ADVANCES IN

Applied Microbiology

Edited by WAYNE W. UMBREIT

Department of Bacteriology
Rutgers, The State University
New Brunswick, New Jersey

VOLUME 6

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PREFACE

The present volume, the sixth in this series, represents an expansion into areas of applied microbiology other than those solely related to the laboratory. The applied microbiologist has an impact upon and is responsive to changing conditions in the world. The "global impact of microbiology" is discussed as well as some opinions on what kind of training an applied microbiologist ought to have. The range of the other articles remains broad and considers the microbial action on minerals, the nonmedical uses of antibiotics, water pollution control, some aspects of industrial enzymes, the preparation of radioactive substances by microbial processes, and the influence of some factors, normally considered minor, upon fermentation processes.

One difficulty for an Editor, but of course one advantage to the science, is that the area of knowledge covered by applied microbiology is so broad that it is most difficult to cover adequately. Various individuals working in it have quite different views of what ought to be considered in a publication such as "Advances." Should you find that an area of particular interest to you is not being adequately covered, please let the Editor know and perhaps something can be done about it. It is the object of "Advances" to be as useful as possible and to take advantage of the virtues of the eighteenth century essay as a medium of communication and exchange of useful information.

W. W. UMBREIT

Rutgers University
June, 1964

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A conference, bearing the imposing title "Global Impacts of Applied Microbiology" (GIAM), was held in Stockholm from July 29 to August 3, 1963. This conference bore the subtitle "A Projection of the Microbiological Research of Today to the Needs of Tomorrow." Since the future needs of the world will certainly be most pressing in the developing areas, it was natural for this conference to focus on microbiology as applied to the solution of problems indigenous to such regions. Actually, the Stockholm conference might be regarded as a continuation—within one particular field—of the United Nations Conference on the Application of Science and Technology For the Benefit of the Less Developed Areas held in Geneva in February, 1963.

The Stockholm GIAM conference, which was attended by some 350 representatives of 30 countries, was arranged by the Section for Economic and Applied Microbiology of the International Association of Microbiological Societies (IAMS) in collaboration with the Royal Swedish Academy of Engineering Sciences. It was cosponsored by the World Academy of Art and Science, a relatively new

organization devoted to questions concerned with the interplay of science and society. Professor A. Tiselius and Dr. M. Tveit served as President of the Conference and Secretary-General, respectively.

This conference was an interesting and quite unique experiment in that it brought together specialists from many unrelated disciplines: soil microbiology, medicine, fermentation, phytopathology, immunology, food technology, economics, and science administration—to name but a few. It was structured to provide a forum for various viewpoints, and to generate programs for action which could be presented to different governmental and international agencies. Many of the deliberations should, however, be of considerable interest to the individual scientist working in the field of applied microbiology; hence, we have summarized here some of the high points of the GIAM conference. We have neither the ambition nor the competence to present a comprehensive and substantive review of the multidisciplinary field covered by the conference. Rather, we shall prepare a concentrate of some salient ingredients, an "instant" and, we hope, thought-provoking brew, which the reader should dilute with his own experience and imagination. We may have spiced the preparation with a few personal views and prejudices; therefore, we recommend that a factual and unbiased view of the Stockholm conference be obtained by consulting the complete proceedings which are now in press under the title "Global Impacts of Applied Microbiology" (edited by M. P. Starr, published jointly by Almquist & Wiksell, Uppsala, and Wiley (Interscience), New York). Since that book comprises the main reference source, we have omitted here citations to the literature which are annotated in that volume.

I. Human Ecology

The prevailing concern among scientists for the population crisis was evident in the introductory remarks made by S. Brohult who referred to the latest United Nations report on population increase, with its disturbing news that earlier demographic prognoses had been too low. Actually, the 1960 population census estimate surpassed the 1958 prognosis by 75 million. There has been an increase in the food production of our globe, certainly, but, during the 1950's, the productivity per inhabitant had remained essentially constant. The Food and Agricultural Organization estimated in 1962 that continued growth in population, in accordance

with the United Nations forecast, would necessitate doubling the world supply of food by 1980 and trebling it by the turn of the century, in order to provide a reasonably adequate level of nutrition for all peoples. The GIAM speakers and confrères were gravely concerned that half of the peoples of the world are presently suffering from hunger and disease.

G. Borgström discussed the biological and chemical limitations in the continued growth of the human biosphere, and threw serious doubt on the possibilities of providing sufficient food to banish the specter of starvation. Agriculturists have been confident that they can continue to raise yields with the aid of modern science and technology. Borgström calls this a tragic fallacy and points out that the law of diminishing returns is already operating with regard to minerals, water, etc., in several highly advanced countries. Notwithstanding the potentialities of synthetic chemistry, we must accept the fact that our main source of food, now and in the remote future, must continue to depend on sunlight and carbon dioxide.

Borgström formulates a new population density concept in which the total biomass within man's action sphere is related to soil resources, and he shows that the total human biomass has now acquired dimensions which far overshadow those of any other higher mammal. It is, for instance, interesting to consider that the total weight of livestock of all major countries is 860 million metric tons compared with the total calculated weight of humans (187 million metric tons). The livestock is under the direct control of man within his biosphere, and if the biosphere is recalculated in terms of Borgström's population equivalents, it becomes startlingly clear that green plants must carry a feeding burden which is far in excess of the 3 billion humans we normally consider to be the beneficiaries of photosynthesis. A closer estimate would be the equivalent of 17.5 billion human consumers! Horses still require a protein intake that corresponds to that of 653 million people; in other words, the equine consumptive force itself equals that of the humans in the most populous country of the world, China.

It is unfortunate that man has thus far been almost completely unable to relate himself properly to his environment. In a situation in which man's attention is concentrated on the struggle with other human beings, he may tend to forget that he may be in an even more serious struggle with other living organisms, be it insects or

bacteria. It has been estimated that insects eat, steal, or destroy one-third of everything which man grows and stores for the future. Moreover, the World Health Organization has estimated that insects cause one-half of all human deaths, disease, and deformity. A single insect-borne disease, malaria, still infects one-sixth of the human race and claims a human life every 10 seconds!

In discussing human ecology and infectious diseases, S. Mudd reminded his audience that an infectious disease is a struggle between two biological systems, each adapted by long evolution to survive under conditions inimical to the other. In earlier days, the birth and death rate and the natural resources necessary to support human populations approached a steady-state condition. Now, a reduction of mortality has brought about unbalanced increases in population out of proportion to our augmented resources. Consequently, it is no longer possible to provide a minimum adequate diet for each member of the human family, and a net increase in its collective misery is the result.

This is, of course, particularly true in the newly independent nations in which, as pointed out so eloquently by the Deputy Prime Minister of Israel, A. Eban, there is the sad realization that a nation can be free in every institutional sense of the word and yet lose the essence of freedom in the throes of starvation and want. As mentioned before, much of the discussion at the Stockholm meeting was actually focused on the need for helping the underdeveloped countries and the problems encountered in the limitations of their capacity to accept and adopt a science and technology based on presuppositions and value systems different from their own. This problem is undeniably complex as may be illustrated by a quotation made by E. M. Mrak from a work by G. Hardin: "If we include freedom to breed as one of man's inalienable freedoms, and if we accept the obligation to share excess food with those who are starving, then how can any nation, class, or religious group that responsibly controls its numbers survive competition with any nation, class, or religious group that refuses to act responsibly?" Our main consolation is that there has been a reduction not only in death rates but also in birth rates in every country that has changed from a predominantly agrarian society to one whose predominantly industrial urban pattern has extended its public education.

II. The Social Responsibility of Scientists

The fact that the Stockholm conference was initiated by scientists speaks against the popular notion that scientists are indifferent to the social consequences of their work. The great number of world authorities participating also illustrates the widespread feeling of responsibility and concern for the present trends in science administration and sociological development. These factors are much too dynamic to be steered unerringly by means of shortsighted local planning. Furthermore, the potentialities of science and technology are now so enormous that the consequences may be disastrous if decisions are made by power-seeking and parochially oriented individuals. No doubt the freedom of action, "the political latitude," is shrinking in an environment in which the general training level is high and whose complex social structure requires specialists at the highest levels, but the application of science and technology in the developing countries certainly involves dangers.

Eban elaborated on the problems of controlling the great powers inherent in scientific investigation, which must be enormous when 80 or 90% of all scientists who have ever lived are living now. He stressed that there is no room today either for a scientist without social conscience or for a politician who lacks a basic understanding of the impact of science upon the life of nations and the world community. Beyond the great problems created by nuclear weapon technology, the most urgent human issue now concerns the awakening continents. Eban projected the population increase and the more modest growth of resources into the next century and pointed out the tensions which will ensue. He found monstrous the suggestion that science is somehow responsible for the perils of nuclear war, for the prospect of world famine, or for the gap between the greater and lesser advanced countries. "The responsibility lies not in science, but in our failure to determine the social direction of scientific progress."

A former United Nations adviser in economic affairs, G. Myrdal, was of the opinion that the world is headed for an economic and political cataclysm if radical changes are not made. In his opinion, the current and now foreseeable economic and social trends in most of the underdeveloped countries have more serious, not to say sinister, directions than is commonly recognized. Particularly dis-

turbing is the accelerated rate at which the gap in income between the underdeveloped and industrially advanced countries is widening.

It was stimulating to hear the bacteriologist, J. Birkeland, discuss the psychological and sociological climate for scientific investigation, coining terms such as "ecology of science." He reminded his audience of the Middle Ages when man was preoccupied with problems of salvation and sin, and of the plagues and pestilences that were explained on the assumption that people had sinned. Too great a preoccupation with life in the hereafter does not provide a favorable intellectual climate for developing the knowledge that will furnish the food and shelter and eliminate the disease of our present world.

As perceptively noted by E. C. Stakman, the degree to which man's intelligence and enterprise enable him to master his environment—instead of being a mere servant of it—is a measure of civilization. In this connection, the relatively young science of microbiology is essential because it is directly concerned with two of the most elemental of all human needs—health and food. The microbe is a prime natural resource of all mankind, regardless of national boundaries. If man makes an effort to understand, control and utilize this resource it may affect his future most profoundly. Science has taught us to live longer and more abundantly by combating dangerous microbes and by utilizing beneficial ones, and applied microbiology now holds a major key to this needful future. As expressed by Stakman, "its potential role is tremendous and it is tremendously important." The scientists who, together with the international agencies of health and welfare, philanthropic foundations, and pharmaceutical industries, share the responsibility for the present imbalance between mortality and fertility, must continually stress this point. It is a biological certainty that the steady state will be restored but, as rational and compassionate human beings, we cannot, as pointed out by Mudd, leave the restoration to the Horsemen of the Apocalypse, War, Famine, and Pestilence.

III. Applied Microbiology and Medicine

Man has many enemies in the microbiological world and some, such as the etiological agents of smallpox, yellow fever, and malaria, are of undoubted ecological importance. In the Western world, control measures have been developed gradually, but in the new

nations the development phase has been bypassed and low-cost measures of controlling disease have been imported. As a consequence, the approximate steady-state equilibrium between the available nutrition and actual number of human beings has been disturbed, and individuals, in larger numbers than ever before in the history of the world, are now living in a state of hunger and malnutrition.

W. C. Cockburn, from the World Health Organization, discussed the implications of large-scale programs for the control of infectious disease. Apart from smallpox, whose eradication is now a possibility, such programs are relatively recent, but present community campaigns include vaccination programs aimed at tuberculosis, poliomyelitis, pertussis, diphtheria, tetanus, and trachoma. Measles vaccine will follow, and perhaps even preparations active against infectious hepatitis. Immunization methods against tetanus, diphtheria, smallpox, and poliomyelitis have been remarkably effective; their reduced incidence may have its repercussion in the population increase. However, Cockburn emphasizes that not only do immunization procedures save lives, they also ensure a state of health which improves productivity; certainly, they reduce the cost of the health services, a case well illustrated by diphtheria.

Such positive contributions to the population balance were also emphasized by J. Ungar, who mentioned the importance of the recently developed trachoma vaccine which may control a disease afflicting approximately one-sixth of the world population. In the population balance, we should not forget that parasitic worms, which infect the people of certain tropical countries, are said to metabolize more of the produce of those countries than do the inhabitants. Obviously, the development of immunization programs against helminthic infections and protozoal diseases may be of the greatest importance in the tropics, but a forecast cannot be attempted in the present state of our knowledge.

Much research must go into the development of vaccines having greater safety, potency, and stability than are possessed by present preparations. The economic advantages of large-scale production of vaccines should be exploited, but much remains to be learned about techniques. P. van Hemert emphasized that specialized study of unit processes may offer a way to a better understanding of production, and thus also lead to improvements.

Among the possible immunization procedures of the future,

aerosol vaccination was mentioned as a means of reducing the cost and administrative problems of major campaigns. That this is a realistic concept is obvious when one considers the advances in aerobiology which are by-products of the research in biological warfare. It is now known that it is possible to cover large areas with viable microbial aerosols. However, L. D. Fothergill, who discussed the potential ecological consequences of air contaminated with infectious agents, pointed out that the situation is very complicated.

Major immunization schemes must always be planned and executed against a background of sound ecological knowledge. For instance, nature's own immunization activities must never be forgotten, otherwise immunization as well as improvements in the environmental and social conditions may bring about unexpected consequences. The pasteurization of milk had its repercussions in the loss of "natural" immunity to tuberculosis, and no one will deny that an increase in the age of infection with poliomyelitis has been an undesirable consequence of incomplete community immunization in combination with improved hygiene.

Specific responses as well as nonspecific microbiological stimulators are both important in immunology. Pyrogenic lipopolysaccharides might be mentioned, as should also the deoxyribonucleic acid (DNA) digest factor noted by W. Braun, as a stimulator of antibody response. Immunity is the sum of a complex interplay of many known and possibly more unknown factors. Some of those may certainly be manipulated by microbiological techniques, and J. G. Harrar, touching on the importance of the normal bacterial flora of the human intestinal tract, even speculated on the possibility that microorganisms might one day be found that could synthesize compounds which could protect against diseases such as cancer, or that others might slow down the process of aging.

A. Wettstein and his collaborators made a general survey of microbiological syntheses of pharmacologically active substances. This served as a very striking illustration of the utilization of the biosynthetic capacities of bacteria and molds in modern pharmaceutical research and industry. The long list of useful substances ranges from macromolecules, such as enzymes used as digestive aids or for tissue removal, polysaccharides used as plasma volume expanders and iron carriers, through a number of vitamins, to the ergot alkaloids used by both the obstetrician and the psychiatrist,

and the siderochromes which are useful in the treatment of iron-storage diseases. Last, but not least, come the antibacterial and antimycotic antibiotics, some of which are even being used in tumor chemotherapy.

Perhaps the most impressive career during the last 20 years is shown by the antibiotics, a history which is astonishingly short considering the fact that antibiosis has been observed almost since man learned to grow microorganisms on artificial media. E. B. Chain reviewed briefly the history of modern antibiotics, and his comparison of death rates from selected causes during the years 1920 and 1960 served as an impressive illustration of the success of modern therapy. He regards the screening of microorganisms for the production of new antibiotics as having been so thorough that it is unlikely that entirely novel structures will be discovered. Against this background, the development of semisynthetic antibiotics is particularly relevant, for example, preparations based on 6-aminopenicillanic acid and the tetracycline derivatives. Even if the danger of creating resistant strains by the continued use of antibiotics has been exaggerated, the development of a wide spectrum of semisynthetic preparations should be a relief to many members of the medical profession.

The semisynthetic antibiotics constitute an example of the utility of microorganisms in providing modifications of complex molecules. An even more striking example in the pharmacological field is found in the steroids, the transformation of which was discussed from various points of view by A. Wettstein, D. H. Peterson, and O. Hanč. The future of microorganisms in the pharmaceutical industry is, of course, difficult to predict, but one has reason to be optimistic, considering the advantages that Wettstein and colleagues list for them as compared to higher organisms: 1. great physiological similarity between the individual cells in the population; 2. the possibility of using artificial media; 3. great versatility; 4. relative ease of the preparation of genetic modifications; 5. as compared to chemical synthesis, the microorganism products have the advantage of stereospecificity.

IV. General Aspects of the Exploitation of Biological Resources

Recent calculations indicate that the total mass of microbial life on earth is approximately 25 times the total mass of animal life.