Bacteriological Diagnosis of Pneumonia in Relation to Chemotherapy*

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THE introduction of various sulfonamide compounds has contributed greatly to the therapy of pneumonia. Important as this contribution is, it leaves unanswered the fundamental question—that of prevention. The development of therapeutic measures serves to emphasize the fact that the prophylaxis of pneumonia still remains an unsolved problem.

Cole has pointed out that lobar pneumonia is not a single disease but rather a group of diseases, each with a specific etiology. This point of view is as valid from the public health aspect as from that of therapy. It is well to remember that our ideas of the epidemiology and pathogenesis of pneumonia are far from complete and will remain so until further careful study and evaluation have been made of the various factors involved. The type incidence of pneumonia is as baffling a problem as ever; for example, why do infections due to Type I comprise approximately 30 per cent of all cases of pneumococcal pneumonia, or why are 80 per cent of all cases due to but 7 of the many specific types of pneumococci?[1] Knowledge of the factors which account for the selective incidence of these particular types will undoubtedly throw great light on the prophylaxis of this group of diseases. Until fuller knowledge of these factors has been gained it is necessary to study the problem from the standpoint of the type-specificity of the bacterial incitant.

The fact that pneumococci are usually secondary invaders in the wake of a non-bacterial upper respiratory infection such as the common cold, in no way detracts from the significance of the observation that Type I pneumococcus is the most important epidemic strain. It is equally significant that the epidemic strains are encountered infrequently in the normal throat except in individuals who have been in intimate contact with patients suffering from pneumonia due to one of these types. Furthermore, although the control of pneumonia may ultimately be achieved through prevention of the antecedent upper respiratory infection, this is as yet not possible. Meanwhile all precautions should be taken to prevent the spread of the epidemic strains of pneumococci. How this may be accomplished is far from clear, but intensive epidemiological studies offer an approach to the problem.

In addition to these general considerations, the bacteriological diagnosis of

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pneumonia has immediate practical importance from the point of view of therapy.

Upon the introduction of any new therapeutic agent there is a tendency to discard previous procedures or else minimize their importance. With the advent of sulfapyridine, the first effective antipneumococcal drug, it was considered by many that the use of specific antisera was outmoded, and that the much less exacting procedure of administering a sulfonamide drug by mouth to all cases of pneumonia, irrespective of the specific nature of the etiological agent, solved the problem of therapy. This point of view was based on inadequate clinical and experimental evidence, so that now opinion is gradually shifting back to a middle ground where the use of serum and the sulfonamide drugs may be more properly evaluated.

It is the opinion of most investigators that the therapeutic action of the sulfonamide drugs can be explained by their bacteriostatic properties. Fundamental as is this mechanism, it should be remembered that the disposal of the still living and virulent pneumococci is a function which can be performed only if the various defense mechanisms of the host are active. This point may be illustrated by reference to the chemotherapy of experimental pneumococcal infections with sulfapyridine.[2] If mice are infected with Type I pneumococcus and treated with sulfapyridine for 3 days, practically all of the animals survive. If treatment is carried out for 2 days, only 60 per cent of the animals survive, and if for only 1 day practically all of the mice die. It has been shown that approximately 3 days are necessary for the development of active immunity to pneumococcus Type I. Hence, in infected mice which are treated with the drug for only 1 or 2 days it is probable that the deaths which occur are attributable to the fact that the drug has been discontinued before the animals have had sufficient time to develop specific immunity.

If for any reason the body is not able to develop antibodies rapidly enough to sensitize the invading bacteria, then even prolonged administration of the drug may not be effective in inducing recovery. This is illustrated in the case of experimental infections with pneumococcus Type III. Very few mice infected with this organism survive even though treated with sulfapyridine for a prolonged period, and it has been shown that it is difficult to induce active immunity in mice to pneumococcus Type III, whereas this is readily accomplished in the case of Type I.[2]

It appears likely that the differences in the antigenicity of pneumococcus Type I and Type III may explain the difference in the response to sulfapyridine in experimental infections with these two types. The differences in the antigenic behavior of pneumococcus Type I and Type III in mice are observed in human beings as well.[3] Due to this fact, as well as to the serious prognosis in Type III pneumonia, it is our practice to treat these patients with a combination of an appropriate sulfonamide compound and Type III antipneumococcus serum. A survey of the literature indicates that the case mortality rate in patients with Type III pneumonia, treated with sulfapyridine alone, is in the neghborhood of 17 per cent, whereas in a small series of patients which we have treated with a combination of serum and drug, the mortality rate has been only 4.3 per cent. From clinical experience as well as from experimental considerations we feel that the combined therapy with drug and serum offers much more promise than either agent alone in the treatment of Type III pneumonia.

The necessity for making a bacteriological diagnosis applies also to infections due to pneumococci other than

Type III, since here also the indications for the use of specific antisera are well defined. In addition to the sulfonamide drug, specific serum therapy should be used in all patients who are critically ill, in whom clinical examination indicates a prognosis of more than usual severity due to advanced age, the presence of complications, or bacteremia.

When a patient with pneumonia is first seen by a physician, it is frequently possible to state that the prognosis is fair or poor, as the case may be. Certain laboratory data will supplement the clinical impression, and one of the most important examinations is to determine whether or not bacteremia is present. In a large series of cases collected from various sources the mortality rate in bacteremic patients treated with sulfapyridine alone was 23 per cent, whereas in the non-bacteremic group the death rate was only 4.5 per cent. If one waits for information as to whether the blood culture is positive or negative, enough time may elapse for the intoxication to become so profound that no therapeutic measures will avail. For this reason a rapid bacteriological diagnosis by sputum examination as early as possible is of great importance, so that sulfonamide therapy may be supplemented by specific serum therapy when necessary.

Another group of cases in which the bacteriological diagnosis is important is that in which no response to chemotherapy is obtained even though the patient's condition is apparently favorable at the time treatment is begun, and in whom, despite adequate blood sulfonamide levels, the acute process remains active or becomes progressive. In the absence of complicating lesions, for example, empyema or some other purulent focus, lack of response may be due to sulfonamide-fastness of the invading pneumococcus. Susceptibility to the bacteriostatic action of the sulfonamide drugs varies somewhat in different strains of pneumococci, even though contact with a particular drug has never occurred. Furthermore, fastness may develop during treatment, so that the organisms become resistant to the bacteriostatic action of the drug. It is fortunate, however, as we have shown,[4] that upon the acquisition of fastness the organisms do not lose their type-specific characteristics and are still fully susceptible to the therapeutic action of type-specific antipneumococcus serum.

It is of great interest that once sulfapyridine-fastness has developed in a strain of pneumococcus this characteristic is retained even though the organism is passed serially in many normal animals or in artificial culture media. Because of the persistence of acquired fastness, it is possible that the occurrence of localized epidemics due to drug resistant strains may appear. It is also well to remember that pneumococci which are fast to sulfapyridine are also fast to other sulfonamide derivatives, so that in order to treat patients suffering from infections due to fast strains, the sulfonamide drugs are of little avail, and use must be made of type-specific antiserum.

In vitro tests for the rapid and accurate determination of sulfonamide-fastness have not been practical up to the present, since the usual culture media contain varying amounts of substances which inhibit or annul the bacteriostatic action of the sulfonamide drugs. Inhibitors are present both in peptone [5] and in the meat infusions [6] used in the preparation of culture media. The importance of inhibitors of the sulfonamide drugs is only gradually being recognized, but it is well to remember that they occur not only in culture media, but in the bacteria themselves and in certain tissues and fluids of the animal body.

The presence of inhibitors in bacteriological culture media masks the *in*

TABLE 1

Bacteriostatic Effect of Sulfapyridine on Pneumococcus Type I in Peptone Broth and in Liver Infusion

	*Growth of Pneumococcus Type I * Concentration of Sulfapyridine*							
Medium	1:5,000	1:10,000	1:20,000	1:50,000	1:200,000	1:500,000	1:1,000,000	0
Peptone broth	—	++	+++	++++	++++	++++	++++	++++
Liver infusion	—	—	—	—	—	++++	++++	++++

* Degree of growth estimated by gross turbidity after incubation at 37° C. for 24 hours
++++ = maximum growth
— = no visible growth
Inoculum: 4,000 cells in a volume of 2.0 cc. of the respective media

vitro effect of the drugs and is the greatest source of error in determining accurately the susceptibility of bacteria to these compounds. It has been possible to devise a simple *in vitro* test to determine the susceptibility of various bacteria to the sulfonamide drugs. This test depends for its accuracy upon the use of a culture medium which is free of sulfonamide inhibitors and which will support the luxuriant growth of such fastidious microörganisms as the pneumococcus or hemolytic streptococcus, without the addition of peptone.[6] An infusion of fresh calf liver prepared on the acid side, and sterilized by filtration, has proved satisfactory, since pneumococci and many other microorganisms grow profusely in this infusion to which no peptone has been added. Moreover, if the infusion is prepared from fresh, unautolysed liver it is free of sulfonamide inhibitor.

The difference in the bacteriostatic effect of sulfapyridine upon the growth of a strain of pneumococcus Type I in peptone-containing broth and in the specially prepared liver infusion is shown in Table 1. In plain broth sulfapyridine in a concentration of 1:10,000 is required to cause bacteriostasis, whereas in the liver infusion bacteriostasis occurs in dilutions of the drug as high as 1 part in 200,000.

The bacteriostatic effect of sulfapyridine on the parent and sulfapyridine-fast variants of the same strain of pneumococcus Type I is shown in Table 2. The tests were carried out in the liver infusion. In the case of the fast strain a 1:10,000 concentration of sulfapyridine is necessary to inhibit growth, whereas a dilution of the drug as great as 1:200,000 is partially bacteriostatic for the parent strain.

It should be emphasized that unless an inhibitor-free medium is used, tests for the susceptibility of bacteria of any species to the sulfonamide drugs are unreliable and may be wholly misleading. It is important, therefore, that a standard technic be employed in labora-

TABLE 2

Bacteriostatic Effect of Sulfapyridine on Parent and Drug-fast Strains of Pneumococcus Type I in Liver Infusion

Strain of Pneumococcus Type I	*Growth of Pneumococci * Concentration of Sulfapyridine*							
	1:5,000	1:10,000	1:20,000	1:50,000	1:200,000	1:500,000	1:1,000,000	0
Parent	—	—	—	—	+	++++	++++	++++
Sulfapyridine-fast	—	+++	++++	++++	++++	++++	++++	++++

* Degree of growth estimated by gross turbidity after incubation at 37° C. for 24 hours
Inoculum: 4,000 cells of the respective strains in a volume of 2.0 cc. of liver infusion

tories generally, in order to determine the occurrence of sulfonamide resistant strains and to evaluate their importance as a cause of failure of chemotherapy in pneumonia. Sulfonamide resistant strains have been encountered in a small proportion of pneumonia cases, but their general incidence is unknown. From the point of view of therapy it is well to emphasize that strains of pneumococcus which are sulfonamide-fast are fully susceptible to the action of type-specific antiserum.

In the course of this discussion mention has not been made of pneumonia due to agents other than pneumococci, since under ordinary circumstances other bacteria are responsible for only a relatively small proportion of the total number of cases. From the point of view of epidemiology and prognosis the desirability of knowing whether hemolytic streptococcus, or staphylococcus, or *Hemophilus influenzae* is the infecting agent, should not be overlooked. From the therapeutic point of view this is also of interest, since already there is a limited amount of evidence which indicates that one chemotherapeutic agent may be more useful than another in the treatment of pneumonia due to one or other of these infectious agents.

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