PHENOLIC DISINFECTANTS

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Phenol was discovered in 1834 but it was 1860 before it was first recommended as a disinfectant[1] and, in the same year Lemaire[2] used it on wounds. In 1867 Lister[3] introduced it in antiseptic surgery and in 1877 Jeyes patented what must have been the first coal tar disinfectant, which was a creosote-soap solution.

Because of Lister's work and as phenol itself was comparatively easy to obtain in a pure form, it was adopted as a reference substance in disinfectant work about the beginning of the century and is still accepted as such in most of the disinfectant industry.

Its toxicity, especially its leucocidic power which is involved in sloughing of wounds, prevented its wide use as an antiseptic.

Mode of Action

It has been stated that phenols act by denaturing bacterial proteins, and this idea of direct chemical action by coagulation of proteins is supported by Bancroft and Richter[4] and Lobes[5].

As early as 1909 Reichal[6], after studying the distribution coefficients of phenol between oil and water and their relation to bactericidal activity, suggested the action to be physical rather than chemical, an idea that found support from Richardson and Reid[7].

Pulvertaft and Lumb[8] noted that lysis of bacteria often occurred in presence of bacteriostats, and Gale and Taylor[9] studied the leakage of glutamic acid from phenol-treated bacteria and concluded that phenol alters the permeability of the cell wall and allows essential cell material to leak out. Whether this leakage causes death or death precedes the leakage is not known, but the work of Bean and Walters[10] on the growth of phenol-treated organisms in the presence of the eluate from phenol-killed organisms suggests that death may precede lysis.

The work of Quastel and Wooldridge[11], Bach and Lambert[12], Sykes[13] and other workers, has shown that some bacterial enzymes are not completely inactivated by phenol at concentrations above those lethal to the organism itself, indicating that it is unlikely that the bactericidal action follows from complete enzyme inactivation.

Evaluation of Phenolic Disinfectants

Many adverse criticisms of the use of a phenol coefficient as a measure of bactericidal activity have been raised[14–17] but these have had little effect within the field of commercial disinfectants. Here, far too much importance is still attached both by manufacturers and customers to the Rideal Walker, Chick Martin, and Food and Drug Administration Phenol Coefficients. The tests used to ascertain these 'coefficients' are all of the extinction type and use phenol as a reference substance. The variable factors are numerous, some are controlled, often inadequately, by the specifications for the tests. Very little or no replication is suggested in the specifications. In the design of the tests, and in the calculation of

the phenol coefficients, no regard is paid to the assessment, of extinction time data, of the type suggested by Mather[18], and the use of such tests for other than batch to batch control is fundamentally unsound.

Unfortunately the published results of the "evaluation" of phenolic disinfectants abound with "phenol coefficients" the conditions of determination of which, in many instances, are not stated. Thus it is difficult to draw conclusions from, or make comparisons between, the results from different laboratories when evidence about the conditions attaining; or where the repeatability and reproducibility is not available. An example of this difficulty is given by Coulthard[19] who in assessing the phenol coefficients of 4-n-amyl-*m*-cresols suggested that the differences between his results and those of other workers could be attributed to the use of alcohol or alkali to maintain the phenols in solution.

Although it would be fallacious to compare the bactericidal value of different phenols by comparing phenol coefficient values, especially where these were from different laboratories, it is possible to note gross differences and trends.

Factors affecting Action of Phenolic Disinfectants

Concentration. Tilley[20] obtained values of between 7 and 9 for the dilution coefficient of several phenols against *Salmonella typhi* and *Staphylococcus aureus*, the higher molecular weight homologues giving slightly higher values than phenol. These values are higher than many other classes of disinfectant and make the Use Dilution Confirmatory Test seem pointless since with a phenolic disinfectant with a phenol coefficient (F.D.A. Test) of 3 then the concentration of the disinfectant used in the confirmatory test should kill the organism in less than 1×10^{-4} minutes. In the test 10 minutes is the permitted reaction time, a safety margin of 100,000. On the other hand one dessertspoonful of solution of chloroxylenol in a handbasin of water would need 3 days' contact time to approach disinfection of the objects immersed, if the dilution effects depended solely on the chloroxylenol content.

When phenolic disinfectants are used in practice these high dilution coefficients demand that care be taken not to dilute beyond an effective concentration.

Temperature. There are two aspects of the effects of temperature on disinfection by phenols. The first is that the bactericidal activity of phenols increases rapidly with increase in temperature. The second follows from the work of Grubb and Edwards[21] that some strains of *Salm. typhi* and *Staph. aureus* are more resistant to phenol when the cells were grown at higher temperatures, which means that a higher concentration of a phenolic disinfectant may be necessary to disinfect material contaminated by bacteria from human sources than if contaminated with soil organisms.

Hydrogen ion concentration. In general phenols have greater antibacterial activity at an acid than at an alkaline pH[22,23]. With an amyltricresol the antibacterial activity against *Staph. aureus* decreased with increased pH whereas with *Escherichia coli* it increased with pH[23].

Oxidation-reduction potential. Gould, Frigeris and Hovanesia[24] and other workers have shown that anaerobic organisms are usually more resistant to phenols than aerobic organisms. Their findings with facultative organisms (bacteria that are able to grow with or without oxygen) are perhaps more significant, in that these organisms are more resistant to phenols under anaerobic conditions.

The ability of some bacteria when grown in conditions of low redox potential to oxidise phenols was first reported by Wagner[25] and more recent work [26] concludes that there are diverse groups of bacteria which can oxidise phenols under a variety of conditions.

Development of resistance to phenols. There are conflicting reports on the abilities of bacteria to acquire a resistance to phenols[24,27,28] but the reported resistance was not very great and was not retained for long periods if subcultured in the absence of the phenol.

Organic matter. It is well known that organic material can interfere with the antibacterial activities of phenols, a fact recognised in the design of the Chick Martin Test. This interference is stronger in some other kinds of disinfectant, for example the quaternary ammonium compounds. It also varies with different phenols and different kinds of organic matter.

Chemical nature of phenols. Dihydric and polyhydric phenols are generally less active than monohydric phenols.

Coulthard, Marshall and Pyman[29] have shown that alkylation of monohydric phenols potentiates their activity. This effect is maximum where there are 5 carbon atoms in the substituent group.

A similar enhancing effect is produced by halogenation of phenols and increases with increasing atomic weight of the halogen; it is less in the *ortho* than the *para* position[30]. This increase in activity on halogenation generally has the effect of an increased specificity of action against the different genera of bacteria.

Increase in molecular weight of the phenol is usually accompanied by decrease in solubility, and this has led to the use of soaps in the formulation of phenolic disinfectants to bring insoluble phenols into solution.

Cresol B.P. is a mixture of *ortho*, *meta* and *para* cresols together with small amounts of xylenols. It is more bactericidal than phenol, less toxic, and less soluble. Pentachlorphenol is extensively used in timber preservation and has an odour too strong to recommend its use in disinfectants. Chlorocresol B.P. used as a bactericide and bacteriostatic in pharmaceutical preparations has slight irritant properties. Chloroxylenol B.P. is only slightly soluble in water and is used extensively in preparations similar to Solution of Chloroxylenol B.P. This preparation was designed for use against haemolytic streptococci, it has very poor action against staphylococci and pseudomonads; it is to be regretted that it has been recommended as a substitute for lysol for general disinfection as it is often used in concentrations which are quite inadequate. Dichloroxylenol has been suggested as a substitute for or adjunct with chloroxylenol. It is more bactericidal than chloroxylenol when tested against salmonellae, staphylococci and streptococci but is ineffective against pseudomonads.

Phenols and Soaps

Since the patent by Jeyes in 1877 soaps have been an almost constant feature in phenolic disinfectant formulae. The earliest pharmacopoeial formula was that of lysol in the 1914 B.P. Lysol is still widely used but the production of a standard poses a problem. The official monograph is so loosely drawn that variations in bacteridical power can occur which are too large for this important preparation. The soap content plays an important part. Berry and Stenlake[31] have shown that the bactericidal value of a lysol depends upon the nature and amount of the soap used. With the same sample of cresol, variations occurred ranging from 1·4 to 3·2 when measured as the phenol coefficient against *Salm. typhi.* Moreover the raising or lowering of the coefficient using this organism is not reflected in a similar effect using other organisms such as streptococci or staphylococci. It can also be shown that an optimum effect can be obtained in the presence of organic matter by a careful selection of the soap or blend of soaps. The official monograph however permits the use of any sodium or potassium soap or mixture to be used providing the physical characteristics of the preparation are maintained. The formulation for Liquor Cresolis Saponatus B.P. 1914 would produce much less variation, but economically it could not compete in price with the present formula recommended by the trade.

Berry[32] is correct in stating that by raising the standard of the chemical and physical specifications of the cresol and the soap used in making lysols more reproducible bactericidal values for the lysols would follow. It is recognised that a good standard lysol could be prepared from a pure *ortho*, *meta* or *para* cresol and a specified soap but such a lysol would have a poor reception in the economic field because of cost. Nevertheless there is room for a further effort either by the Pharmacopoeial authorities or the trade itself to improve the standardisation of this important disinfectant, the use of which is on the increase. Lysol has a wide bactericidal spectrum including activity against *Pseudomonas pyocyanea.* It undoubtedly plays an important and valuable role in hospital practice and general hygiene and because of this should receive attention. Its greatest limitation is its irritant effect on the skin, but "lysols" have been formulated which are much less irritant than those using cresol.

Many attempts have been made to explain the effect of soap on the bactericidal activity of phenols, and results are still contradictory.

Soaps are surface-active agents which exhibit the phenomenon of micelle formation. McBain[33] postulated that in dilute aqueous solution soap behaves as a normal electrolyte, but at higher concentration reassociation takes place to form "micelles." These he regarded as being spherical and consisting of an aggregate of the hydrophobic hydrocarbon chains of the soap molecules jumbled together and away from the water with their hydrophilic end groups projecting into the surrounding water and the whole aggregate surrounded by an atmosphere of the hydrophilic ions of the soap. Stauff[34] postulated lamellar micelles consisting of double layers of soap molecules closely packed side by side. These micelles begin to form when the concentration of the soap reaches the critical

micellar concentration. With a sample of pure potassium laurate, this occurs at about 0·03 M and the micelles increase in size and number until 0·05 M. The critical micellar concentration is a characteristic of each soap under constant conditions but is affected by temperature, presence of electrolytes and other substances, for example, hydrocarbons.

The most important property of these soap solutions, in relation to phenolic disinfectants, is their ability to solubilise insoluble phenols in the micelles, and the effect this has on the bactericidal activity of the resultant solution.

Figure 1 shows typical results obtained by workers in this field[35]. This shows (dotted line) the solubility of a comparatively water insoluble

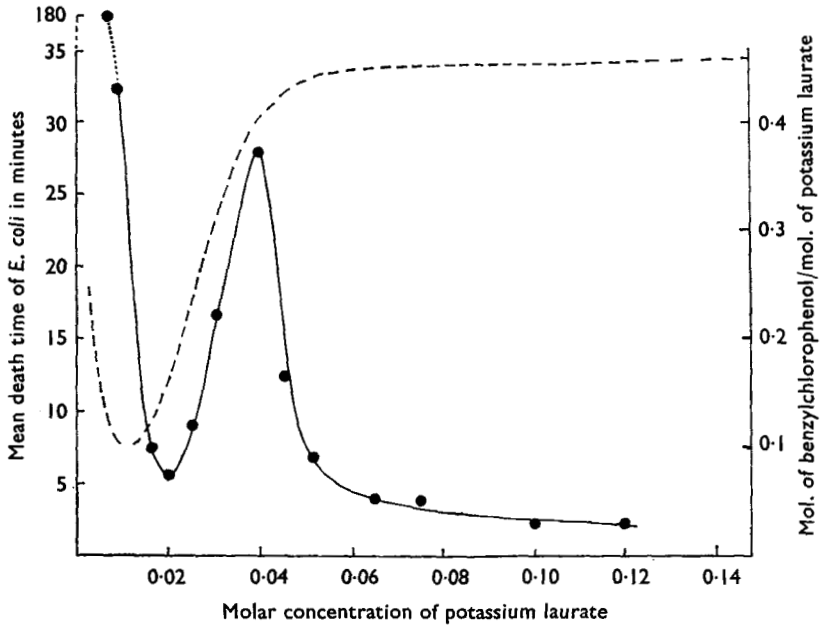

FIG. 1. Solubility of benzylchorophenol in potassium laurate and bactericidal activity of solutions containing a constant molar ratio of phenol to soap of 0·0653 (after Berry and Briggs). Broken line is solubility curve.

phenol in solutions of potassium laurate and the death time of *E. coli* in a solution with a constant phenol to soap ratio with differing soap concentrations. It shows that the death time decreases with increasing soap concentration up to and just above the critical micelle concentration. Then there is a rapidly increasing death time up to about 0·04 M which thereafter decreases.

Alexander and Tomlinson[36] used Aerosol MA, an anionic surface active agent, to solubilise a constant concentration of phenol with varying concentrations of the solubiliser. Their results are not very explicit. Thus when their concentration was above the critical micellar concentration they did not get an inflection in the curve indicating minimal activity

as reported by Berry at 0·04 M potassium laurate, and they postulated that the curve continued upward until it met the curve representing the death times in aerosol MA alone.

In an effort to elucidate this apparent contradiction, Berry, Cook and Wills[37], used potassium laurate and three phenols of differing solubilities, and plotted similar curves both at constant phenol to soap ratios and constant phenol concentrations (Fig. 2 and 3). They confirmed the presence of the peak and showed that there was also a smaller second peak with the constant phenol concentration mixtures, this second peak was highest with the most water soluble phenol. With the constant phenol to soap ratios they confirmed the presence of the first peak but it was least well marked with the most water soluble phenol.

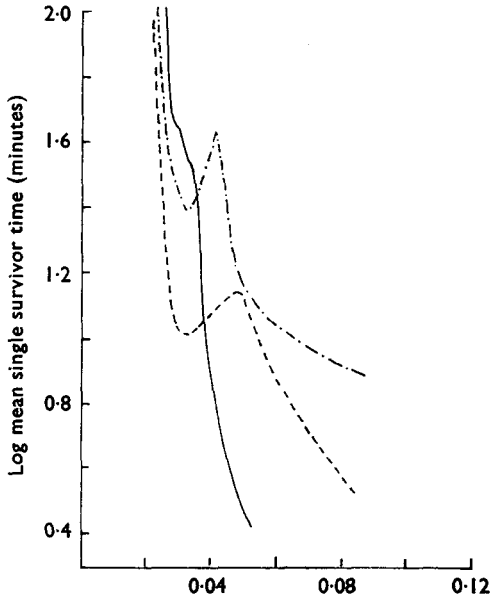

FIG. 2. Bactericidal activity of solutions of phenols in potassium laurate solutions with a constant phenol/soap ratio.
—— Phenol; – – – 2-hydroxydiphenol; –·–·– 4-benzylphenol.

Alexander ascribed the effect of the solubiliser to the formation of an interfacial complex at the bacterium-water interface, and, at concentrations in excess of the critical, the phenol passed into the micelles and the activity was that of the solubiliser itself.

Berry's explanation of the peak was that soap micelles and bacteria were competing for the phenol. When the soap micelles were saturated with phenol the increased activity was re-established.

These two explanations adequately cover the findings reported in the respective papers and are in some ways complementary. Both agree about the rapid decrease in death-time with increasing concentration until

the critical micellar concentration. Above this concentration, there is a difference between systems with a constant phenol concentration (Alexander) and a constant molar ratio of phenol to soap (Berry). The later work[37], with a constant molar ratio, supports Berry's earlier explanation but results with a constant phenol concentration, where the micelles are not saturated with phenol and the inflections in the curve still appear, detract from this explanation. More information about the distribution of phenol between micelles and the surrounding medium should help to answer this problem.

From the point of view of practical disinfection the results at constant phenol-soap ratio are more important, since this represents the dilution of

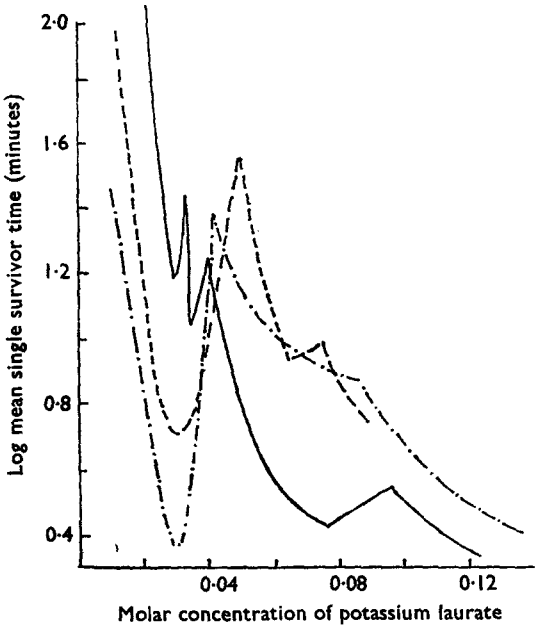

FIG. 3. Bactericidal activity of solutions of phenols in potassium laurate solutions with constant phenol concentrations.
—— Phenol; – – – 2-hydroxydiphenol; –·–·– 4-benzylphenol.

a concentrated disinfectant with water. Unfortunately, the findings are difficult to apply to commercial disinfectants for a number of reasons. These are summarised.

1. The critical micellar concentrations of different soaps are different, and this affects the bactericidal activity[3].

2. In many commercial disinfectants the soap used is impure or is formed from a hydroxyacid. In these circumstances, estolides may be formed[38] and so the critical micellar concentrations may vary from batch to batch.

3. The critical micellar concentration varies with temperature and alters when other substances, such as electrolytes, hydrocarbons and

alcohols, are added and most formulations contain one or more of these substances.

4. With many commercial disinfectants, especially the coal-tar group, the composition of the phenols varies from batch to batch.

Where the concentration of the disinfectant that is to be used is greater than that of the critical micellar concentration, then no great advantage is to be gained by any further knowledge except that it may be possible to dilute the substance further and get similar or greater activity.

If the Rideal-Walker test is used as an assessment of the disinfectant, then anomalous results are inevitable if dilutions around the critical micellar concentration have a death time of about 7 minutes.

A great deal of information is needed on the critical micellar concentrations of different soaps and the effects of added substances before true assessment of these disinfectants can be attempted.

Phenolic Disinfectants

Most commercially-available phenolic disinfectants are the coal-tar disinfectants. The aim of the manufacturer here is to offer a concentrated solution which can be diluted for use. Since, as mentioned earlier, many of these phenolic substances are insoluble, concentrated solutions must be formulated. This leads in turn to the main classes, the first of which is (*a*) the clear fluids which, on dilution, give clear solutions or emulsions, and (*b*) the concentrated emulsions which are stable on dilution.

The phenols which are used are classed as coal-tar derivatives.

There are three main types of carbonisation of coal—in all of which the tar is of secondary importance.

1. Low temperature carbonisation (for smokeless fuels), the phenols are separated from the tar and used, but the hydrocarbons which are present have too high a paraffin content to be of much use in disinfectants.

2. Vertical retorts in which the hydrocarbons contain about 20 per cent of paraffins and hence are of limited use.

3. Horizontal retorts (coke ovens) in which the hydrocarbons are almost free from paraffin.

Tars from the various methods are often mixed for distillation purposes. Low temperature and vertical retort phenols usually have a higher proportion of polyhydric phenols present which become discoloured, especially in alkaline solution.

Modern fractionation methods usually collect the phenol, *ortho*-cresol, a mixture of *meta*- and *para*-cresols, the xylenols and ethyl phenols in a high degree of purity. The main use of these is in the plastic industry with a smaller use for cresol used for lysol.

The middle oils, distilling between 205°–230°, are usually washed with alkali to leach out cresols and phenol which are separately recovered, and the rest is used for the preparation of low coefficient black fluids which are often reinforced with xylenols.

The high boiling tar acids (HBTA) distilling over 230° are very complex, usually containing more than 30 different phenols. The HBTA from low temperature carbonisation tars which contain a high proportion of

polyhydric phenols are usually treated to remove these. The HBTA from vertical retort tars are used without treatment, but they often redden if no antoxidant is present in the formula and so give what is sometimes known as red-emulsion type black fluids. The HBTA from horizontal retort tars give white-emulsion type black fluids. The hydrocarbons from the horizontal retort tars are used as carriers in black fluids.

Black fluids contain about 20 per cent of water and are clear solutions of coal-tar phenols with hydrocarbon carriers solubilised by a suitable soap. Resin, castor oil, palm kernel, coconut, fish oil or naphthenic acid soaps are used. White fluids are concentrated emulsions of the phenols stabilised with protective colloids such as glue and contain 45 per cent or more of water.

Black fluids dilute to emulsions with soft waters whereas white fluids dilute with hard or soft waters.

Black fluids are more stable on storage. A black fluid made with the same phenolic fraction as a white fluid is more bactericidal. The bactericidal activity increases with increase in phenol content, with the boiling range of the phenol used, and can also be increased by careful addition of carriers, which are usually aromatic hydrocarbons, especially in white fluids and soap-based fluids.

Organic matter reduces the bactericidal activity (based on Chick Martin test) of all fluids but those based on HBTA and those with added carriers are most affected.

The bactericidal power of lysol, which may be regarded as the simplest black fluid, varies with the soap used to formulate it, a useful point to remember is that soaps that give lower bactericidal activity usually give less opalescent solutions when the lysol is diluted.

Formulations of the Solution of Chloroxylenol type can be regarded as special cases of black fluids but, as stated earlier, the use of chlorinated phenols, whilst increasing the bactericidal power against some organisms, usually produces in a narrower specturm.

Hydrocarbon oils are used as "carriers" in black and white disinfectant fluids. Alone, they have no bactericidal value but they enhance the effect of the phenols. The phenolic fraction dissolves in the carrier which forms the disperse phase in the white fluids and is solubilised by the soap in the black fluids from which it is thrown out of solution on dilution.

It is to be regretted that the bactericidal activities of these formulations have been judged by phenol coefficient tests against *Salm. typhi.* HBTA, as was stated earlier, do show specificity and *Salm. typhi* exhibits higher specific sensitivity to HBTA than to phenolic fractions of lower boiling point.

There is little published information on the sporicidal activity of the phenols, and it has been suggested that some bacterial spores will survive for long periods in 5 per cent phenol, but all attempts by the author to isolate such a spore have so far proved unsuccessful.

Uses of Phenolic Disinfectants

Phenolic, especially the coal-tar disinfectants, are amongst the cheaper preparations, and having a broad spectrum they can be recommended as

good general disinfectants. But, because of their irritant properties, prolonged contact with the skin or mucous membranes should be avoided.

In most problems of cross-infection, staphylococci are implicated and, because some results show chlorinated phenols and HBTA to be comparatively less effective against staphylococci than formulae based on unchlorinated phenols of lower boiling point, the latter should be used.

Phenols, too, are less affected by organic matter than other types of disinfectant, and the soaps used in their formulation have detergent properties.

In conclusion, since, it seems likely that phenolic disinfectants will retain their place as good general purpose disinfectants, continued research to elucidate the problem of soap-phenol solutions, mode of action, and methods of evaluation are well justified.

References

1. Kuchenmeister, *Dtsch. Klinik*, 1860, **12**, 123.
2. Lemaire, *Germer*, Balliere, Paris, 1867.
3. Lister, *Lancet*, 1867, **2**, 353.
4. Bancroft and Richter, *J. phys. Chem.*, 1931, **35**, 511.
5. Lobes, *Arch. exp. Path. Pharmak.*, 1934, **174**, 255.
6. Reichal, *Biochem. Z.*, 1909, **22**, 149.
7. Richardson and Reid, *J. Amer. chem. Soc.*, 1940, **62**, 413.
8. Pulvertaft and Lumb, *J. Hyg. (Camb.)*, 1948, **46**, 62.
9. Gale and Taylor, *J. gen. Microbiol.*, 1947, **1**, 77.
10. Bean and Walters, *J. Pharm. Pharmacol.*, 1955, **7**, 661.
11. Quastel and Wooldridge, *Biochem. J.*, 1927, **21**, 148.
12. Bach and Lambert, *C.R. Soc. Biol.*, Paris, 1937, **126**, 298.
13. Sykes, *J. Hyg. (Camb.)*, 1939, **39**, 463.
14. Lockemann and Ulrich, *Z. Hyg. Infectionkraft.*, 1932, **113**, 475.
15. Berry, *J. Pharm. Pharmacol.*, 1951, **3**, 639.
16. Topley and Wilson, *Principles of Bacteriology and Immunity*, Arnold, London, 1955, p. 160.
17. Cook, *Pharm. J.*, 1959, **129**, 333.
18. Mather, *Biometrics*, 1949, **5**, 127.
19. Coulthard, *Brit. J. exp. Path.*, 1931, **12**, 331.
20. Tilley, *J. Bact.*, 1939, **38**, 499.
21. Grubb and Edwards, *ibid.*, 1946, **51**, 205.
22. Kuroda, *Biochem. Z.*, 1926, **169**, 281.
23. Lundy, *J. Bact.*, 1938, **35**, 633.
24. Gould, Frigeris and Hovanesia, *Antibiot. Chemother.*, 1957, **7**, 457.
25. Wagner, cited by Bennett, *Adv. appl. Microbiol.*, 1959, **1**, 135.
26. Walker, *Plant and Soil*, 1954, **5**, 194.
27. Wild and Hinshelwood, *Proc. Roy. Soc.*, 1933, B., **142**, 427.
28. Philips and Hinshelwood, *J. chem. Soc.*, 1953, 3679.
29. Coulthard, Marshall and Pyman, *ibid.*, 1930, 280.
30. Suter, *Chem. Rev.*, 1941, **28**, 269.
31. Berry and Stenlake, *Pharm. J.*, 1942, **148**, 112.
32. Berry, *Pharm. J.*, 1959, **129**, 340.
33. McBain, *Trans. Farad. Soc.*, 1913, **9**, 99.
34. Stauff, *Kolloidzschr.*, 1939, **89**, 224.
35. Berry and Briggs, *J. Pharm. Pharmacol.*, 1956, **8**, 1143.
36. Alexander and Tomlinson, *Surface Chemistry*, Butterworth, London, 1949, p. 317.
37. Berry, Cook and Wills, *J. Pharm. Pharmacol.*, 1956, **8**, 425.
38. Berry and Cook, *ibid.*, 1950, **2**, 217.