Editorial

The Impact of Chemotherapy on the Tubercle Bacillus and Its Significance

Chemotherapeutic agents used in the treatment of bacterial diseases produce drug-resistant organisms which create difficult problems in therapy. Extensive use of such agents may produce profound changes in the host and his bacterial flora. The result is enhancement of the number, virulence, and invasiveness of many of these organisms which under normal environmental circumstances present no special difficulty. Less generally understood is the mechanism of bacterial mutation as a consequence of chemotherapy and the resultant new varieties of organisms, some of which produce serious and often fatal disease.

The influence of antimicrobial drugs and other agents on bacterial mutation has been described by numerous investigators. For example, Graesse and Frost\(^4\) and Bellamy and Klimek\(^5\) observed significant changes in morphology, staining, and metabolic activity for Staphylococci made resistant to penicillin and streptomycin in vitro. Dienes\(^6\) found that penicillin causes the production of "L" forms of Streptobacillus moniliformis and the Bac teroides. Vourek\(^a\)\(^4\) showed that profound morphologic and cultural alterations, including loss of virulence, may sometimes result in stains of E. coli and P. aeruginosa obtained from the urine of patients receiving chloramphenicol. When a strain of E. coli was treated with specific antiserum and chloramphenicol, alterations in morphology, sugar fermentation, resistance to inimical agents, and antigenic structure could be induced. The effect of streptomycin and x-radiation on strains of E. coli and the role of genetic mechanisms in variation was also discussed by Tatum,\(^7\) Newcombe and Hawirko,\(^8\) and Lederberg.\(^9\)

Mutation is not confined to these organisms. It occurs in numerous other bacterial species, including the mycobacteria. Despite the concept of bacterial monomorphism, first supported by Koch and Cohnheim and later by others, investigators, soon after the discovery of the tubercle bacillus, began to observe changes in this organism. These changes concerned not only morphology, but also staining properties, metabolic activity, virulence, and other characteristics. Thus Yersin,\(^a\) as early as 1888, reported that human tubercle bacilli exhibited varying degrees of virulence, giving rise in some instances to a new type of disease without tubercles. Several years later Straus and Gamaleia\(^a\) observed the chromogenic nature of certain mycobacteria. They demonstrated that by changing the culture medium, it was possible to alter the morphology and virulence of these organisms. In 1918 Corper\(^1\) reported that human tubercle bacilli were not always virulent for guinea pigs. Later Griffith\(^4\) observed that human tubercle bacilli isolated from skin lesions resembled avian tubercle bacilli in their general characteristics. Still later, Sweany\(^a\)\(^4\) described numerous alterations in morphologic and growth characteristics of human tubercle bacilli which he felt were probably the result of spontaneous variations in these organisms in apparently normal environments. About the same time Petroff and his associates\(^a\) called attention to the phenomenon of dissociation in tubercle bacilli. During this process the organisms, under certain cultural conditions, may assume two colonial forms—a virulent smooth type and a less virulent or avirulent rough type.

That mycobacteria may be altered as profoundly in morphology, staining, metabolic activity, virulence, and other characteristics as other bacterial species under the influence of antimicrobial drugs and other agents has been demonstrated in numerous more recent studies. For example,
Yegian and Budd\textsuperscript{16,17} noted the heterogeneous character of streptomycin-dependent mutants obtained from strains of mycobacteria, and called attention to the possible role of bacterial inheritance in variation. Marshak\textsuperscript{18} reported the differences in response of the H37Rv and H37Ra strains of human tubercle bacilli to a number of metabolites and presented evidence of their differences by gene mutation. The effect of isoniazid, streptomycin, cycloserine, \textalpha;-ethyldithiocarbamoyl amide (TH 1314) on morphology, growth, metabolic activity, and loss of acid-fastness of the H37Rv strain of \textit{M. tuberculosis} and other mycobacteria was reported by Schaefer,\textsuperscript{19} Koch-Weser and associates,\textsuperscript{20} Barclay and Russe,\textsuperscript{21} and Dunbar.\textsuperscript{22} By serial passage of the H37Rv strain in media containing increasing concentrations of streptomycin and isoniazid, the present writer\textsuperscript{23,24} was able to obtain highly resistant, atypical, chromogenic variants which differed significantly from the parent strain in morphology, staining, metabolic activity, virulence, and allergenicity. Similar results have been reported by Xalabarder,\textsuperscript{25} Di Marco and his associates,\textsuperscript{26} and Lucchesi and his co-workers.\textsuperscript{27}

Work in recent years on bacterial inheritance and genetic aspects of bacterial resistance to antimicrobial drugs demonstrates that mutation can be accomplished with various mycobacteria and a wide variety of atypical strains can be produced. Because many of these organisms are highly resistant and produce serious disease, they add further difficulties to the disquieting problem of drug-resistant bacterial diseases.

Since the advent of the antituberculosis drugs, changes in the tubercle bacillus have been observed with increasing frequency. On the basis of recent research, suggestive evidence indicates that some strains of the so-called unclassified ("atypical") mycobacteria, which have been the subject of much controversy, could probably have been derived as a consequence of drug therapy. Numerous investigators have long suggested that chemotherapy favors production of mutant strains. These have the potential of causing not only diseases related to those caused by the parent organisms from which they have been derived, but also new and perhaps even more serious diseases.

There has been much controversy regarding the matter of managing the recent tuberculin converter. Some do not feel that all such individuals require antimicrobial therapy. They point out that many persons, especially children, can cope with minimal infection without therapy, that drugs given too early serve to suppress the additional immune response to the invading \textit{Mycobacterium}, and that therapy should be withheld until a definite lesion can be found. It is also argued that the lack of decline in the incidence of tuberculosis has demonstrated the urgency for reservation in placing too much reliance on chemotherapy even for advanced disease as a control procedure. These considerations, together with the recognition that antituberculosis drugs are becoming more limited in usefulness as a consequence of bacillary resistance or toxicity, emphasize the need for greater effort on preventive or early treatment possibilities in tuberculosis control. Others have stressed the need for specific indications for the use of antimicrobial therapy in the recently infected person. Such criteria are well known and need not be reiterated.

The increase in drug-resistant strains of tubercle bacilli and the potentiality of the origin of other serious types of mutant organisms have made the problem of antimicrobial therapy complex. In the light of recent contributions in the field of bacterial genetics and the knowledge regarding the influence of antimicrobial drugs on bacterial mutation, is it not time perhaps to take a new, a longer, and a more critical look at what antituberculosis chemotherapy is doing to the tubercle bacillus? There is urgent need for more knowledge regarding the mechanisms which operate to produce mutant strains of tubercle bacilli. Without such information it will not be possible to
cope adequately with present problems nor with problems which appear certain to develop.

Of importance is the need for better methods of increasing host resistance against not only the tubercle bacillus, but also other pathogens such as some of the unclassified mycobacteria against which currently available antimicrobial drugs are only of limited value.

No less important is the need for greater utilization of some of the basic research methods for delving more deeply into these difficult problems. Electron microscopy has been exceedingly useful in studying morphologic changes in organisms which have been subjected to the influence of various antimicrobial drugs, x-rays, and other agents. Infra red spectroscopy, electrophoretic techniques, and Warburg intermediary metabolism procedures have been proving fruitful in studies relating to the chemical similarities and differences in mycobacteria. Biochemical and x-ray techniques are contributing to our knowledge of the genetics of living systems, particularly in reference to the molecular structure of the genes and the role of ribonucleic (RNA) and deoxyribonucleic (DNA) acids. The radio-active isotopes, such as carbon-14, nitrogen-15, and phosphorous-32, have also been helpful in genetic studies dealing with the biochemical changes which occur during mutation. Agar diffusion precipitation and complement fixation methods are being applied to studies on the antigenic relationship between human tubercle bacilli and other acid-fast organisms. The use of bacteriophage and cytochemical techniques are contributing to better methods of classifying mycobacteria, whereas fluorescent antibody and tissue culture procedures are aiding to broaden our understanding of immunologic and host-parasite relationships.

These, then, are some of the more useful procedures modern research has designed for providing the type information which is needed and which, it is hoped, will prove even more fruitful as their versatility is extended. Never in the field of infectious disease has there been a greater need than now for a pooling of minds. Only through joint effort of every discipline at our command can we hope to understand and solve some of the urgent problems created by the impact of chemotherapy on the tubercle bacillus.

References
Ventricular Premature Beats in Diagnosis of Cardiac Infarction

Experimental and clinical studies on the significance of ventricular premature beats in the diagnosis of myocardial infarction are reported. The unipolar patterns of VPB that are diagnostic of myocardial infarction are of the QR type (Qr, Q, and Qra complexes). The post mortem studies revealed that the interventricular septum was always involved. The conclusion is reached that any ectopic beat with aberrant conduction, irrespective of its site of origin (right or left ventricle, ventricular or supraventricular), is diagnostic of myocardial infarction when the ectopic beat presents a QR type of morphology in leads reflecting the potential variations of the ventricles. A comparison of the diagnostic value of ectopic beats and sinus beats with normal conduction can be summarized according to the three main possibilities, thus:

1. The infarction may be diagnosed from sinus beats as well as from ectopic beats:

2. The infarction may be diagnosed from sinus beats and from ectopic beats, but the latter are of greater value in defining its localization and extent;

3. The infarction may be diagnosed only by the patterns of the ectopic beats and not by those of the sinus beats.


High Body Sodium

Measurements of total body water and total exchangeable sodium were made by Carroll and Farber in patients with heart disease rendered free of edema following congestive heart failure. The total exchangeable sodium in most of the patients was higher than would have been predicted on the basis of their body weight and total body water. Serial measurements showed that some patients gradually lose their excess sodium over a period of months without a loss of body water; others maintain an elevated ratio of body sodium to body weight and body sodium to body water for periods of at least several months.