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 consensus 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 gonorrhea 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 gonorrhea 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 gonorrhea.

The second factor which must be recognized is the possibility of the simultaneous
occurrence of gonorrheal and syphilitic infection with the latter in its innocuous
primary stage being masked by the earlier clinical onset of gonorrhea. Under such
circumstances, superficial healing of the unrecognized primary chancre may occur
with the dosage of penicillin used to treat gonorrhea. 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 combating 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 investi-
gators 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 angioneurotic 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.