

RECENT ADVANCES IN PHARMACOLOGY AND MATERIA MEDICA

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Any brief report on the present status of pharmacology involves the careful selection of those topics which seem to be of major importance, and even these must be treated somewhat cursorily. I have, therefore, chosen to divide this report into two sections; the first dealing with the present status of, and the future outlook for, the chemotherapy of infectious diseases, and in the second section to discuss miscellaneous advances in divergent areas.

In dealing with the present status of chemotherapy, the discussion can be conveniently divided into two phases: (1) the sulfonamides, and (2) the ever-increasing group of substances derived from living organisms and ambiguously called "antibiotics." Of the ten or twelve clinically useful sulfonamides which have been developed over the last ten years, it seems safe to say that at the present time only one of these—sulfadiazine—need be given serious consideration. It is generally recognized that when a sulfonamide is indicated sulfadiazine should be the drug of choice. The only serious exception to this general statement would be in the case of those sulfonamides, represented by sulfasuxidine, which are not absorbed, and which have a certain limited usefulness through their local action in the gastro-intestinal tract.

There have been no new developments in the case of sulfadiazine, but certain factors involved in its clinical application have become more clearly defined. Among these, the following are worthy of note:

- (1) Clinical effectiveness following systemic administration is equal or superior to that following local application.
- (2) The efficiency of sulfadiazine prophylaxis has been definitely established, particularly in those diseases caused by the hemolytic streptococcus. Prophylactic use must, however, be balanced against:
- (3) The increasing incidence of patient sensitivity to the drug and the development of strains of sulfonamide-resistant organisms;
- (4) And finally, it seems possible to predict, on the basis of physico-chemical studies, that other substitutions of the basic sulfonamide nucleus will not produce drugs which will have any greater therapeutic effectiveness than does sulfadiazine.

Available data in the field of antibiotic research are undoubtedly incomplete, but it seems certain that some 50 to 75 antibiotic substances have been partially or completely isolated and are in various stages of investigation; however, only two—penicillin and streptomycin—can be said, at present, to have widespread clinical importance.

Penicillin is now available in adequate quantities, although the supply is not unlimited and precludes, for the time being at least, any widespread application of unproven methods of administration. The concensus among clinical investigators is that for maximum effectiveness penicillin must be administered parenterally. There is, as yet, too little clear-cut experimental or clinical evidence to enable one to predict the possibilities for the oral administration of penicillin. Herein lies a major difficulty in penicillin therapy. In most instances, the physician will feel that the patient must be hospitalized before he is given penicillin. This is to insure the all-important factor of maintaining adequate blood levels by means of controlled day-and-night administration. The choice between sulfadiazine and penicillin in the management of disease produced by susceptible organisms is, of course, determined primarily by the susceptibility of the organism in question to

each drug. Where either drug will satisfactorily combat a given organism the choice frequently hinges on the difficulties encountered in administering penicillin.

The special cases of syphilis and gonorrhoea require separate mention. It must be emphasized that the use of penicillin the therapy of syphilis is as yet in the experimental stage, and will retain that status until sufficient time (2-5 years) has elapsed to permit the proper evaluation of results. It is not possible to state definitely whether penicillin alone or in combination with heavy metals will significantly advance the therapy of this disease. In the case of gonorrhoea two factors must be recognized. The first of these is the extraordinary susceptibility of the gonococcus to many forms of therapy, and its equally extraordinary ability to develop resistance to any given therapeutic agent. Penicillin-resistant strains of gonococci have been reported, and it is as yet too early to predict the final status of this agent in the therapy of gonorrhoea.

The second factor which must be recognized is the possibility of the simultaneous occurrence of gonorrhoeal and syphilitic infection with the latter in its innocuous primary stage being masked by the earlier clinical onset of gonorrhoea. Under such circumstances, superficial healing of the unrecognized primary chancre may occur with the dosage of penicillin used to treat gonorrhoea. This quantity of penicillin is grossly inadequate to ensure the destruction of all the spirochaetes and the patient is thus exposed to the possibility of developing treatment-resistant syphilis and to the hazards accompanying the inadequate treatment of this disease.

The clinical usefulness of streptomycin is still in the process of evaluation. The quantities available at present are too small to permit extensive controlled investigation. In general, streptomycin is effective against many gram-negative bacilli, whereas penicillin is ineffective, and the sulfonamides have only limited usefulness in infections caused by these organisms. The effect of streptomycin in controlling three diseases—brucellosis, tularemia, and typhoid fever—hitherto unaffected by chemotherapeutic agents has received considerable attention recently. At the present time the outlook for its usefulness in the treatment of tularemia is good; in combatting brucellosis, less than fair, and for typhoid fever, poor.

Even less can be said about the effectiveness of streptomycin, or any other chemo-therapeutic agent for that matter, in the treatment of tuberculosis. At the present time no optimism is justifiable.

No report of the present status in the field of chemotherapy would be complete without mention of the enormous possibilities which have been opened to investigators by the elucidation of the mechanisms of action of the agents just discussed. All of them are effective by virtue of the fact that they interfere with some essential metabolic activity of the organism. The application of this basic principle renders possibilities for the control of infectious agents virtually unlimited.

Of the host of advances which have been, or are being, made in other areas, time permits the mention of only three:

Thiouracil—This synthetic pyrimidine derivative possesses the unique property of inhibiting, in a manner not entirely clear, the production of the thyroid hormone. This activity had led to the use of thiouracil in the control of hyperthyroidism. However, its place in the general management of hyperthyroid patient has not yet been satisfactorily evaluated. It seems clear at the present time that thiouracil may not be depended upon to control completely such a patient, but that it must be used in conjunction with other procedures, including surgery. Its use is attended by a fairly high incidence of toxic reactions, the most alarming of which is agranulocytosis. This toxicity could conceivably lead to its abandonment as a therapeutic agent, but only time and wider clinical experience will determine this possibility.

Benadryl—It is a well recognized fact that histamine plays a very large part in the production of those lesions which characterize allergic reactions of all kinds. A long-held theory has supposed that if some substance could be found which

would antagonize the action of histamine it should be possible to relieve or prevent the manifestations of allergic disturbances. Benadryl seems to be such a compound. It is by no means a panacea for all types of allergic disturbances, but it seems to be outstandingly effective in providing symptomatic relief in angio-neurotic edema, allergic rhinitis, and allergic bronchospasm. The drug does not affect antigen-antibody relationships or formation, and in this respect represents a purely symptomatic approach to a very complex problem.

Digitalis—It would be misleading to confine a review of recent advances to new drugs exclusively. Both clinical and experimental pharmacologists devote a large share of their time and effort to the improvement of therapeutic agents of known values. The gain which has been made in the direction of a more complete understanding of the chemical characteristics, the mechanism of action, and the rational clinical application of the digitalis bodies represents an outstanding example of this type of continuing progress. Until very recently the infinite complexity of digitalis in all its relationships has made the crude leaf the preparation of choice, and the oral route the only reliable method of administration. There is now, however, reason to believe that the limitations and uncertainties imposed by this combination may be overcome. More refined chemical techniques and more accurate and detailed pharmacological observations have resulted in the isolation, identification, and use of the active glycosides of digitalis in pure, unaltered form. Two of these compounds, digitoxin and digilanid C, are especially worthy of mention. They are receiving widespread clinical trial, and the reports on their effectiveness are very encouraging. This trend, supported by continually accumulating data, permits the prediction that the pure glycosides may eventually supplant the crude leaf, and it is very probable that their use will materially enhance our ability to control cardiac failure and, at the same time, increase our knowledge of the abnormal physiology of the failing heart.