biomedical research was directly responsible for converting this natural phenomenon to a practical commercial process by combining low temperatures under vacuum conditions to accelerate the rate of sublimation. The process was first developed as a laboratory procedure for the drying of biological specimens such as antisera, rabies virus, tissue, and blood by Shackell (1) in 1909.

The procedure of lyophilization remained a laboratory tool until 1933 when the first products for clinical use were freeze-dried at the University of Pennsylvania School of Medicine (2). Earl W. Flosdorf and Stuart Mudd, working with Dr. Joseph Stokes and Dr. Harry Eagle, prepared freeze-dried convalescent human sera, which were used and distributed by the Philadelphia Serum Exchange under the direction of Dr. Aims C. McGuinness (3).

The firm of Sharp and Dohme, Inc., in Philadelphia installed the first commercial equipment for the processing of serum in 1935 and the first commercial freeze-dried blood plasma was in distribution by 1940. The Red Cross began using freeze-dried plasma during World War II and its use soon spread throughout the world.

Industrial Application(s)

During and following World War II the use of freeze-drying to preserve biological products expanded rapidly to include vaccines, hormones, vitamins, and other pharmaceutical products. Interest soon spread to its potential as a method for food preservation. Individuals such as E. W. Flosdorf and J. Stokes, as well as government laboratories such as the Aberdeen Research

(Continued)

Freeze-Drying (Continued)

Establishment and the Quartermaster Food and Container Institute in Chicago, conducted both fundamental and developmental work on the use of freeze-drying for food preservation.

General Foods and Nestle pioneered freeze-dried coffee in the mid 1960's and MAXIM was test marketed in 1967-1968. Since then, freeze-dried coffee has become a major industry (4). Several companies in the United States (e.g., General Foods Corporation; Campbell Soup Company; T. J. Lipton, Inc.) and Europe (e.g., Hartog's Fabriken, N.V.; Irish Sugar Co.; and Magii, G.m.b.H.) also began producing freeze-dried meat, poultry, and vegetable pieces for dry soup mixes in the early 1960's and this continues to be a major application (5).

Armour first introduced its Start Lite brand of freeze-dried meals for campers in 1961 (6) and, in the late 1960's, United Fruit began marketing freeze-dried shrimp to the institutional trade (5). Thus, freeze-drying, which was brought from folk art to a commercial process through biomedical research, is now a key process in the food industry.

Financial Impact (7,8,9)

The following products from the 1977 industry census of manufacturers, conducted by the Economic, Statistical, and Cooperative Service of the U.S. Department of Agriculture are applicable to freeze-drying: coffee -- all instant, including freeze-dried and, less commonly, spray-dried -- retail sales value of $1.87 billion; powdered tea ($0.288 billion); and dehydrated fruits, vegetables, and soups ($1.62 billion). Although the freeze-drying techniques contributed by biomedicine were tested for use in the frozen orange juice industry, a low-temperature evaporation process has been found to be more cost-effective and, therefore, is not included as a totally freeze-dried process. The total annual retail value of these freeze-dried and dehydrated products can thus be estimated at $3.8 billion.

IMMOBILIZED ENZYMES

The technique of immobilizing enzymes on solid supports has expanded from biomedicine to multiple industrial uses such as the production of high fructose corn syrup and sugar beet molasses.

Biomedical Contribution

The technique of immobilizing or forming water-insoluble derivatives of enzymes and other biologically active proteins had its genesis in biomedical research. Prior to the development of these techniques, enzymes used as catalysts could not be recovered in stable form from the reaction mixture. When they are bound to an insoluble carrier, however, they can be used in suspension or column form and can be utilized repeatedly to induce specific changes in larger amounts of substrate. These immobilized enzymes also mimic the form of the enzyme in the living organism and provide simple models to study their mode of action.

Grubhofer and Schleith (10) first immobilized enzymes such as carboxypeptidase, diastase, pepsin, and ribonuclease in 1953 at the Institute of Viral Research in Heidelberg, Germany, using diazotized polyaminopolystyrene resin. The technology grew slowly until the 1960's when Professor Katachalski and his co-workers at the Weizmann Institute of Science's Department of Biophysics in Israel -- working under NIH grants AM 3083 and AM 8464 from 1960 through 1965 -- carried out extensive studies on new immobilization techniques and the properties of immobilized enzymes (11). Research also flourished in the United States, Japan, and Europe during the 1960's. Much of this work proceded concurrently with the development of affinity chromatography, wherein specific ligands are bound to column supports and used to selectively separate macromolecules of biological interest such as antibodies, antigens, and nucleic acids. Many of the binding techniques used in these areas are interchangeable.

The first commercial process utilizing immobilized enzymes for the optical resolution of D,L-amino acids using immobilized aminoacylase was established in Japan in 1969 (12). This application also had biomedical significance, since racemic mixtures of amino acids are not as desirable in chemically-defined diets as are specific blends of the biologically active isomers.

Industrial Application(s)

The use of immobilized enzymes has expanded beyond the bounds of medical and pharmaceutical applications to include analytical tools and food-processing technologies. Numerous immobilized-enzyme electrodes for many industrial applications have been demonstrated (13). Perhaps the best known analytical application has been the glucose analyzer, which employs immobilized glucose oxidase and is used in the food industry.

(Continued)

Immobilized Enzymes (Continued)

The introduction of high fructose corn syrup has had a dramatic impact on the food industry. This is the largest scale process using immobilized enzymes. The Clinton Corn Products Division of Standard Brands pioneered the introduction of this technology using glucose-isomerase immobilized on DEAEcellulose (14). Nine companies now have production capabilities in the United States using various forms of supported enzyme reactors. High fructose corn syrup has replaced sucrose as a sweetener in many food products, giving the food processor flexibility in responding to the serious fluctuations in the price of sugar. In turn, the consumer has benefited since the price of the processed food has not risen as sharply as it would have if only sucrose were available to the processor.

Corning Glass Works is currently marketing an immobilized enzyme system for the hydrolysis of lactose from cheese whey to glucose and galactose (15). This is one step in helping to solve the serious whey disposal problem faced by the dairy industry. SNAM-Progetti in Italy also uses immobilized enzymes to process cheese whey and to produce a reduced-lactose fluid milk product (16). Persons with an intolerance to lactose can enjoy this milk without the discomfort experienced with regular milk consumption.

Great Western Sugar Company and Holly Sugar Company in the United States and other companies in Japan use immobilized enzyme reactors to hydrolyze raffinose in sugar beet molasses (17,18). In Japan, the Tanabe Seiyaku Company (13) produces L-malic acid from fumaric acid in addition to separating L-amino acids from racemic mixtures.

Other potential applications of immobilized enzymes being studied include the conversion of starch to glucose, beer chillproofing, fruit juice clarification, and cheese making (19). Other commercially important applications for this technology are likely in the future.

Financial Impact (20,21)

The high fructose corn syrup that depends upon immobilized enzymes is sold principally to manufacturers (under such brand names as "Isomorose," "Sweetose," "Iso-Sweet," etc.). The "iso-" stands for the chemical process of isomerization. The total sales volume of high fructose corn syrup in the United States in 1980 was $1.25 billion. By-products of this process are corn oil and animal feed, which have an estimated additional annual sales value of $0.25 billion. In addition, because of the production and marketing of high fructose corn syrup from immobilization of enzymes, corn refiners are buying an additional $0.5 billion in farm value corn in order to produce the high fructose syrup. Thus, the total annual retail value of high fructose corn syrup is estimated at $2 billion.

The Holly Sugar Company estimates that the sugar beet molasses industry has a retail value of approximately $80 million annually; Corning Glass Works holds sales figures relative to its process of hydrolyzing lactose

(Continued)

Immobilized Enzymes (Continued)

from cheese whey to be proprietary. Even without this figure, however, the annual value of these other products that are based upon a process of enzyme immobilization can be estimated at $2.1 billion.

KERATIN BIOCHEMISTRY

Biomedical research into the structure of hair in the 1930's and 1940's led to the development of hair permanent kits that are used in millions of homes today.

Biomedical Contribution

Keratin is the fibrous protein of mammalian hair and nails. A great deal of research begun in the 1930's led to a better understanding of the structure and properties of this protein. Because keratin is extremely resistant to chemical action, early attempts to solubilize the protein were based on the use of strong acids or strong bases to degrade the material.

A key discovery was reported in 1934 by Goddard and Michaelis (22) of the Rockefeller Institute for Medical Research, who demonstrated that thioglycolic acid could be used to reversibly break the disulfide bonds in keratin, sparing the peptide bond and thus preserving the integrity of the hair protein. In this way, the protein could be solubilized without hydrolysis or other appreciable chemical change.

Industrial Application(s)

The waving of hair for cosmetic reasons, originally based on the use of hot irons or strong alkalis, was revolutionized in the late 1930's and early 1940's based on the discovery of Goddard and Michaelis as well as work at the University of Leeds (23,24) and the National Bureau of Standards (25) on textile fibers.

The use of thioglycolic acid for the cold waving of hair came into general use in 1943 and the first home use kit was introduced in Chicago the same year (26). Today, millions of home permanent kits based on the salts of thioglycolic acid are used each year.

Financial Impact (27)

Gillette, which manufactures "Toni" and a number of other waving products, reports that the total retail market for home permanent kits in the United States in 1980 was 34.5 million units sold at a cost of $122.7 million. This represents a sizeable dollar increase (28.3%) over 1979, when 30.8 million units totalling $95.6 million were sold. Gillette estimates that the home permanent kit industry has more than doubled in sales since 1977, largely due to individual changes in hairstyles (which, in the late 1960's and mid-1970's, tended to be longer and straighter than they are today).

LABORATORY INSTRUMENT COMPUTER (LINC)

Developed under NIH sponsorship, the LINC was the first desk monitor that could perform biomedical configurations and interact with experimental equipment in the laboratory.

Biomedical Contribution

The early development of computer technology was directed primarily at larger and more powerful units for handling large volumes of information and solving complex mathematical problems. These capabilities were well advanced by the early 1960's. However, the biomedical scientist was looking for something more. There was a real need for a unit that could not only store and process data, but also interact with experimental equipment.

The Laboratory Instrument Computer, or LINC, evolved out of recognition of the need for such a capability and the experience gained through several years of collaboration by members of the Digital Computer Group of the MIT Lincoln Laboratory and the Communications Biophysics Group of MIT's Research Laboratory of Electronics (28). The LINC prototype was built in early 1962 at the Lincoln Laboratory under the direction of W. A. Clark and C. E. Molnar. The development and practical demonstration of the LINC as a workable system were conducted in the MIT Center Development Office for Computer Technology in the Biomedical Sciences under Contract PH 43-63-540 with the Division of Research Facilities and Resources of the National Institutes of Health, in cooperation with the Bio-Sciences Office of the National Aeronautics and Space Administration.

The LINC was developed as a small stored-program digital computer designed to: accept analog as well as digital inputs directly from experiments; process data immediately; and provide signals for the control of experimental equipment. Early applications of the LINC in biomedical research included averaging of evoked electrophysiological responses, processing of single-unit data from the nervous system, and analysis of arterial shock wave measurements.

Industrial Application(s)

The LINC not only had an impact on biomedical research, but also on the computer industry. The original prototype led directly to several commercial systems. These were the LINC-8, PDP-12 and MINC (Digital Equipment Corporation), the microLINC-300 (Spear Corporation), and the PC-1200 (Artonix Corporation) (29). In addition to the direct descendants of the LINC, the technology associated with the system such as its miniature tape drive, point plotting display, and CRT-based console had a significant impact on the minicomputer field in general. These features had a strong influence on the design of the PDP-4

(Continued)

and PDP-5 (30), which in turn led to the PDP-8, PDP-9, and PDP-15. Similar features of the personal computers now being marketed can be traced to the LINC.

Financial Impact (29,30,31)

The estimated sales of the PDP-12, LINC 8, PC 1200, and microLINC 300 systems exceed $100 million, to which can be added approximately $25 million annually for the sales of DEK tape (which directly traces its heritage to LINC tape and which is used extensively with the PDP-10 series of computers as well). The Digital Equipment Corporation, developers of the PDP-8, acknowledge the debt to the LINC and estimate that the PDP-8 has generated revenues approaching $1 billion.

The Digital Equipment Corporation representative states, "Whatever we are today is based on the PDP-8." Today, Digital Equipment -- which clearly was built on the PDP-8 and, hence, owes a great debt to the LINC, developed under NIH sponsorship -- has annual worldwide sales revenues that exceed $2.4 billion. Adding the aforementioned descendents of the LINC, the value of the innovation can be estimated at over $2.5 billion.

Viral oncology work conducted and supported by the NIH led to a vaccine that has proven highly effective in reducing the incidence of Marek's disease in chickens.

Biomedical Contribution

In the mid-1960's, the National Cancer Institute placed additional emphasis on studies involving the role of viruses as causative agents of neoplasia in animals and man. The program stimulated the development and refinement of many techniques and instruments -- methods for cell culture, immunoassays, virus isolation and purification, the ultracentrifuge, and the electron microscope (32). A better conceptual understanding of the entire cancer process resulted from these studies.

Industrial Application(s)

Marek's disease is a lymphoproliferative disease of chickens and is caused by a herpesvirus, Marek's disease virus. [Biggs, et al. (33); Witter et al. (34)]. The disease, first characterized by Marek in 1907, is epizootic in nature and is seen in all countries, especially those with large poultry industries.

In conjunction with the Department of Agriculture (USDA), the NIH supported many projects to study the role of immune factors in controlling herpesvirus infections. In animals, Marek's disease of chickens is the best example of a herpesvirus causing neoplasia under natural conditions. The incidence of this disease was significantly reduced by vaccination with a related virus isolated from turkeys. The virus vaccine, eventually produced inexpensively in large amounts, has eliminated a major problem for the poultry industry (35,36). Hilleman (37) commented that "perhaps the most outstanding achievement in the animal virus cancer field in the last decade or two" was the "development of highly effective vaccines against Marek's disease of chickens."

Financial Impact (38)

Before the vaccine was developed and marketed in 1976-1977, Marek's disease was the number two cause of economic loss in "broilers." The disease occurred within 6 weeks of birth.

In 1970, 1.5 percent of all chickens inspected had Marek's disease and had to be condemned (the disease accounted for one-half of all the chicken condemnations that year). In 1980, as a result of the vaccine, only 0.1 percent of all chickens inspected had Marek's disease (a 15-fold reduction). The

(Continued)

Virology/Oncology (Continued)

vaccine costs approximately $8 million annually to administer and, according to the USDA, prevents a loss of approximately $56 million annually in condemnations. Thus, the total annual savings (i.e., the dollar loss prevented minus the cost of administering the vaccine) can be conservatively estimated at $48 million.

CHLOROTETRACYCLINE

Antibiotics have been adopted as a supplement used in animal feed for promoting growth and increasing feed efficiency in the production of meat animals.

Biomedical Contribution

The introduction of antibiotics to the physician's armamentarium has had a profound effect on the practice of medicine and has saved countless thousands of human lives. The discovery of penicillin by Fleming and the all-out effort to bring it into production during the final years of World War II was one of the finer moments in biomedical research.

The commercial success of penicillin, coupled with its humanitarian value, encouraged several research teams in academia as well as industry to initiate large screening studies to uncover new materials with antibiotic properties. Waksman and co-workers at Rutgers University soon discovered a series of materials produced by actinomycetes with antibiotic properties. Among these was streptomycin, which was first announced in 1944 (39).

The Lederle Laboratories Division of the American Cyanamid Company was one of the companies that initiated a search for new antibiotics. In 1948, the head of the Lederle team, Dr. Benjamin M. Duggar, reported the discovery of Aureomycin to the New York Academy of Sciences (40). Aureomycin is the trade name for the broad-spectrum antibiotic chlorotetracycline that is produced by the mold Streptomyces aureofaciens.

Duggar (41) was awarded a patent on chlorotetracycline in 1949. The product was put into commercial production and soon became the most important antibiotic developed since penicillin.

Industrial Application(s)

In 1948, Rickes et al. (42) discovered that the culture broths of various bacteria and actinomycetes contained vitamin B_{12} activity. As a result, culture filtrates from Aureomycin fermentations, formerly discarded, were now concentrated and became an important source of crystalline vitamin B_{12} (for clinical use) and, in the form of "Animal Protein Factor" (APF), for use in the animal nutrition market.

At the Lederle Laboratories, Stokstad and his co-workers were studying the effects of APF on the growth response of chicks. In 1949, they made an important discovery when they observed that the growth response obtained using APF from Aureomycin culture filtrates was greater than that expected from the vitamin B_{12} content alone (43). They demonstrated that the effect was due to traces of Aureomycin in the APF ration (44). Similar effects

(Continued)

Chlorotetracycline (Continued)

were found with turkey poults (45) and pigs (46). Other antibiotics were also found to be effective. The use of Aureomycin as an animal feed supplement to promote growth resulted from this discovery and had a significant impact on the production of meat animals.

Financial Impact (47,48)

The annual estimated dollar value of all animal feed used in the United States in 1979 was $14 billion -- representing approximately 90 million tons of feed. In 1979, the International Trade Association conducted an "Industry Survey of Animal Health" and reported that 5.58 million kg of antibiotics were used. The principal antibiotics used were tetracyclines and penicillin (which combined for more than half the total usage), as well as sulfamethezine and sulfathiazole (in hogs) and several types of nitrofuran compounds (which are fed principally to turkeys).

The estimated value of the antibacterials used in animal feed (principally Aureomycin) was $243.7 million. To that should be added the pharmaceutical usage of antibacterials for subtherapeutic uses (e.g., to increase feed efficiency), which was valued at $170 million in 1979. Thus, the total value of the antibacterial compounds in animal feed in 1979 was set at $413.7 million.

The ultimate value of these antibacterials, however, should be measured in terms of their growth-promotion capabilities and the increased feed efficiency realized from their use. It was estimated in a recent USDA study that if the antibiotics currently used were taken off the market and banned in animal feed, the "Market Basket Price" (the average weekly grocery items necessary to feed a typical family of four) would increase by $32 to $99 in the first year. The price increase to the consumer thereafter would depend upon the ability of the agricultural industry to discover alternative feed additives and growth promoters.

In terms of dollars, the USDA attributes considerable value to the use of antibiotics in animal husbandry. The following chart summarizes estimates from the aforementioned study as to the net effects that could be expected in the first year if antibiotics were eliminated from animal feed. The figures represent the loss in carcass weight meat (i.e., after the waste has been discarded) anticipated following the hypothetical removal of both high- and moderate-efficiency antibiotics. Because efficiency data are proprietary, and since USDA estimates that high- and moderate-efficiency antibiotics are used with approximately equal frequency, we have used the average between the expected losses in order to calculate the estimated dollar value effect.

(Continued)

Chlorotetracycline (Continued)

Loss in Meat Production

Animal Type	High Efficiency Antibiotics	Moderate Efficiency Antibiotics	Average for All Antibiotics	Retail Price (as of 8/80)	Estimated Value of Loss in Meat Production
(unit)	(millions of pounds)			($ per pound)	(millions of $)
Hogs	2,200	598	1,399.0	1.46	$2,042.5
Broilers	1,870	739	1,304.5	0.52*	678.3
Turkeys	312	127	219.5	0.63*	138.3
All Beef	73	50	61.5	2.42	148.8
TOTALS	4,455	1,514	2,984.5		$3,007.9

Therefore, the total annual retail value of antibiotics used in animal feed -- including their estimated benefits in growth promotion and increasing feed efficiency -- can be estimated at $3.422 billion.

* Because the retail prices for broilers and turkeys vary tremendously, and because the volume is so great and the reduced-price sales so frequent, the USDA uses wholesale prices for these two poultry categories.

NOTE: The Food and Drug Administration has continued to investigate the health risks of creating bacteria resistant to these antibiotics used in animal feed. Our survey represents the market as it is today; it is not meant as an endorsement of the current practice.

WARFARIN

Biomedical research into human anticoagulants led, as a by-product, to the development of warfarin, an extremely common and effective rodenticide.

Biomedical Contribution

Warfarin, a rodenticide, is a derivative of coumarin, the agent of hemorrhagic sweet clover disease.

In 1934, K. P. Link and his associates at the University of Wisconsin began their studies to determine the agent of hemorrhagic sweet clover disease. Cattle that were fed spoiled clover would begin to hemorrhage and would eventually die if untreated. Treatment before Link's research consisted of removing all spoiled clover from the cattle's diet. If the offending clover was removed from the diet in time, the hemorrhagic disease would reverse itself. Link and his co-workers at Wisconsin isolated and described coumarin as the agent in spoiled clover responsible for the hemorrhaging (49). Subsequently, this research team endeavored to synthesize coumarin and other anticoagulant derivatives of coumarin. A considerable number of coumarin derivatives were synthesized in the 1940's. The 42nd derivative so synthesized was a 4-hydroxy coumarin (also known as dicumarol) (50).

That same year, 1944, the anticoagulant activity of the 4-hydroxy coumarin group was demonstrated (51).

Research into the nature of hemorrhagic sweet clover disease was paralleled by medical research in analytical procedures needed to assess anticoagulants. As soon as coumarin and its derivatives were synthesized by Link's group and became available, the medical community began clinical trials as to their effectiveness (52). Subsequently, the use of anticoagulants such as dicumarol and other closely related compounds became routine in selected types of surgery and in some heart conditions.

Industrial Application(s)

In 1945, K. P. Link (53) became interested in using coumarin or its derivatives as rodenticides. Coumarin, however, demonstrated relatively poor anticoagulant activity in rats. In time, Link came to examine those coumarin derivatives synthesized by the Wisconsin research group. Of the 4-hydroxy coumarins in this group (#40-65) one compound, #42, showed 100 times the activity in rats as did coumarin. Link appealed to the Wisconsin Alumni Research Foundation (WARF) to fund the development of this compound as a rodenticide. In 1948, WARF decided to promote Compound #42, the name of which was first changed to WARF 42, and then finally to warfarin. Warfarin

(Continued)

Warfarin (Continued)

thus appears in the literature under many names, such as: 4-hydroxy coumarin, dicumarol, compound 42, and WARF-42, as well as warfarin.

Financial Impact (54,55)

The Wisconsin Alumni Research Foundation -- the biomedical developer of warfarin -- reports that over 400 different companies currently market products containing the compound.

The Environmental Protection Agency (EPA) reports that 1977 data are the latest available to the public (current sales are proprietary information). The 1977 figures reveal that warfarin is used in very minute amounts -- the most common product has a composition of 0.025 percent warfarin. It is used for 15 to 30 days continuous feeding in order to be effective. The breakdown of use for warfarin-based products is estimated as follows:

Sector/Site	Quantity of Active Ingredient Lbs.	% of Market
Residential	2,000-3,000	30
Commercial	1,000-2,000	20
Agricultural	3,000-4,000	50
	6,000-9,000	100

Thus, due to the small quantity used in most formulations, the total domestic sales of warfarin as an active ingredient (A.I.) annually are between 6,000 and 9,000 pounds. (One of the difficulties faced by the rodenticide industry, according to EPA, is the small amounts of active ingredient needed in most formulations). At the manufacturer/distributor level, this warfarin A.I. would have an annual market value of $12-16 million. This 6,000 to 9,000 thousand pounds of A.I., however, is used in approximately 25-40 million pounds of formulated product, with an estimated retail value of $200-$250 per pound. Thus, the total retail market for warfarin-based rodenticide products can be estimated at $50-$100 million annually.

In order to draw a complete picture of the value of warfarin-based rodenticides to the U.S. economy, we endeavored to discern the annual savings -- in terms of grain loss and property damage prevented -- accruing from the use of rodenticides. The EPA can make no such estimates, however, principally because: a) these compounds are almost always used in tandem with other pest control means (e.g., traps, strychnine), thus making the actual degree of use on farms difficult to measure; and b) the efficacy of the rodenticides has thus far only been tested under laboratory conditions,

(Continued)

Warfarin (Continued)

where the rodenticides have thus far only been tested under laboratory conditions, where the rodent has only the warfarin-treated grain to eat, and these results cannot be extrapolated to natural conditions, where the animal has greater freedom of choice in what it consumes.

Thus, the actual dollar savings realized from the use of warfarin-based rodenticides cannot be measured. For the purposes of this study, then, we can only include the retail value of the U.S. warfarin market which, as stated above, can be estimated at $50-$100 million annually.

FIBER OPTICS

The development of flexible endoscopes in biomedicine represents a critical event in the development of fiber-optics technology -- a rapidly growing field, particularly in the area of telecommunications.

Biomedical Contribution

The early development of fiber optics technology is inextricably linked with the development of flexible endoscopes. While it is true that John Tyndall demonstrated that light was conducted in a stream of water before the Royal Society in England in 1870, and that patents were issued on image transmission in uncoated fibers in Britain in 1927 (56) and the United States in 1930 (57), the concept was not developed further for the next 20 years.

In the mid and late 1950's, Kapany and co-workers (58,59,60) began to actively develop the technology of fiber optic bundles for image transmission. Hirschowitz and his co-workers in 1956 saw the possibility of using fiber-optics for a flexible endoscope and demonstrated the first practical application of image transfer by this method (61,62,63). He continued his work at the University of Michigan -- supported by a series of NIH research grants -- and perfected a gastroenteroscope (62) through a joint effort by the Departments of Internal Medicine and Physics. Then Kapany applied fiber optics to bronchoscopy, rectoscopy, and cystoscopy, in addition to gastroscopy (64). While the field of fiberoptics would undoubtedly have evolved independently, it is fair to say that the work of Hirschowitz was seminal, giving direction and impetus to the exploitation of this physical method. Hirschowitz's work has been supported by the NIH for more than 20 years.

Industrial Application(s)

Fiber optics technology is in a logarithmic growth phase. Both the basic technology and applications are changing rapidly. Current major applications include telecommunications, industrial process controls, and military applications (65).

Telecommunications is the most significant area of application for fiber optics technology today. Communication networks are being converted to fiber optics transmission systems around the world (66). Interactive cable television is a rapidly growing industry in the United States, Canada, and Japan. Fiber optics technology is revolutionizing the communications industry and is still in its infancy in many respects.

Process controls utilizing fiber optics technology are used in the chemical, nuclear, and petrochemical industries and will surely move into other industries soon (65).

(Continued)

Fiber Optics (Continued)

The military is investigating the use of fiber optics for communications in aircraft, ocean surface vessels, submarines, missles, and various ground communication links (65).

The use of fiber optics in computer aplications promises to be a significant application in the near future (66).

Financial Impact (67)

Approximately 90 percent of the fiber-optics market is currently in telephone communications systems; the other 10 percent is used in the computer industry, the cable television market, and the military for inspecting weapons systems. Corning's sales figures are proprietary, but it is able to estimate the size of the overall fiber-optics/communications market as follows:

Fiber optics components in telecommunications (used as connectors, cables, couplers, transmitters, receivers, repeaters, etc.) for FY 1980	$80 - $120 million
Recently published estimate for the market by FY 1985	$350 - $800 million
Recently published estimate of the market by FY 1990	$1.5 - $4.0 billion

Thus, the fiber-optics market is expected to increase during the next nine years by as much as 4,000 percent, to approximately a $4 billion annual industry. For the purposes of this study, its current annual value can be averaged out to approximately $100 million.

STEROID HORMONES

Biomedical research into the nature of steroidal hormones in humans has contributed to the use of testosterone and progesterone derivatives in the animal feed industry.

Biomedical Contribution

The secretions of the endocrine glands -- such as the pituitary, thyroid, parathyroid, adrenal, sex glands, and pancreas -- contain hormones that play important roles in tissue metabolism. The process of tissue synthesis, or anabolism, is controlled in part by steroid hormones. Our knowledge of the nature of steroidal hormones and the role they play in physiology has evolved over several decades and has been directly linked to biomedical research. The developments in this field are too numerous to review here. Two brief examples are presented below as illustrations.

Studies on androgens or male sex hormones, date back to the 1800's, but the first androgen to be isolated was androsterone, which was found in urine of normal males by Butenandt (68) in 1931. In 1935, David and co-workers isolated the active form of testosterone from bull testes (69); it was then soon possible to synthesize testosterone from cholesterol (70). Testosterone stimulates the growth of skeletal muscle, in addition to other functions.

Progesterone was first isolated from corpora lutea extracts (71). The basic principles of its extraction and purification were developed by W. M. Allen (72). Progesterone also has anabolic activity and affects the deposition of body fat.

Industrial Application(s)

The use of steroid hormones to stimulate the growth of cattle was a natural extension of the knowledge of their anabolic functions. The growth rate and body conformation of steers and heifers can be altered by the selective use of hormone derivatives. This application has had a significant impact on the animal husbandry industry.

Melengestrol acetate, a progesterone derivative, is marketed by the Upjohn Company under the trade name MGA as a feed additive for cattle.

The Syntex Agribusiness Company markets Synovex S, containing progesterone, for implant in steers and Synovex H, containing testosterone, for implant in heifers.

(Continued)

Steroid Hormones (Continued)

Financial Impact (73,74,75)

There are only a few steroidal hormones that are still allowed as additives in animal feed in the wake of the banning of diethylstilbestrol (DES). These include: melengesterol acetate (MGA), with estimated annual sales of $8.5 million (used in 65 to 75 percent of all heifers); Synovex S and H, with 1977 estimated sales of $5.5 million; and Ralgro, with 1977 sales of $1.3 million. The total sales of these hormones can conservatively be estimated at $15.3 million.

DES was the prototype for steroidal hormones used in animal feed and, prior to its removal from the market in 1979, USDA estimated its annual retail value in terms of consumer expenditures at $363 million. Following the removal of DES, the use of the aforementioned steroidal hormones was increased.

To estimate the growth promotional value of these hormones, USDA performed a study to determine the effects of completely removing MGA, Synovex, Ralgro, etc., from the market. Their conclusions were that steers would be 40 pounds lighter on the average, and that heifers would have 35 pounds less weight without any steroidal hormone additives. The resultant reduction in beef output the first year would amount to 665 million pounds live beef which, after waste and unusable portions were discarded, would equal 393 million fewer pounds of carcass equivalent brought to market.

With U.S. per capita beef consumption now at approximately 100 pounds per year, the resultant 2.9 percent retail price increase would translate to $7 per person. Thus, USDA concluded, the loss in meat production from the removal of steroidal hormones in animal feed would necessitate a $1.6 billion increase in consumer expenditures in the first year. If one subtracts the annual cost of the hormonal implants (approximately $100 million), the total increase due to meat loss would be $1.5 billion. When this is added to the $15.3 million sales market of the hormones, their annual retail value can be estimated at $1.515 billion.

ENZYME BIOCHEMISTRY

Enzyme biochemistry, a field that has received significant contributions from biomedicine, has been applied to the production of (among other things) beer, leather, and laundry detergents.

Biomedical Contribution

The genesis of enzyme biochemistry can probably be attributed to early workers in Germany such as Kuhne (76) and Hofmeister's (77) work on protein digests, and Cohnheim's (78) discovery that the intestinal mucosa elaborates an enzyme he called "erepsin" that cleaves peptones to amino acids. Buchner's work on cell-free extracts was also highly significant. These early workers, whose basic interest was to elucidate the biological activity of proteins and the physical basis of life, set the stage for a long series of biomedical studies involving enzymatic processes in biological systems.

Modern enzyme biochemistry probably owes its beginning (as much as anything to the work of Dr. James B. Sumner and Dr. John H. Northrop. Sumner (79) was the first to purify an enzyme by crystallization (urease), and Northrop and his co-workers crystallized pepsin and several other proteases and proved conclusively that they were protein in nature (80,81). Sumner and Northrop shared the 1946 Nobel prize for chemistry for their contributions to enzyme biochemistry.

Industrial Application(s)

The early interest in enzymes involved in the digestive process of man soon led to attempts to use these biological catalysts in industrial processing applications. Initially, crude preparations of organ or plant extracts with enzymatic activity were applied to industrial problems where protein, starch, or lipid hydrolysis was desired under mild conditions. As the knowledge of enzyme biochemistry grew, new sources of materials were developed and purer enzyme preparations became available. Several companies were established for the production and distribution of enzymes for industrial use. Today, enzymes are used in numerous industrial processes. Three examples are described below. Other typical examples include dough conditioning in bread baking, meat tenderizers, milk coagulation in cheese production, wine and fruit juice clarification, and desugaring eggs for dehydration.

1. Chillproofing of Beer

At the turn of the century, almost all beer was consumed in draught form within a short time after it had been brewed. With the introduction of bottled beer, and particularly pasteurized bottled beer, the product began to be shipped for long distances and stored for longer periods of time at low temperatures. Under these conditions, protein instability led to an undesirable haze in the product.

(Continued)

No matter what steps the brewers took in the selection of raw materials and fermentation control, they were unable to make a beer that would not develop turbidity and sediments when chilled for extended periods of time. The problem became a major concern throughout the industry, and the U.S. Brewmasters Association offered cash awards in 1909 and 1910 for the best research papers on the cause of the instability. Still, the problem remained unsolved.

The problem came to the attention of Leo Wallerstein of Wallerstein Laboratories, which had been established in 1902 as analytical and consulting chemists for the brewing industry. Wallerstein began experimentation in 1907 and, by 1911, had worked out a process for using the proteolytic enzyme papain to modify the colloidal proteins in beer to prevent their instability when chilled (82). Two patents were issued to Wallerstein in 1911 for this process (83,84).

Wallerstein's research was rather empirical in nature and based on the current understanding of enzymes, which had been developed by the European biomedical investigators. Nevertheless, the process based on crude papain was a success and a commercial product called "Collupulin" was soon introduced to the industry. As knowledge of enzyme chemistry and enzyme kinetics advanced, new enzyme combinations were selected for use in "Collupulin," which further improved its performance in beer stabilization.

Enzymatic chillproofing of beer has been adopted as a standard treatment worldwide. The wide acceptance of this technology based on earlier biomedical research made possible the enormous growth in bottling and canning of beer. Prior to 1910, considerably less than 10 percent of beer production was bottled (82). Today in the United States, bottled and canned beer represent nearly 80 percent of all beer produced.

2. Leather Bating

Leather tanning developed as a cottage industry in Europe and continues as such today in some areas. Early tanners kept dehaired hides in a warm suspension of the dung of dogs or birds to prepare the hides for tanning. This crude, unpleasant process, called bating, removed the spongy irregular protein layer from the hide and gave a smoother finished leather. As the basic knowledge of enzyme degradation of proteins grew through biomedical research, it became possible to put this industrial process on a scientific basis. Wood (85) was the first to demonstrate that the age-old bating practice was indeed an enzymatic process. This led to the first commercial bate, Erodin, which contained a bacterial protease and eliminated the need for the use of dung suspensions. In 1907, Rohm (86) patented a bating agent based on a pancreatic extract, a patent made possible by the biomedical research completed in the preceding decades. This product, called Oropon, is still sold to the leather industry by Rohm and Haas Company around the world, and is essentially unchanged in composition. Newer products based on bacterial proteases are also being used today.

(Continued)

Enzyme Biochemistry (Continued)

3. Enzyme Detergents

The basic knowledge that enzymes were responsible for the degradation of proteins and lipids led to an important application in the cleaning of clothing. The use of enzyme preparations to assist in the removal of food and other biological stains from clothing dates back to the turn of the century (87). Preparations from trypsin were first used in dry cleaning applications. For a number of years, it was impractical to use enzymes in laundry detergents because the enzymes available were ineffective in the harsh alkaline conditions used in laundering.

The first commercial product for home laundry use was introduced in Holland in 1963 under the tradename of Biotex (88). This product, which was based on a bacterial protease, was developed by A. G. Gebr. Snyder and Company of Switzerland and marketed by the Dutch firm, Kortman and Schulte. Soon, stable bacterial protease materials were being produced in the United States and enzyme and presoak products began to flourish.

In 1968-1969, the industry suffered a setback when it was discovered that workers handling enzyme concentrates were suffering allergenic reactions. While it was shown that the detergent user was not at risk, the products were discontinued in the United States although their production was continued in Europe. The intoduction of dust-free, encapsulated enzyme products eliminated the risk of handling the enzyme concentrates and enzyme detergents have been reintroduced to the United States market and have grown steadily (89).

Financial Impact (90,91,92,93)

Proteolytic enzymes have made possible the packaged sale of beer in bottles and cans. In 1979, more than 148 million barrels of packaged beer were shipped (1 barrel = 31 gallons), at an estimated retail value of approximately $21.6 billion.

The Tanner's Council of America reports that the use of pancreatic enzymes for bating is "a key process in the treatment of leather" and acknowledges that "we could not have a leather industry in this country without [the process]." Currently, the tanning industry in the United States represents a $1.6 billion annual enterprise.

The reintroduction of enzymes into laundry detergents sold in the United States is a relatively recent development. Therefore, it is difficult to fully estimate the domestic market -- particularly since labeling regulations do not require that laundry detergent manufacturers list all of their product ingredients. The U.S. Soap and Detergent Association reports that there is no separate listing for laundry detergents "with enzymes," but its figures show that enzyme-based, pre-soak "laundry boosters" had retail sales of $89.3 million in 1979. Finally, the prime manufacturer of enzymes

(Continued)

Enzyme Biochemistry (Continued)

for laundry detergents in Europe, Novo Laboratories of Copenhagen, Denmark, estimates that annual magnitude of the European and Asian market to be $100 million.

Excluding this last figure -- since our financial impact is confined to domestic retail value -- the total estimated U.S. retail value of these three applications of enzyme biochemistry is $23.3 billion annually.

REFERENCES AND NOTES

REFERENCES AND NOTES

Freeze-Drying

(1) Shackell, L.F., An improved method of dessication, with some applications to biological problems. Am. J. Physiol., 24:325-340 (1909).

(2) Flosdorf, E.W., and Mudd, S., Procedure and apparatus for preservation in 'Lyophile' form of serum and other biological substances. J. Immunol., 29:389 (1935).

(3) Flosdorf, E.W., Freeze Drying, Reinhold Publishing Corp., New York (1949).

(4) Sivetz, M. and Desrosier, N.W., "Freeze Dried Coffee Production" Chap. 13 in Coffee Technology, AVI Publishing Company, Westport, Conn. (1979).

(5) Anon. What's coming in freeze-drying? Food Eng., 35(2):64-67 (1963).

(6) Anon. Commercial freeze-drying expands in U.S. and Europe. Food Eng., 34(5):123 (1962).

(7) Data Source: Almanac of the Canning, Freezing, and Preserving Industries, Edward E. Judge and Sons (Publishers), Westminster, Maryland.

(8) Data Source: National Coffee Association (NCA) of the U.S.A., 120 Wall Street, New York, New York 10005.

(9) Data Source: Supermarketing 1979, an annual consumer expenditures study prepared by Supermarketing Business, Inc., New York, New York.

Immobolized Enzymes

(10) Grubhofer, N. and Schleith, L., "Modifizierte ionenaustauscher als spezifische adsorbentien." Naturwissenschaften 40:508 (1953).

(11) Silman, I.H., and Katchalski, E., Water insoluble derivatives of enzymes, antigens, and antibodies. Ann. Rev. Biochem., 35:873-908 (1966).

(12) Chibata, I. and Tosa, T., Applied Biochemistry and Bioengineering, Vol. 1, p. 329, Academic Press (1976).

(13) Chibata, I., Immobilized Enzymes, John Wiley & Sons, New York, p. 213 (1978).

(14) Thompson, K.H., et al., U.S. Patent 3,788,945 (1974).

(15) Moore, K., Immobilized enzyme technology commercially hydrolyzes lactose, Food Product Development, 14(1):50-51 (1980).

(16) Marconi, W., et al., Improved whey treatment by immobilized lactase. Presented at 1979 Engineering Foundation Conference on Enzyme Engineering V, Henniker, New Hampshire, Aug. 2, 1979.

(17) Obera, J., and Hashimoto, S., Sugar Technology Review 4(3):209-228 (1977).

(18) Olsen, A.C. and Korus, R.A., "Immobilized Enzymes" in Enzymes in Food and Beverage Processing, R.L. Orz and A.J. St. Angelo, Eds., ACS Symposium Series 47, American Chemical Society, Washington, D.C. (1977).

(19) Vieth, W.R. and Venkatasubramanian, K., Enzyme Engineering Part I. The utility of supported enzyme systems. CHEMTECH, 677 (Nov. 1973).

(20) Data Source: Corn Refiners Association, Office of Public Affairs, 1001 Connecticut Avenue, Washington, D.C.

(21) Data Source: Holly Sugar Company, Agricultural Division, Torrington, Wyoming.

Keratin Biochemistry

(22) Goddard, D.R. and Michaelis, L., A study on keratin. J. Biol. Chem., 106:605 (1934).

(23) Speakman, J.B. and Hirst, M.C., Tran. Faraday Soc., 29:148 (1933).

(24) Astbury, W.T. and Bell, F.O., Nature of the intramolecular fold in alpha-keratin and alpha-myosin. Nature 147:696-699 (1941).

(25) Patterson, W.I., et al., Role of cystine in the structure of the fibrous protein, wool. J. Res. Nat. Bur. Stand., 27:89 (1941).

(26) Wells, F.V. and Lubowe, I.I., Cosmetics and the Skin, Reinhold Publishing Corp., New York, p. 458 (1964).

(27) Data Source: Gillette, Inc., Personal Care Division, Sales Planning Branch, Boston, Massachusetts.

Laboratory Instrument Computer (LINC)

(28) Clark, W.A. and Molnar, C.E., "The LINC: A description of the Laboratory Instrument Computer" in Computers in Medicine and Biology, Ann. New York Acad. Sci., 115(2):653-668 (July 31, 1964).

(29) Cox, J., Personal communication (1980 and 1981).

(30) Bell C.G., Mudge J.C., and J.E. McNamara, Computer Engineering: A DEC View of Hardware Systems Design, Digital Press, Bedford, Mass. (1978).

(31) Data Source: Digital Equipment Corporation, Maynard, Massachusetts.

Virology/Oncology

(32) Tooze, J., "Origin of contemporary tumor virus research" in The Molecular Biology of Tumour Viruses. Cold Spring Harbor Laboratory, p. 53 (1973).

(33) Biggs, P.M. et al., "The etiology of Marek's disease. An oncogenic herpes-type virus." Perspectives in Virology (M. Pollard, Ed.) Academic Press, New York, 6:211-237 (1968).

(34) Witter, R.L., et al., Evidence for a herpesvirus as an etiologic agent of Marek's disease. Avian. Dis. 13:171-184 (1969).

(35) Churchill, A.E., et al., Immunization against Marek's disease using a live attenuated virus. Nature 221:744-747 (1969).

(36) Purchase, H.G., et al., Field trials with the herpes virus of turkeys (HVT) strain FC 126 as a vaccine against Marek's disease. Poultry Sci. 50:775 (1971).

(37) Hilleman, M.R., "Prospects for vaccines against cancer" in Viruses, Evolution and Cancer. E. Kurstak and K. Maramorasch (Eds.) Academic Press, New York, 549-550 (1974).

(38) Data Source: U.S. Department of Agriculture, Economic Research Service, Food Protection and Research Analysis Section, Washington, D.C.

Chlorotetracycline

(39) Schatz, A., Bugie, E., and S.A. Waksman, Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. Proc. Soc. Exper. Biol. & Med., 55:66-69 (1944).

(40) Duggar, B.M., Aureomycin: A product of the continuing search for new antibiotics. Aureomycin: a new antibiotic. Annals of the N.Y. Acad. of Sci., 51:177-181 (1948).

(41) Duggar, B.M., Aureomycin and preparation of same. U.S. Patent No. 2,482,055 (Sept. 13, 1949).

(42) Rickes, E.L. et al., Comparative data on Vitamin B_{12} from liver and a new source, Streptomyces griseus. Science 108:634-635 (1948).

(43) Stokstad, E.L.R., et al., The multiple nature of the animal protein factor. J. Biol. Chem., 180:647-654 (1949).

(44) Stokstad, E.L.R., and Jukes, T.H., Further observations on the animal protein factor. Proc. Soc. Exper. Biol. & Med., 73:523 (1950).

(45) McGinnis, J.E.L., et al., Response of chicks and turkey poults to Vitamin B_{12} supplements produced by fermentation with different organisms. Abstr. of Paper, 116th meeting of the Am. Chem. Soc., p. 42A (1949).

(46) Jukes, Thomas H., et al., Growth-promoting effect of Aureomycin on pigs. Archives of Biochem., 26:324-325 (1950).

(47) Data Source: U.S. Department of Agriculture, Economic Research Service, Food Protection Research and Analysis Section, Washington, D.C.

(48) Data Source: Animal Health Institute (AHI), 1717 K Street, N.W., Suite 1009, Washington, D.C.

Warfarin

(49) Stahmann, M.A., A. Huebner, C.F., and K.P. Link, Studies on the hemorrhagic sweet clover disease V. Identification and synthesis of the hemorrhagic agent. J. Biol. Chem., 138:513 (1941).

(50) Ikawa, M., M.A. Stahmann, and K.P. Link, Studies on 4-hydroxy-coumarins V. The condensation of alpha, beta unsaturated ketones with 4-hydroxycoumarin. J. Am. Chem. Soc., 66:902 (1944).

(51) Overman, R.S., et al., Studies on the hemorrhagic sweet clover disease. XIII, Anticoagulant activity and structure in 4-hydroxy-courmarin group. J. Biol. Chem., 153:5 (1944).

(52) Meyer, O.O., J.B. Bingham and F.J. Pohle, Studies of the hemorr-hagic agent 3,3'methylene-bis (4-hydroxycoumarin): Its effect on the prothrombin and coagulation time of the blood of dogs and humans. Am. J. Soc., 202:593 (1941).

(53) Link, K.P., The Discovery of dicumarol and its sequels. Cir. 19, 97-107 (1959).

(54) Data Source: Sterling Drug Company, De-Con Division, New York, New York.

(55) Data Source: U.S. Environmental Protection Agency, Economic Analysis Branch, Benefits and Field Studies Division, Office of Pesticide Programs, Washington, D.C. (staff estimates)

Fiber Optics

(56) Baird, J.L., Br. Patent No. 20,969/27 (1927).

(57) Hansell, C.W., U.S. Patent No. 1,751,584 (1930).

(58) Hopkins, H.H., and Kapany, N.S., A flexible fibroscope, using static scanning. Nature 173:39 (1954).

(59) Kapany, N.S., et al., Fiber Optics - Image transfer on static and dynamic scanning with fiber bundles. J. Am. Opt. Soc., 47:117, Abstact FC62 (1957).

(60) Kapany, N.S., Fiber Optics VI. Image quality and optical insulation. J. Am. Opt. Soc., 49:779 (1959).

(61) Curtiss, L.E., Hirschowitz, B.I., and Peters, C.W. A long fiberscope for internal medical examinations. J. Am. Opt. Soc., 46:1030 (1956).

(62) Hirschowitz, B., et al. Demonstration of a new gastroscope, the "Fiberscope." Gastroenterology, 35:50 (1958).

(63) Hirschowitz, B., Endoscopic examination of the stomach and duodenal cap with the fiberscope. The Lancet, 1:1074 (May 20, 1961).

(64) Kapany, N.S., in Proc. Intern. Congr. of Gastroenterology, p. 577. Excepta Medica Foundation, Amsterdam (1961).

(65) Elion, G.R. and Elion, J.A. "Economics and Applications" in Fiber Optics in Communication Systems, Marcel Dekker, Inc., New York (1978).

(66) Proceedings FOC '79, Fiber Optics and Communications, M.A. O'Bryant and P. Polishuk, eds.; Published by Information Gatekeepers, Inc., Brookline, Mass. (1979).

(67) Data Source: Corning Glass Works, Engineering Sales Division, Corning, New York.

Steroid Hormones

(68) Butenandt, A., and Z. Angew. Chem., 44:905 (1931).

(69) David, K., et al., Z. Physiol. Chem., 233:281 (1935).

(70) Ruzicka, L. and Wettstein, A., Helv. Chim. Acta, 18:986 (1935).

(71) Pincus, G., and Pearlman, W.H., Vitamins and Hormones, 1:294 (1943).

(72) Allen, W.M., Am. J. Physiol. (London), 92:174, 612 (1930); 100:650 (1932).

(73) U.S. Department of Agriculture, Economic Research Service, Food Protection Research and Analysis Section, Washington, D.C.

(74) Data Source: The Upjohn Company, Technical Services Division, Animal Health Research and Development, Calverton, Michigan.

(75) Data Source: Syntex Agribusiness Company, Technical Services Division, Des Moines, Iowa.

Enzyme Biochemistry

(76) Kuhne W., Arch. fur Path. Anat. 39:130-174 (1867).

(77) Hofmeister, F., Z. Physiol. Chem. 5:126-151 (1881).

(78) Cohnheim, Z., Z. Physiol. Chem. 33:451-465 (1901).

(79) Sumner, J.B., J. Biol. Chem., 69:435 (1926).

(80) Northrop, J.H., J. Gen. Physiol. 13:739-766 (1930).

(81) Northrop, J.H., Crystalline Enzymes, Columbia University Press, New York (1939).

(82) Wallerstein, L., Chillproofing and Stabilization of Beer. Wallerstein Lab. Comm. 24:158-167 (1961).

(83) Wallerstein, L., Beer and method of preparing same. U.S. Patent No. 995,820 (June 20, 1911).

(84) Wallerstein, L., Method of treating beer or ale. U.S. Patent No. 994,824 (June 20, 1911).

(85) Wood, J.T., J. Soc. Chem. Ind. 17:1011 (1898).

(86) Rohm, O., Ger. Patent 200,519-28a. (June 7, 1907).

(87) Aunstrup, K. et al., Proteases from alkalophilic Bacillus species. Proc. IV IFS: Ferment. Technol. Today, ed. by Gyozo Terui, Society of Fermentation Technology, Japan, 299-305 (1972).

(88) Anon., Will enzymes trigger a detergent revolution? Chem. Eng. 108-109, Sept. 23, 1968.

(89) Aunstrup, K., et al., Production of microbial enzymes, Chap. 9 in Microbial Technology, ed. by H.J. Peppler and D. Perlman, Academic Press, N.Y. Second Ed., Vol. 1: 281-309 (1979).

(90) Data Source: U.S. Brewers Association, Research Department, Washington, D.C.

(91) Data Source: Rohm and Haas Company, Technical Division, Philadelphia, Pennsylvania.

(92) Data Source: Tanners Council of America, Washington, D.C.

(93) Data Source: U.S. Soap and Detergent Association, Consumer Affairs Department, New York, New York.

(94) Data Source: International Association of Soap and Detergents (AIS), Brussels, Belgium.

(95) Data Source: Novo Laboratories, Copenhagen, Denmark.