actions with other gene products or with the host are usually not important. However, there are other organisms and products that are worthy targets for this novel scientific approach and in fact, in the case of small molecules, the types of problems to be solved are very different from those encountered in the cloning and expression of single genes. The problem is much more difficult, but also worthwhile. Are not the majority of pharmaceuticals, used at the moment, classed as small molecules? Virtually none are proteins! Therefore it is natural that recombinant DNA should want to turn to engineering of microorganisms. In addition, the possibilities of engineering higher yields and altered molecules of pharmacologically active chemicals such as the alkaloids provides a strong impetus for studies of plant biosynthesis.

The problems lie not in the fact that small molecules are involved but that one has to control multiple enzymatic reactions. Small molecules, whether they be the products of primary or secondary metabolism, are made by complex biosynthetic pathways which possess, in many cases, delicately balanced regulatory and control mechanisms. For example the genetic engineering approach to increasing antibiotic production is an obvious application, but not an easy one. The producing hosts are often not well studied or characterized biochemically, the biosynthesis of the small molecule (and its regulation) is not well known, and appropriate host/vector systems are not available. This creates a situation in which, to augment or to modify a given antibiotic, a complete analysis of the producing organism must be completed and suitable vectors for this organism constructed. Substantial progress has been made and several approaches to antibiotic yield improvement using recombinant DNA techniques have shown promise. One important finding is that many of the biosynthetic genes for antibiotics may be clustered on the chromosome and therefore easy to pluck out and manipulate. In addition, antibiotic resistance genes are found within these clusters, providing convenient probes to identify the biosynthetic pathway genes.

Genetic engineering methods are novel, exciting and undoubtedly useful. To be effective in a broad range of applications will require a better knowledge of the physiology and biochemistry of the organisms that need to be manipulated, and of the systems to which recombinant DNA products will be applied.

Of microbes and man

H. Mahler
World Health Organization, Geneva, Switzerland

Infectious disease, which preceded the emergence of mankind, will last as long as humanity itself and will surely remain one of the fundamental parameters and determinants of human history, but not with the same interaction/impact worldwide. In the early ages, life in small family clusters was not conducive to wide-spread infection. When these clusters expanded, microbes could spread further and cause illness which became more feared as they would frequently appear in several members of the tribe at one and the same time. The wrath of the gods appeared to be a reasonable explanation to this phenomenon, and the priest/healer was chosen to act as the intermediary to appease the gods and prevent disease.

The industrial revolution brought people closer together in urban conglomerations thus increasing the opportunities for infections to spread. However, during the second half of the 19th century mortality declined almost entirely due to a decrease in deaths from infectious disease, especially tuberculosis, typhus, typhoid and related fevers, scarlet fever, cholera, dysentery and diarrhoea, and smallpox. The most important factors responsible for this decline in mortality were firstly, a rising standard of living, of which the most significant feature was probably improved diet, secondly, improved hygiene, and thirdly, a favorable trend in the relationship between infectious agent and human host.

By the turn of the century 'Man the Technician' was well on the way to 'conquering' microbes in the industrialized countries, just as he was becoming aware of their existence. It was at that time that the great discoveries of Pasteur and Koch were claiming worldwide recognition. Twentieth century data show that the continued decline in the death rate after 1900 in industrialized countries was also due mainly to a decrease in deaths from infectious disease such as measles, scarlet fever, whooping cough, smallpox and diphtheria, as well as tuberculosis, typhoid, paratyphoid, dysentry, influenza and syphilis. Lower mortality was also noted from groups of communicable diseases such as diarrhoea and enteritis, convulsions in infancy (usually associated with infection) and the respiratory infections – bronchitis and pneumonia.

In 1935 the first real antimicrobial drug the sulphonamide was introduced by Paul Ehrlich. The key discovery was that certain dyes would be taken up by, and would kill, parasites and bacteria, while leaving patients' tissues alone. In short, Ehrlich introduced the notion of drug specificity, of the 'magic bullet'.

The attack on microbes did not become a worldwide reality until after the Second World War when antimicrobial agents such as penicillin and sulphonamides became widely available. In addition, vaccines against specific diseases were being developed at a fast rate. The conquest of infectious diseases seemed to be near in the 1950s, and an aura of elated optimism reigned. However since then, morbidity rates of infection have not decreased significantly and in some cases have actually increased. In addition, changes in the structure of society and in social behavior as well as changes in medical practice (especially the extensive use of blood and blood products) have favored the spread of 'new' diseases in the community such as Legionnaire's disease and AIDS. The indiscriminate use of antibiotics has meantime favored the selection of antibiotic-resistant organisms.

Only a minority of the world's population have benefited from the development engendered by the industrial revolution. In the developing world, communicable diseases, complicated by malnutrition and other adverse socioeconomic factors, continue to contribute greatly to the unacceptably high levels of morbidity, mortality and disability particularly in the under-five age group. It is estimated that five million deaths occur annually from diseases which can be prevented by vaccines available today, and that another five million people are being crippled,

blinded or mentally retarded as a result of the same diseases.

The launching of the ambitious target 'Health for All by the Year 2000' is tied up in the developing world in the attempt to break the vicious circle of disease, meagre resources, the frustrating struggle to make the slightest dent in morbidity and mortality and the failure of the health services to participate effectively in social development. The challenge to WHO is to use these technological breakthroughs to the best advantage in the overall developmental process. The developing countries and WHO are committed to primary health care. Diagnosis has to be made first and foremost in the family, in terms which are simple enough to be understood but at the same time sufficiently discriminatory to indicate a line of action. The *rational* use of antibiotics at the primary health care and first referral levels is encouraged. In order to make a continued review of clinical diagnosis at these health care levels, WHO has invested heavily in the development of simple, rapid laboratory diagnostic techniques that can be used in the peripheral laboratory in the developing world. Another approach is the reinforcement of immunoprophylaxis which has proved to be extremely efficacious in preventing many communicable diseases. The WHO Expanded Programme on Immunization has selected the following target diseases: tetanus, diphtheria, pertussis, tuberculosis, poliomyelitis and measles.

In order to take full advantage of the latest findings in biomedical sciences, WHO launched a new Programme for Vaccine Development in 1984. The Programme is currently dealing with five diseases for which vaccines do not exist or for which vaccines have not proved entirely satisfactory in every environment. These diseases are tuberculosis, dengue, hepatitis A, acute respiratory virus diseases and diseases caused by encapsulated bacteria.

There are two other programmes that the Organization is fostering. One is the further development of simplified techniques for rapid diagnosis for case-management and monitoring of primary health care. The second programme which should be launched during 1985 aims at the rational designing of drugs built on defining the molecular structure of microbes.

Influenza hemagglutinin structure and antigenicity

J. Skehel
National Institute for Medical Research, Mill Hill, London

An influenza virus membrane contains two sorts of virus specified glycoproteins the majority of which are hemagglutinins (about 500–1000 per virus), the others are neuraminidase molecules (about 100–500 per virus). The more abundant hemagglutinins are the glycoproteins which interact with infectivity-neutralizing antibodies and because of their consequent importance in antigenic variation, their structure and their antigenicity are the topics of this contribution. The hemagglutinins of viruses of the H_3 antigenic subtype, the Hong Kong influenza viruses will be considered primarily because detailed information on the three-dimensional structure of a hemagglutinin is at present only available for the hemagglutinin of the 1968 Hong Kong virus. This molecule is a 220,000 dalton trimer of identical submits each made up of two disulphide-linked glycopolypeptide chains – HA_1 and HA_2. HA_1 contains 328 aminoacids and 6 asparagine-linked carbohydrate side-chains, and HA_2, 221 amino acids and a single carbohydrate side-chain. The hemagglutinin is associated with the virus membrane through a region of uncharged amino acids near the C-terminus of each HA_2 glycopolypeptide and can be released from this association by detergent extraction or proteolytic digestion. Digestion with bromelain at a single site, HA_2 175, releases the soluble trimer, BHA, crystals of which have been used to solve the structure of the molecule. X-ray crystallographic analyses indicate that the amino terminus of HA, as well as the carboxy-terminus of HA_2 is near the membrane of the virus. The HA_1 chain extends from this position through a fibrous region into a peripheral β-structure rich region and then returns to terminate about 30A from the virus membrane. The most prominent features of the submit composed of HA_2 residues are two antiparallel α-helices, one 29A long which proceeds distally from the membrane end of the molecule to connect through an extended chain with the other helix, the major component of the central fibrous stem of the molecule, which stretches 76A back towards the membrane. Hemagglutinins have two functions in virus infection; they bind virus particles to sialic acid-containing receptors and following endocytosis, they appear to mediate fusion between virus and endosomal membranes which results in transfer of the genome-transcriptase complex into the cytoplasm and initiation of virus replication. Probably as a consequence of inhibiting these functions antibodies neutralize virus infectivity and impose selection pressures which lead to the emergence of antigenic variants. In the Hong Kong viruses, following the initial pandemic of 1968, pandemics occurred in 1972 and 1975 and more limited epidemics in 1977 and 1979. On each occasion the viruses responsible were antigenically distinct from previous isolates and consequently were able to infect individuals in what had become a non-immune population. Nucleotide sequence analyses indicate that the amino acid differences detected in the hemagglutinins of these viruses are located almost exclusively in the distal HA, region of the molecule and because of this and the correspondence of their locations with those of substitutions found in monoclonal antibody-selected variant hemagglutinins, this conclusion is firmly based. The relationship of these substitutions to defined sites of antibody binding and to the regions of the molecule with specific functions were discussed.