THE ROLE OF THE HOST IN THE CHEMOTHERAPY OF TUBERCULOSIS*

BY

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In the chemotherapy of tuberculosis, as of many acute infections, it is usual to consider principally the drug-parasite relationship. This concept has been very valuable, but it is becoming increasingly recognized that it takes insufficient account of the host. In a chronic infection like tuberculosis, host resistance may even influence the value of agents with direct and specific antibacterial action, while after discontinuation of chemotherapy many important tasks remain for the body's defences to tackle, aided, of course, by other forms of treatment. Furthermore, certain antituberculous drugs produce their beneficial effect through the host's defence mechanisms and not by directly damaging the bacillus. I propose, therefore, to discuss some aspects of the complicated relationship between the host, the tubercle bacillus, and the drug. I shall not attempt a general review of the factors believed to influence native and acquired resistance to tuberculosis, or of the varied mechanisms whereby the body's defences may destroy, or prevent, or in varying degrees even permit, bacillary multiplication; this has been done excellently by others.

First, it is necessary to mention briefly some obvious host factors that may limit the efficacy of the drugs within the diseased tissues.

Physiological and Biochemical Factors

The maintenance of an effective concentration of a drug in a lesion will be determined by the levels attained in the blood; the structure and vascularity of lesions, and other factors affecting the ease of dissemination to the site of infection (Florey, 1952); the ability to penetrate cells, especially monocytes (macrophages)—isoniazid penetrating well, streptomycin poorly, and *p*-aminosalicylate (P.A.S.) hardly at all (Mackaness, 1952; Mackaness and Smith, 1952); the destruction or alteration within the body—for example, by binding with proteins; the susceptibility to antagonism by normal or pathological tissue constituents (Dubos, 1953a); the effect of the pH in the tissue environment; and, finally, the rate of excretion.

Toxicity

Toxicity also may restrict the efficacy of the agent by setting an upper limit to dosage. There are sometimes marked species differences. Thus the dog is much more susceptible to isoniazid toxicity than man, and the monkey less (Schmidt *et al.*, 1953). As another striking example, a few years ago certain benzphenoxazines were reported to be more active than streptomycin against

tuberculosis in mice, but, whereas toxicity for this species was found to be gratifyingly low, larger animals developed a haemolytic anaemia and humans could not tolerate even 1/100 of the mouse dose, body weight for body weight. Apart from such species differences, tests on animals may fail to show minor symptoms (for example, the gastro-intestinal disturbances associated with P.A.S.), or rare but more serious toxic manifestations (for example, drug allergic sensitivity to streptomycin and/or P.A.S.). It may be concluded that, whereas experimental animals may be a good guide to the clinical value of antibacterial agents, this is sometimes not the case for toxicity, and the first use in man himself must always be approached with the greatest caution.

THE INTERPLAY OF HOST RESISTANCE AND SPECIFIC ANTIBACTERIAL CHEMOTHERAPY

The natural history of an infectious disease largely reflects the native and acquired immunological resistance of the host. If the disease is chronic the prolonged course will give greater time for the defence forces to be deployed. If, in addition, a drug having a direct and specific effect upon the invading bacteria is administered, there will be some interplay between the host resistance and the antibacterial action of this chemotherapy. I shall suggest that there are two important phases in this interplay—an initial phase when the host may influence the destruction of the bacilli by the drug, followed by a phase, after discontinuation of the chemotherapy, when the ability of the body's defences to clear up residual infection, and of its repair processes to heal the lesions, may determine the outcome. Ultimately there may remain irremediable damage: destroyed lung, established bronchiectasis, cardiac complications, etc.

I shall consider in turn the phase of chemotherapy, and the subsequent phase after discontinuation. For simplicity a single course, without retreatment, is referred to. By combined therapy I mean treatment with more than one drug simultaneously.

(i) During the Chemotherapy

Early Improvement

Experiment and experience of human tuberculosis show that acute recent disease is, to begin with, particularly responsive to chemotherapy. Such acute forms of the disease indicate a relative failure of the host, due either to a low resistance or to an overwhelming dose of bacilli. From this it may be inferred that in some instances a low host resistance may actually favour chemotherapy, though this does not necessarily imply a greater overall benefit to the host.

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Let me give some examples. In the highly susceptible guinea-pig, chemotherapy is more effective in acute tuberculosis than in the chronic disease (Steenken, Wolinsky, *et al.*, 1952). In more resistant man, too, acute recent exudative and acute miliary tuberculosis respond more quickly than do chronic forms (Medical Research Council, 1952b, 1953a; Bernard *et al.*, 1953; Zeichner and Childress, 1953). Patients under 40 tend to respond better than those older (Tucker, 1953), possibly because many of the latter have long-standing lesions. In the trial of streptomycin (without other drugs) in acute, progressive, recent pulmonary tuberculosis in young adults (Medical Research Council, 1948), the less ill patients showed greater radiographic improvement on streptomycin combined with bed rest than did the more acutely ill, presumably because of a higher host resistance in the former. Yet a comparison of the early progress of the streptomycin group with that of a control group treated by bed rest alone, so as to isolate the part played by the chemotherapy itself, showed that there was a better response to chemotherapy in the more acutely ill than in the less ill—that is, the contrast between the progress of the streptomycin and the control groups was greater for the more acutely ill than for the less ill patients. Similar results in acute and less acute cases were obtained in a U.S. Public Health Service trial (Long and Ferebee, 1950). It is also common clinical experience that in the chemotherapy of patients with chronic disease and recent spread, the recent spread shows the greater response. In a trial proceeding under Professor A. W. Williams and Dr. P. W. Hutton at Mulago Hospital, Uganda, in association with the Tuberculosis Research Unit, preliminary study of African patients with radiographically hyperacute pulmonary tuberculosis suggests that on similar regimes (streptomycin plus isoniazid, or P.A.S. plus isoniazid) their response over a three-months period was at least as great as the response of acute disease in Europeans.

If all this appears obvious now, it shows how our approach has changed. Ten or more years ago the selection of cases of acute pulmonary or miliary tuberculosis for clinical trial of a promising drug would have brought the protest that this was not giving the drug "a fair chance."

In the view of some, the greater responsiveness to chemotherapy of acute than of chronic, and even of hyperacute than of acute, lesions is related not so much to reduced host resistance as to anatomical differences—for example, in vascularity affecting arrival of the drug, and in elasticity and fibrosis affecting ease of healing (Carvalho, 1954). High fever itself has been proposed as promoting responsiveness to antibacterial agents, by enhancing their bactericidal action (Marks, 1951; Knox *et al.*, 1952). These considerations may well also be of importance, and in laying stress on host resistance I recognize that I am attempting to isolate a single factor out of many. Yet the very difficulty of clinical elucidation justifies a closer examination of a thesis that receives some support from recent laboratory studies.

Host Resistance and Drug Action

I should like here to discuss the experimental basis for believing that host resistance may influence response to drugs in tuberculosis.

There are three main issues: (1) Are the drug regimes currently used mainly bacteriostatic or bactericidal? (2) How far is their effect due to ability to penetrate into lesions and into macrophages within lesions? (3) What is the relative importance of the intracellular and extracellular battlefields during chemotherapy? It is still often assumed that the action of streptomycin, isoniazid, and P.A.S. *in vivo* is bacteriostatic rather than bactericidal (see d'Esopo, 1954). Moreover, certain types or parts of lesions are thought by some to be relatively inaccessible—for example, cavity walls; and drugs clearly vary much in their ability to penetrate into certain cells, such as macrophages (Barski, 1948; Magoffin and Spink, 1951; Mackaness and Smith, 1952, 1953; Suter, 1952). Thus the idea has grown that while chemotherapy inhibits the multiplication of tubercle bacilli they may survive and continue to multi-

ply in certain protected sites. But a different view may well be taken. There is evidence that in full dosage isoniazid, and probably streptomycin, achieve bactericidal concentrations in many, if not all, types of lesion, particularly when given in combination (Steenken, d'Esopo, and Wolinsky, 1947; Smith and Waksman, 1947; Garrod, 1948, 1950; Barclay *et al.*, 1953; Canetti and Grumbach, 1953; Weiser *et al.*, 1953; Singh and Mitchison, 1954).

As regards penetration into cells, isoniazid, alone or with streptomycin, appears able to reach bactericidal concentrations even in macrophages (Mackaness and Smith, 1952, 1953). There is evidence, too, that with efficient antibacterial chemotherapy intracellular multiplication *in vivo* is less important in allergic animals and man than might be expected. (a) Since isoniazid enters macrophages well, streptomycin poorly, and P.A.S. hardly at all, the combinations P.A.S. plus isoniazid, and P.A.S. plus streptomycin, would be less effective than streptomycin plus isoniazid in preventing drug resistance, if intracellular multiplication were important: in actual fact, the efficacy of the three combinations in human pulmonary tuberculosis is of the same order (Medical Research Council, 1950, 1953a, 1953b, 1953c). (b) In pre-allergic guinea-pigs, lesions continue to enlarge and bacilli to proliferate intracellularly in spite of streptomycin treatment (Jensen, 1949; Steenken and Pratt, 1949), whereas in allergic (but susceptible) animals where the bacilli are more extracellular—for example, in guinea-pigs or in rabbits infected with bovine-type bacilli—the disease can be suppressed for long periods by continued treatment with streptomycin alone. (c) When macrophages die the intracellular bacilli will be liberated and therefore accessible to extracellular drug action, unless or until rephagocytosed. So the concept has developed that during efficient chemotherapy, such as with the usual combinations in full dosage (Medical Research Council, 1953a, 1953b), multiplication of bacilli is largely suppressed, and bactericidal action is the dominant event (Mitchison, 1954).

Let us consider the implications of this concept. Many workers have shown that for a rapid bactericidal effect by streptomycin or isoniazid *in vitro* a culture medium favourable to cell division is required, since the proportion killed in a medium that does not readily support growth is small or nil (Middlebrook and Yegian, 1946; Garrod, 1948; Szybalski and Bryson, 1953; Mackaness and Smith, 1953; Schaefer, 1954). If these findings hold good *in vivo*, then tubercle bacilli dividing slowly or not at all—for example, in quiescent or "closed" necrotic foci—will not be killed rapidly even by contact with bactericidal concentrations of drugs, while those accessible bacilli that have been multiplying rapidly will be particularly susceptible. Rapid growth will be favoured by weak or ineffective host defences; and, similarly, so will rapid killing of the bacilli by drugs.

It could thus be argued that it would be advantageous for a tuberculous patient to have a low resistance and a rapid division of the bacteria accessible to the drugs. Such might indeed be the case if specific drugs were so powerfully bactericidal as to overshadow the normal host defence mechanisms, resembling the successful chemotherapy of certain acute pyogenic infections that have not yet produced much pus or necrosis; for here the host's defences, at least its phagocytic activity, may play a minor part in overcoming the infection (Kaplan *et al.*, 1952; Gowans, 1953a; Bowden, 1953). This approximation to the test-tube may not yet be true of tuberculosis, even during prolonged combined therapy. The position here may be more comparable to acute infections treated with small doses of penicillin, where it can be shown that the host assists in disposal of the bacteria (Jawetz, 1946; Eagle *et al.*, 1950; Gowans, 1953b); or, better, to acute infections in the presence of pus and necrotic tissue (Florey, 1952). But in tuberculosis both the growth of the bacilli and the mobilization of the defence forces are much slower than in acute pyogenic infections.

Although it may be unwise to draw a close analogy between a tuberculous host on chemotherapy and an infected

culture containing a bactericidal agent, there remains, nevertheless, the possibility that organisms dividing slowly in the body or "resting"—for example, in necrotic foci—are an obstacle to effective tuberculocidal therapy. Short of drugs able to kill resting bacilli within tissue cells, a stimulus both to multiplication of such refractory organisms and to their liberation into the extracellular drug pool might assist. The stimulus might come from an agent that lowers host resistance—for example, cortisone, which has been reported to improve the therapeutic response when given with large doses of isoniazid to tuberculous mice (Ilavsky and Foley, 1953). Apart from the risk of stimulating such growth, any improved chemotherapeutic action in human tuberculosis would have to be weighed against the possible danger of reducing the help given by normal host defences in overcoming the infection. In this connexion, it would be interesting to know whether suitably selected patients with non-acute lesions would do better than a comparable group treated in bed if the host's defences were lowered by keeping the patients ambulant during a course of chemotherapy.

Meantime, further knowledge of the early reaction to chemotherapy of comparable forms of tuberculosis in persons with presumably low and high host resistance is desirable—for example, in the malnourished as compared with the well-nourished, diabetics with non-diabetics, as well as in the presumed "susceptible" ethnic groups in which the disease is expected to run a more rapid course than in others (Daniels *et al.*, 1948). With increasingly powerful chemotherapy does the apparently disadvantageous factor of low resistance matter less? Or may it be a positive advantage? And if this is the case initially, what is the position after discontinuation of chemotherapy? Does a lower native resistance, often combined with a bad environment, assert itself by a tendency to later reactivation—a vital therapeutic problem in underdeveloped communities? And, granted that the patient already possesses some degree of allergy, what effect might tuberculin desensitization, which it is claimed can be produced in man by large oral doses of B.C.G. (see Fourestier and Blacque-Belair, 1954), have upon his response to chemotherapy? Answers to some of these questions might be aided by experimental work on the chemotherapeutic response in animal families inbred so as to be either highly susceptible or highly resistant to tuberculosis (Lurie, 1950; Lurie *et al.*, 1953b), and in susceptible animals whose resistance has been increased by B.C.G. immunization (Jensen, 1949).

Drug Resistance

Having discussed the effect of the host on the antibacterial activity of drugs, I shall now turn to an aspect of the initial phases of chemotherapy which concerns more particularly the parasite-drug relationship—namely, drug resistance. This plays an important part in the response to treatment, especially by a single drug. If, as is usual, it is assumed that resistant strains emerge owing to the selection of resistant mutants, then the appearance of such strains in a patient treated with a single drug will depend upon the number of such mutants present before treatment, the degree of their drug resistance, and their rate of growth. The larger the initial bacterial population, the greater will be the number of resistant mutants present before treatment. The rate at which they grow may be determined not only by the dosage of the drug given but by the state of the host's defences.

Thus, as is well known, after some weeks' treatment of acute pulmonary tuberculosis with either streptomycin, isoniazid, or even P.A.S., used alone, drug-resistant strains of bacilli are frequently found in the sputum (Medical Research Council, 1948, 1950, 1952b), and eventually may largely replace a declining population of sensitive organisms (Crofton and Mitchison, 1948; Mitchison, 1950; Joiner *et al.*, 1952). This emergence is particularly rapid and intense in patients with large cavities and, in the case of streptomycin at least, with severe constitutional disturbance, when treatment is started—that is, in those patients who probably

have a large initial bacterial population and weak host defences (Medical Research Council, 1948, 1950, 1954b). The drug-resistant bacteria may be so numerous that in the dosage given the drug is no longer effective. This has been clearly demonstrated in treatment with streptomycin (Daniels and Hill, 1952). Failing the use of another drug, the subsequent course of the disease will be determined by other general measures, by collapse therapy or resection, and by the host's defences. The part played by the last is discussed later.

Combined chemotherapy has a decisive effect on drug resistance, provided the bacilli before treatment are sensitive to both drugs. If the drugs and doses are correctly chosen, not only may there be an additive or synergistic antibacterial effect, but drug resistance is largely prevented. In the Medical Research Council trials of streptomycin plus P.A.S., streptomycin plus isoniazid, and P.A.S. plus isoniazid, only 1–5% of patients with initially sensitive strains yielded cultures resistant to either drug after treatment for three months (Medical Research Council, 1950, 1953a, 1953b, 1953c), while in some 70% of patients the sputum was bacteriologically "negative." Information is not clear on how far the tendency—noted in certain single-drug treatments—for drug resistance to be commoner in patients likely to have a large initial bacterial population and poor defence mechanisms holds under combined therapy; the small numbers of resistant strains make analysis difficult (Medical Research Council, 1950, 1952a). The possibility that drug resistance during combined therapy can be transitory is discussed by Mitchison (1954).

(ii) After Discontinuation of the Chemotherapy

After the chemotherapy has been discontinued the role of the host's defences is more straightforward. In the, as yet unlikely, event of complete eradication of the infecting bacteria from the lesions, the danger of relapse would be removed, though resulting damage might persist. If, however, chemotherapy can do no more than help in stabilizing lesions, in closing cavities, and in reducing the volume of infection, the body's defences, together with other medical and surgical measures, may subsequently complete the healing process. A small residual infection may indeed act as a continued immunizing agent, but such possible advantage must be weighed against the risks due to the presence of virulent bacteria.

Relapse in Experimental Tuberculosis

Sterilization of the lesions by chemotherapy is still an uncommon finding in experimental tuberculosis, provided bacteriological examinations are complete (Jensen, 1949; Dubos, 1953a; Hobby *et al.*, 1953; Karlson and Feldman, 1953; Siebenmann, 1953). Nevertheless, recent combinations of drugs may have nearly achieved this object.* Where treatment has not resulted in sterilization, the incidence of relapse after withdrawal has varied with the animal species, as well of course as with the drug. In the guinea-pig, primary infection with a few virulent bacilli is fatal (Wilson and Miles, 1946), and experimental chemotherapy has so far usually left so large a bacterial population, and also so much tissue damage, that the native and acquired host resistance and the repair processes have been unable to cope. Reactivation with slowly progressive chronic but fatal disease usually results after withdrawal of the drugs, similar to that observed in the guinea-pig vaccinated with B.C.G. and subsequently given a small virulent infection (Schwabacher and Wilson, 1938; Steenken and Wolinsky, 1947, 1952; Jensen, 1949; Steenken, Wolinsky, *et al.*, 1951, 1952).

In the more resistant mouse, primary infection with moderate intravenous doses of tubercle bacilli kills with acute disease, but sufficiently small doses by this route have, in our hands, produced a chronic, relatively non-progressive, though damaging, disease, and this host-parasite equilibrium has been maintained for many months (Hart and Rees, 1950).

*See McDermott *et al.* (1954) on pyrazinamide-isoniazid combination.

Fatal reactivation, however, occurs if resistance is lowered by cortisone. Although in mice, too, relapse has usually followed sooner or later after withdrawal of chemotherapy (Martin and Stewart, 1950; J. Hirsch, 1953), recently this has not happened after cessation of streptomycin plus isoniazid in the treatment of intracorneal infection of mice (Goulding and Robson, 1952). It may well be that this powerful combination can reduce the bacterial population to a level corresponding to that productive of a non-fatal equilibrium. In the rabbit, whose resistance to human-type bacilli is still higher than that of the mouse, it is even more probable that relapse after chemotherapy could be prevented. On the whole, then, the evidence suggests that with increasingly efficient combinations the tendency to relapse may be reduced or abolished, especially in species with relatively high native resistance.

Relapse in Clinical Tuberculosis

In man the part played by the host defences in subsequent progress and in prevention of relapse after discontinuation of chemotherapy is difficult to disentangle from the part played by further medical and surgical measures, and by any further chemotherapy. Some valuable information is now available from a five-year follow-up of the original streptomycin trial patients mentioned earlier (Medical Research Council, 1948), undertaken in the Tuberculosis Research Unit (Fox *et al.*, 1954). These patients were a fairly homogeneous group of young adults with recent acute extensive bilateral pulmonary tuberculosis. Fifty-five patients had been given bed rest and streptomycin (alone), 2 g. daily, for four months; 52 control patients with comparable disease had received bed rest alone. Over a period of six months the streptomycin patients had fared much the better, as regards both mortality and radiographic change. Incidentally, this generally good initial response in a grave form of tuberculosis showed in 1947-8 what a powerful new weapon had arrived.

Few patients in either group received further chemotherapy, but more of each group received collapse therapy, and allowance for this must be made in interpreting the long-term results. Analysis of the survival figures up to five years from entry shows a gradual deterioration of the position in both groups. Each group, however, shows evidence of host resistance (fortified to some extent by collapse measures), for a proportion have survived and in some of these the disease is arrested, the experience of the streptomycin group being rather better than that of the controls. The follow-up period has been long enough to make the host's resistance the dominant influence at five years. The emergence of drug-resistant bacteria in most of the streptomycin group will account for its limited effect, the period of effective treatment being shortened; consequently the bacterial content of the sputum generally rose during the latter part of the chemotherapy, tending to present the body's defences once again with a bacterial population approaching that at the start of treatment (Medical Research Council, 1948). Another factor to be considered is the virulence of streptomycin-resistant organisms; there is, however, no conclusive evidence on whether these are more or less virulent than sensitive ones (Youmans and Williston, 1946; Steenken and Wolinsky, 1948; Emmart *et al.*, 1949; Feldman *et al.*, 1948; Rosa *et al.*, 1953); if anything they may be somewhat less virulent.

In order to obtain a closer view of the course of the disease in these two groups over the five years, Fox *et al.* have related mortality from four months onwards to the response during the first four months (as shown by x-ray changes and other clinical criteria). This analysis suggests that patients with a high host resistance or less extensive disease tended to survive even without the assistance of streptomycin. In contrast are those with very extensive disease or low host resistance, and a bad immediate prognosis if treated by bed rest alone; for although such patients improved while the bed rest was supplemented with streptomycin, their defences were unable to maintain this advantage and they tended to die later.

It may be concluded that a period on streptomycin assisted some patients with more effective host defences, but did little more than delay the subsequent mortality of most of those with poor or ineffective defence mechanisms. For the host's defences and repair processes to deal satisfactorily—on a long-term basis—with disease of this nature and extent, even with the help of collapse measures, more is clearly needed than bed rest plus therapy with a single drug, at least with streptomycin.

Although the limitations of streptomycin were soon recognized, the follow-up of the ultimate fate of patients treated with it in comparison with an untreated control group is valuable: hence the stress I have laid on this study even though the regime is outdated. We may hope that the long-term follow-up of patients with the same type of acute disease in the Medical Research Council trials, but treated with combinations of antibacterial drugs, will show a very different picture.

Bacteriological data are not available for the later periods of the long-term streptomycin follow-up referred to, but they should be attempted in future inquiries. It would be useful to know, first, what proportion of patients relapse bacteriologically, and, secondly, whether a positive sputum from a patient in relapse contains resistant or sensitive organisms. A negative sputum does not, of course, mean certain absence of organisms from the tissues. When sensitive organisms persist after withdrawal of chemotherapy, it may be because they are in sites containing bacilli either in a resting state or slowly dividing, and have therefore escaped the bactericidal action, as suggested earlier (see also Bigger, 1944; Jensen, 1949; Mitchison, 1954). Thus in closed necrotic lesions the body's defences may discourage bacterial survival or growth; such lesions may even be increased by the chemotherapy, but if resistance is lowered, bacilli surviving in them may multiply and appear in the sputum (see Canetti, 1946; Jensen, 1949; Medlar, 1952; Yegian, 1952; Pagel, 1952; Dubos, 1952, 1953a; d'Esopo, 1954). Sensitive organisms may persist in lesions also because the drugs have failed to reach the bacilli in phagocytic cells (Mackness and Smith, 1952, 1953) or have been antagonized by substances in the lesions (Dubos, 1953a).

Like persistent sensitive organisms, residual resistant bacilli can be a cause of relapse, and there is the added risk that they will become numerous enough to contain mutants resistant to other drugs as well, thus complicating retreatment (Mitchison, 1954).

Some of these points are illustrated by a year's observation of sputum changes in the Medical Research Council isoniazid trial (unpublished data). The patients had various types of pulmonary tuberculosis and had been treated with streptomycin plus isoniazid, or streptomycin plus P.A.S., for three months (no further chemotherapy had been given, but some patients had had collapse therapy). The majority who had negative sputa at the end of the three-months course still had negative sputa nine months later. In a small proportion the sputum had become positive again, though the bacilli were still sensitive; on the other hand, in some of the patients yielding sensitive organisms after three months' treatment the sputum was negative nine months later. There were too few cases with resistant strains after combined therapy for conclusions to be drawn at the end of the year, but we may compare this position with the not inconsiderable incidence of resistant strains present after three months of isoniazid alone and still present nine months later (Medical Research Council, 1954a). Combined therapy, then, produces a fairly satisfactory bacteriological result, but the host's defences also contribute by restraining relapse and reducing residual infection.

To summarize, interplay between host resistance and antibacterial chemotherapy is evidently complex. During chemotherapy we may conceive that a temporarily lowered host resistance may in certain circumstances lead to increased bactericidal effectiveness; but it may also favour the emergence of drug-resistant organisms. The effect of these two opposing tendencies will be influenced by the power and

the type of the chemotherapy. The picture is complicated by the usual struggle between the host's defences and the infection. *After withdrawal of chemotherapy* the role of the host defences in tackling residual infection is obviously more straightforward and akin to the usual host-parasite relationship: further medical and surgical interventions may also have to be taken into account.

I now turn to a further part of the subject, in which the host and its defences against the infection are more essentially involved in the drug's action.

HOST SIDE-EFFECTS OF POSSIBLE RELEVANCE

Apart from their direct antibacterial action, some anti-tuberculous agents have other effects which could influence the therapeutic result. Thus the thiosemicarbazones may reduce allergy and tuberculin sensitivity, and may also have a thiouracil-like effect on the thyroid gland (see Staub, 1953). P.A.S. has antipyretic and other salicylate actions and also an antithyroid action (Hamilton, 1953; Beattie and Chambers, 1953); it is reported to be antihistaminic and anti-inflammatory (Forró and Szegő, 1951). Alterations in vascularity of lesions after isoniazid treatment have been described (Panà *et al.*, 1952; Dick, 1953). According to several authors, P.A.S., streptomycin, and thiacetazone ("conteben") accelerate mobility and phagocytic activity of leucocytes (Ozeki, 1952, 1953), and, it is claimed (Mauer, 1952a, 1952b), affect carbohydrate and intermediate phosphate metabolism, so leading to decreased tissue necrosis.

CHEMICAL AGENTS APPARENTLY ACTING ESSENTIALLY THROUGH THE HOST'S DEFENCE MECHANISMS

A small but interesting group of substances probably influence tuberculous infection through the host, and without direct antibacterial action. Not so long ago most remedies in tuberculosis were, in fact, directed primarily to affecting the host—for example, rest, sunlight, good food, traditional remedies such as cod-liver oil and calcium preparations, and "sanocrysin" (sodium aurothiosulphate) and other metal compounds thought to stimulate the tissues (see Hart, 1946). Thus it was quite reasonable for an authority on chemotherapy to conclude as recently as 1935 that "no treatment at present can be aimed directly against the causal agent . . . and the only procedures commonly approved consist in conserving general health, resting affected parts, and removing necrotic tissue"; though he added the belief that methods of directly attacking the tubercle bacillus would come (Browning, 1935). With successful specific drug treatment interest became focused on the straightforward interaction between drug and bacillus. But the chronic nature of tuberculosis, modified by fluctuating immunity and allergy, encourages the further search for artificial means of enhancing the operation of the host defences.

Lurie (1950), Florey (1952), and others have paved the way to a rational approach by analysing the normal defence mechanisms, with special emphasis on the functions of the monocytes (macrophages) and on penetrability of drugs into inflammatory areas. Discovery of an agent that decreases host resistance could be as valuable in the long run as of one that increases it, for even a "protuberculous" action demonstrates the flexibility of an element in the defence mechanisms, and might therefore give a lead to the discovery of an antituberculous agent involving the same element. Moreover, in certain infections alterations in dosage have been reported to change a protuberculous into an antituberculous effect—for example, cortisone in experimental pneumococcal infection (Robinson *et al.*, 1953).

First is the effect of dietary constituents. Yet in spite of the strong circumstantial evidence of the influence of nutrition upon susceptibility to human tuberculosis (Clarke, 1952; Helweg-Larsen, 1952), animal experiments have only recently begun to throw light on the nutrients involved (see Hart and Rees, 1950; Nègre, 1950; Bloch, 1953; Dubos and Pierce,

1954). Calciferol, it is true, gives undeniable clinical benefit in lupus vulgaris, possibly by enhancing some cellular reaction; but no such effect has been reported in systemic tuberculosis in laboratory animals.

With the exception of cortisone, the effect of hormones is uncertain. Large doses of chorionic gonadotrophin aggravate, and oestrogen suppresses, intracutaneous infection in highly inbred rabbits of genetically uniform stock, and the mechanism of this effect has been carefully analysed (Lurie *et al.*, 1949); but no effect has been shown with these two hormones in chronic mouse tuberculosis (Rees and Hart, unpublished), while large doses of oestrogen are said to accelerate infection in guinea-pigs (Svedberg, 1951). Cortisone, however, is the first hormone to be found capable of producing an unequivocally increased susceptibility to tuberculosis. In pharmacological doses in the mouse, it exacerbates a stable chronic infection and renders an acute infection hyperacute (Hart and Rees, 1950); and our findings have been confirmed not only in this species (Solotorovsky *et al.*, 1951; Engbaek *et al.*, 1952), but also in the rat (Michael *et al.*, 1950; Cummings *et al.*, 1952), to some extent in the rabbit (Ebert, 1952; Lurie *et al.*, 1953a; Morgan *et al.*, 1954), and even in man (American Trudeau Society, 1952).

The characteristics and mechanism of the phenomenon, mediated through the host but to a different degree in different species, are fully discussed by Rees (1954). Our attempts to exploit it have been unsuccessful, since no other structurally related steroid produced the effect in mice, except hydrocortisone (Kendall's compound F) and to a small degree Kendall's compound A (Rees and Hart, unpublished): the chemical specificity of the protuberculous action appears to coincide with that of the antirheumatic effect in man and of the depression of tuberculin sensitivity in the guinea-pig (Long and Spensley, 1954). Moreover, we have been unable to antagonize the protuberculous effect by any structurally similar steroid; and although Lemonde *et al.* (1952) have claimed to have done this with somatotrophic hormone (S.T.H.) in rats, and even to suppress experimental tuberculosis in mice with this hormone, we have failed to produce either effect in mice (Rees and Hart, unpublished). I have already mentioned the possibility of giving cortisone to stir up a stable chronic tuberculous infection, along with antibacterial therapy to deal with the bacilli multiplying and liberated from the cells (Ilavsky and Foley, 1953): the agents must be in maximum dosage, otherwise the use of cortisone might prove a disadvantage (Spain and Molomut, 1950; Bloch *et al.*, 1951; Cummings *et al.*, 1952; Meyer *et al.*, 1952; Jawetz and Merrill, 1953).

There are other instances where a change in the host-parasite relationship in favour of the tubercle bacillus has been brought about by a chemical substance. Quartz dust in the lung increases susceptibility to tuberculosis, as is well known. Even more striking is the observation that in silicotic guinea-pigs infected with B.C.G. the organisms were rendered pathogenic and the animals died with silico-tuberculosis; but the virulence of the B.C.G. when recovered was unaltered (Vorwald *et al.*, 1950). Injection of beryllium chloride in guinea-pigs can also aggravate tuberculous infection (Weimer *et al.*, 1953). Procaine ("novocain"), pentobarbitone sodium, and the antipyretic phenamine (phenocoll hydrochloride) are said to worsen experimental tuberculosis, the suggestion being that neural conductivity is reduced and the influence of the central nervous system upon host resistance consequently disturbed (Kan, 1953). Mice rendered diabetic with alloxan showed no increased susceptibility to tuberculous infection (Hart and Rees, 1950), but rats, similarly treated, did (Roche *et al.*, 1952). None of these protuberculous effects has so far led to the discovery of a counter-agent.

Certain substances, without being themselves antibacterial, have been tested as auxiliaries to specific antituberculous compounds. Potassium iodide, ineffective by itself, but believed to promote digestion of caseous matter and so to liberate the bacilli and render them more accessible,

has been given simultaneously with streptomycin, with superior results to streptomycin alone in the tuberculous guinea-pig (Woody and Avery, 1948) and in tuberculosis of the rabbit's cornea (Rees and Robson, 1950). Phlorizin, stated to reduce tissue necrosis in tuberculous guinea-pigs by action on phosphate and carbohydrate metabolism, without direct effect on the bacteria, is claimed to act synergistically in combination with isoniazid (Mauer and Finkeldey, 1952, 1953). I do not know of any definite information on the clinical value of such auxiliaries.

Attempts have been made to improve the therapeutic effect by changing the level of tuberculous allergy in one or other direction. Tuberculin has been given intrathecally with streptomycin in tuberculous meningitis in order to promote an acute inflammatory reaction, resolve the exudate, and consequently to liberate bacilli to come into contact with the drug (Smith and Vollum, 1950; Smith, 1953). Before the risk was fully appreciated, cortisone and corticotrophin (A.C.T.H.), both of which depress tuberculin sensitivity in the guinea-pig (Long and Miles, 1950) and in man (Lovell *et al.*, 1953), were used clinically in the hope of reducing tuberculous hyperacute inflammatory phenomena (see American Trudeau Society, 1952, and LeMaestre *et al.*, 1953). More recently, however, A.C.T.H. has been used, with apparent safety, together with streptomycin and P.A.S., to desensitize patients with allergic drug reactions (Houghton, 1954).

On account of toxicity, or for technical reasons, none of the other substances shown to reduce tuberculin sensitivity in guinea-pigs (Fisher *et al.*, 1951; Long *et al.*, 1951; Cornforth and Long, 1952) has been tested in human tuberculosis. Nevertheless, on the view that tuberculin allergy has mainly a nuisance value, Brownlee (1953) has expressed the hope that specific drugs capable of blocking this reaction will be found useful clinically. In this connexion, it should be borne in mind that experimentally, and possibly clinically, tuberculin skin sensitivity can be substantially reduced or removed without loss of immunity (Wells and Wylie, 1952; and see Fourestier and Blaque-Belair, 1954), and that the bacillary constituents responsible for inducing allergy and immunity appear to differ (Raffel, 1950).

Surface-active Agents

Recently the first example of substances that exert a powerful suppressive effect on systemic experimental tuberculosis, apparently through the mediation of the host, was discovered at the National Institute for Medical Research (Cornforth *et al.*, 1951, 1954a, 1954b). Certain non-ionic surface-active polyoxyethylene ethers were found to be antituberculous when given parenterally to mice. Later, a curative effect was noted in established disease in guinea-pigs (Rees, 1953). Our original observation was made with commercial "triton A 20," but subsequently many agents with similar structure were synthesized. Two series have been principally studied, both having as starting-point *p*-tert-octyl phenol, which was condensed with formaldehyde. In the first series a complex resinous mixture of linear polynuclear products was thus formed. This intermediate mixture was reacted with ethylene oxide so as to give an optimal average length of polyoxyethylene chains, a soluble surface-active product resulting. In the second, more recent, series the formaldehyde condensation was carried out under different experimental conditions, and two pure crystalline intermediates were obtained having a macrocyclic tetra-nuclear structure and probably representing two of four possible geometrical isomers; these compounds were condensed similarly with ethylene oxide to form soluble surface-active products (mean molecular weight of those with an average of 20 ethylene oxide units per phenolic nucleus = about 4,000).

The biological properties of these products are summarized elsewhere (Rees, 1954). Owing to liver damage after continued administration in experimental animals, they have not been tried in man. In the present context the important

findings are that they are not bacteriostatic *in vitro* and may even facilitate submerged and surface growth; while tubercle bacilli grown in them, or recovered from treated animals, show no decrease in virulence. Nor is there experimental evidence that *in vivo* (in mice) they counteract the toxic effect of the "cord factor," which is believed to contribute to the virulence of tubercle bacilli (Bloch, 1950, and unpublished). A point of special interest is that their antituberculous action is reduced and eventually abolished by lengthening the chains of the attached ethylene oxide units. The effectiveness of simultaneous administration of triton A 20 and dihydrostreptomycin in mouse tuberculosis has been reported by Solotorovsky and Gregory (1952).

That host defence mechanisms are essentially involved in the mode of action of these surface-active agents was first presumed by us on negative evidence—namely, lack of direct antibacterial effect *in vitro*, and failure to obtain evidence of conversion into antibacterial compounds in the body—for example, in the blood (Rees, 1953). Moreover, it seemed that the entire and fully developed host is required for the operation of these substances, since they failed to protect chicken embryos infected with tubercle bacilli when administered to the yolk sac, allantoic cavity, or intravenously (G. E. Davies, unpublished). Two relevant effects upon the host are, however, now known. One is a depression of tuberculin sensitivity in guinea-pigs, comparable in degree to that by cortisone but different in mechanism (Hart *et al.*, 1952). Interestingly, this anti-allergic effect was given only by therapeutically active members of the series tested; it is nevertheless uncertain how far it has any causal connexion with the anti-tuberculous action.

The other host effect is upon the monocytes (macrophages), which was discovered recently at Oxford by Mackaness (1954a). Tubercle bacilli were introduced *in vitro* into preparations of monocytes obtained from animals previously injected with commercial "triton WR 1339" (the effective agent in triton A 20); although the rate of phagocytosis was not increased, the ingested bacilli were killed or their growth was inhibited, in contrast to the free intracellular multiplication seen under these conditions in monocytes isolated from untreated animals. Direct contact of the agent, in the limited concentrations tolerated by the surviving-cell preparations, with monocytes obtained from untreated animals was ineffective. It has since been shown (Lovelock and Rees, to be published) that the monocytes from similarly pre-treated animals contain the agent. These important observations suggest that one site, though not necessarily the only one, of the antituberculous action of these surface-active polyoxyethylene ethers in the body may be within the phagocytic host-cells of the infected tissues. How the agents enhance the operation of the cellular defences is not yet decided. They may bring about an alteration in the monocytes of treated animals, or they may affect the bacilli within the monocytes in some physical manner so as to make them more susceptible to the intracellular environment.

The production of an antituberculous effect by a chemical agent, probably operating through the host rather than by directly damaging the bacillus, opens out interesting prospects. First, it is possible that such agents, having no direct antibacterial action, might not induce drug resistance. Secondly, they might be used in combination with specific antibacterial agents. Thirdly, they might be used to strengthen host defence even after the withdrawal of chemotherapy. In the search for new agents, surface activity and macromolecular nature, and perhaps physical properties as much as chemical structure, might be used as a working guide. A practical difficulty is that assessment of activity of new compounds of this type is laborious, since they would be missed *in vitro*. For example, three leading American investigators (Youmans *et al.*, 1953) recently reported results of 3,500 organic compounds "screened" for antituberculous activity *in vitro*; the 184 active compounds discovered were then tested in mice. To test the remaining 3,316 substances primarily in mice in our own laboratory might have taken 25 years.

CONCLUSION

Consideration of host-parasite relations, complicated by a drug as a third party whose action may both influence and be influenced by them, suggests that we might regard some of the body's own defences as themselves acting like drugs. Such a view has some basis if it be accepted that interference with growth and survival of tubercle bacilli within macrophages is a feature of high native resistance and acquired immunity (Canetti, 1946; Lurie, 1950; Rich, 1951; Lurie *et al.*, 1952, 1953b; Suter, 1953). (The experiments of Brieger *et al.* (1951) and of Mackaness (1954b), however, throw some doubt on this action of monocytes.) In conformity with this concept, Dubos and Hirsch (Dubos, 1950, 1952, 1953b; Hirsch and Dubos, 1952; Hirsch, 1953, 1954) have suggested that certain substances with *in vitro* tuberculostatic or tuberculocidal properties may play a part in host defence by creating an unfavourable physico-chemical environment for the parasite. These include certain organic acids that may arise from metabolism of macrophages and from breakdown of tissue cells in inflammatory and caseous areas; lysozyme, which also occurs in inflammatory areas; and the polyamine spermine, and a peptide, both of which are found in some normal organs. The idea of "combined internal chemotherapy" cannot, of course, be applied to all aspects of defence. It is also one-sided, since the host tissues can also be looked on as a culture medium, some cells giving support and comfort to the enemy. But the idea may stimulate development of knowledge of the host-parasite-drug relationship in tuberculosis, more especially when considering drugs that might strengthen the host's own "chemotherapeutic" contribution to the struggle against the infection.

Ehrlich's famous conception of chemical compounds for which the disease-germ cells have a great affinity, while the body cells have little or none (Galdston, 1940; Hart, 1946), has been fulfilled for bacterial infections by penicillin, and to a less extent by other agents, including some of the anti-tuberculous drugs in current use. The surface-active agents described hold out hope of clinically useful compounds in whose action certain of the body tissues play an essential part, while the tubercle bacillus is not directly injured by the drug. If this turns out to be true it will be a modification of Ehrlich's original conception. Nevertheless, this way too may lead to his objective of chemical substances that will destroy the invading parasite without harm to the host; but the method of arriving there will be different.

In preparing this lecture I have drawn freely on the work and ideas of colleagues associated with the Medical Research Council's investigations in tuberculosis. I am particularly indebted to Dr. R. J. W. Rees, National Institute for Medical Research; Dr. Wallace Fox, Tuberculosis Research Unit; Dr. D. A. Mitchison, Postgraduate Medical School of London; and Dr. Ian Sutherland, Statistical Research Unit (Medical Research Council); as well as to the late Dr. Marc Daniels.

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THE DANGER OF ACCIDENTAL CARBON MONOXIDE POISONING

A REVIEW OF 100 CASES

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Every year in England and Wales some 400–500 cases of accidental poisoning by domestic coal-gas occur—a disquieting toll of life that has for many years been accepted as a natural risk of urban existence (Table I).

TABLE I.—Registrar-General's Figures

	1947	1948	1949	1950	1951
Males	170	166	195	158	215
Females	250	195	226	248	300
Total	420	361	421	406	515

Of the 1951 figure of 515 deaths, only 15 occurred at work; no fewer than 459 occurred at home, and some two-thirds of these involved elderly people—over 60 years of age—exposed to risk through forgetfulness or infirmity. Some means of reducing this carnage of accidental death must be sought, and this review of 100 successive cases from my records is designed to draw

attention to: (a) common dangers inherent in present-day domestic gas usage; (b) other commonly unsuspected sources of CO pollution of air; and (c) the urgent need for adequate warning of danger, and for safety mechanisms in domestic apparatus.

Recognition of CO Poisoning

Although nothing new has come to light in recent years with regard to the treatment of CO poisoning, the importance of recognizing the condition and giving the appropriate treatment for it at the earliest possible moment cannot be emphasized too strongly. A low concentration of CO is easily overlooked, both in a stale atmosphere and in the body. The following review illustrates the ease with which the doctor may fail to recognize CO poisoning, though exercising reasonable care and maintaining an average vigilance for such matters in carrying out his everyday duties. Two examples will suffice.

In 1946 a family of three were found unconscious in the kitchen of a house at Watford; suspicion of foul play had arisen. A police constable left on guard for two and a half hours had become so obviously ill himself while waiting in the room—complaining of the stuffy atmosphere, of headache and nausea—that the possibility of CO poisoning from a vitiated atmosphere was at once suspected. The flue to a kitchen stove burning coke was found to be blocked by two sanitary pads which had been dropped through the top of the stove to burn but had been drawn into the vent. Samples of blood from the victims confirmed the absorption of carbon monoxide. A child already dead showed a figure of 44%: vomit inhalation had precipitated death at this low saturation.

In 1954 six persons—four children and two women—were found unconscious in a single bedroom at the rear of a flat at Waltham Cross. Poisoning with nicotine was suspected, as an empty tin had been found in an adjacent passage; but the atmosphere was thick with the stale fumes of gas, the window curtains were drawn, the window and door were closed, and a gas mantle and gas fire were found still burning. The fire had been lifted on to the mantelpiece to put it out of the way of the children, and it had thereby been deprived of the ventilation approved by the gas authority. All bodies were characteristically pink, and samples of blood revealed HbCO readings of between 20 and 42%. It was an astonishing fact that the persons first called to make entry—a police constable, C.I.D. officers, and a police surgeon—had not thought of CO as a cause for the catastrophe in spite of these pointers. Two of the victims recovered.

Such instances could be multiplied, and do, in fact, form a substantial proportion of the 100 successive cases reviewed here. A doctor called to an elderly person found dead under circumstances which raise no suspicion of violence may—and, it seems likely, commonly does—overlook the real substance of the case: CO poisoning may not be apparent in the first instance and may not be detected until the absence of disease and suspicion of poisoning from the colour of the blood have caused the pathologist to undertake a CO reading.

Age Incidence

In the sample series of 100 successive deaths from accidental exposure to CO taken for the purpose of this study the age incidence in decades was:

Age	No.	Age	No.	Age	No.
0–	6	30–	7	60–	17
10–	5	40–	5	70–	33
20–	3	50–	8	80–	16

The frequency of fatal exposure remains more or less the same until somewhere approaching the age of 60, after which a sharp rise to a level some four times that of any other period in life is reached. Of the 100 persons involved, 66 were over 60, and analysis of the circumstances showed that most of these cases—the figures are too small for more detailed breakdown in this respect—seemed likely to be attributable to increasing age and forgetfulness, senile decrepitude, or frank collapse.

The main causes were, in order of decreasing frequency: (a) trivial accidents with taps or burners, partly turned stop-cocks, etc.; (b) ignorance of the importance of adequate