THE CHEMOTHERAPY OF VIRUS DISEASES, WITH BRIEF CONSIDERATION OF THE INFLUENCE OF DIETARY, HORMONAL AND OTHER FACTORS IN VIRUS INFECTIONS[1]

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I. INTRODUCTION

From the point of view of chemotherapy, animal viruses may be divided into two groups—a smaller more or less effectively controlled by a number of existing remedies, and a larger for which as yet there exist only hints of ultimate therapeutic control. The former comprises viruses of the psittacosis-lymphogranuloma group, the latter all other viruses. The groups are separated also by differences in size, in morphology, and perhaps in manner of replication, and some authors relegate the larger viruses of the psittacosis-lymphogranuloma group to a separate class intermediate between the "true" viruses and the bacteria. Indeed their very susceptibility to known chemotherapeutic remedies is taken as one item of evidence justifying their exclusion from the class of viruses. Without entering the field of taxonomic controversy, we have chosen to include them in this review and to maintain the distinction made in the opening sentence.

[1] Since this article went to the press, there have appeared two noteworthy publications relevant to the subject reviewed. Whereas the present is very largely a factual record of clinical and experimental achievement in the treatment of virus diseases, and of such observations as seem to the authors to have a possible bearing on the chemotherapy of the future, these other and longer reviews approach the subject from different points of view.

Matthews and Smith (275a) discuss at some length the theoretical background to chemotherapy, especially in relation to the metabolism of nucleic acids; the authors cover the field of plant and animal viruses and bacteriophages, though they exclude viruses of the psittacosis-lymphogranuloma group.

The review of De Ritis, Coltorti and Giusti (82a) considers in somewhat greater detail the material included in our section on the smaller viruses, and proceeds to discuss the biochemical manifestations associated with viral growth in the tissues; the latter part summarises adequately the authors' own work on enzymatic activity of the tissues in several viral infections. Once more, viruses of the psittacosis-lymphogranuloma group are excluded.

Viruses have long been recognised as obligatory intracellular parasites, and during recent years several lines of study have further emphasized their close dependence upon the metabolic processes of the host cell, or rather perhaps upon the perversion of those processes, for their own perpetuation. The problem of chemotherapy of diseases caused by the smaller viruses is that of selectively influencing processes very near to those essential to the life of the host without endangering its safety—an objective once widely held to be unattainable even in the case of the relatively independent pathogenic bacteria, but one now realised for these and for the rickettsiae and the larger viruses. As facts accumulate, it would not seem unreasonable to harbour a restrained optimism regarding the future, though whether the objective will be attained by preventing infection of the susceptible cells, by influencing "synthesis" of the virus within the cell, or by direct action on formed virus remains to be seen. However, both on general grounds and from what little direct evidence exists of different metabolic paths concerned in the replication of different viruses, it seems most unlikely that a single chemical substance will operate against all the viruses at present untouched by chemotherapy, and it may well be that in different instances diverse methods of protection will be found.

It is a cliché that in any infection the general health of the host is of prime importance, and nowhere is this more true than in the field of virus diseases. For many years it has been known that the well-being or otherwise of the host may determine the precise response to infection with a virus, and of late many workers have succeeded in influencing the course of events by dietary, hormonal or other means. As the knowledge gained may not be without relevance to the chemotherapy of the future, we have thought fit to include a brief section summarising this work.

II. VIRUSES OF THE PSITTACOSIS-LYMPHOGRANULOMA GROUP

A. Experimental Studies

The sulphonamides. The first substances shown to be therapeutically active against lymphogranuloma were some of the earlier sulphonamides and a closely related sulphone. Although today they have been largely superseded by more potent remedies, this early work is of interest both from the historical aspect and because it established a general pattern of therapeutic response common to all effective agents yet studied.

Following encouraging preliminary reports from the clinics (144, 165, 244, 304, 385, 391), Bär (26), Levaditi (248, 249, 250, 251), and MacCallum and Findlay (269) demonstrated almost simultaneously the activity of several sulphonamides and of 4:4′-diaminodiphenylsulphone against lymphogranuloma in mice or in guinea-pigs. As new sulphonamides appeared other workers established their merit (27, 57, 254, 282, 377). It soon became clear that the different sulphonamides are not equally effective; sulphadiazine, sulphathiazole and sulphaguanidine are among the more active (54, 110, 112, 216). The precise order of activity differs according to whether it is estimated in terms of blood levels of drug

achieved by a given regimen of dosing or according to actual dosage *per os*; on the former basis the order of descending activity is sulphamerazine, sulphaguanidine, sulphadiazine, sulphathiazole, sulphanilamide, and sulphapyridine, on the latter sulphaguanidine takes fourth instead of second place (215). The outcome of therapy may, however, be determined partly by the route of inoculation of virus (110), and by the particular strain used for infection (386)[2]; some strains appear to be but little influenced by the sulphonamides (204). Overdosage is definitely injurious (215).

Most writers failed to detect an action of the drugs on the virus *in vitro*, unless at very high concentrations (57, 215, 248, 269, 359, 377), or in tissue cultures in which neither cells nor virus were actively growing (90). Holder *et al.* (189) claimed a loss of virulence of virus held for one hour at 37°C, one hour at room temperature, and overnight in the refrigerator in the presence of sulphonamides. As apparently, allowing for the natural deterioration of virus so treated, there was no difference between the effect at one hour and at twenty-four hours, the significance of the observation is not wholly clear.

Although growth of virus in the treated animal is partly suppressed, it is not completely inhibited, and clinical symptoms of disease are commonly present during or after the period of therapy; in mice injected intracerebrally, however, virus does not spread so readily to the spleens of treated animals as it does in controls (359). All authors agree that virus persists, for periods of up to a year or more (215, 358, 359), in the tissues of clinically-recovered mice. Jones *et al.* (215) and Rake (345) considered that the carrier-rate is lowered by achieving high mean blood levels (8.5 mg./100 cc.) of the drug at the time of the initial infection, and also by a course of therapy repeated some time after the infection. Carrier-strains of virus may be of lower or higher virulence than those used to initiate infection, and they may possess various degrees of resistance to the drug (215, 345, 359, 377). With other therapeutic agents, evidence exists that it is the immunity engendered during the period of therapy which prevents unrestricted growth of the virus when dosing ceases (202, 204), and the same is no doubt true of the sulphonamides.

The earlier conflicting reports on the effect of simultaneous dosing with *p*-aminobenzoic acid (PABA) (113, 147, 312, 359, 383) probably resulted from different balances struck between the therapeutic potency of the sulphonamide administered and the opposing dose of the inhibitor, which incidentally is excreted much more rapidly than the sulphonamide; these earlier data suggested a degree of inhibition less complete than obtains with some bacteria. In more careful quantitative work, Huang and Eaton (199) found that *p*-aminobenzoic acid reverses the action of minimal therapeutic doses on lymphogranuloma or mouse pneumonitis. In mice the PABA:sulphadiazine reversal ratios were between 800:1 and 200:1, in the yolk-sac between 1:2 and 1:10, that is, many times the figure obtained by Morgan in psittacosis (see below). The PABA:sulphanilamide

[2] A strain of greater resistance than usual was not known to have been previously exposed to the drug, but the possibility exists that the patient providing the strain had acquired infection from a treated case.

ratios in the mouse were between 4:1 and 1:1. By itself *p*-aminobenzoic acid is without action on lymphogranuloma (166).

The different viruses of the psittacosis-lymphogranuloma group are not equally susceptible to the action of the sulphonamides. While experimental mouse pneumonitis responds to therapy with sulphathiazole and sulphadiazine even better than does lymphogranuloma, the viruses of meningo-pneumonitis (antigenically related to psittacosis) and feline pneumonitis are not affected by these drugs or by sulphamerazine (172, 173, 346, 347). Sulphamerazine, however, is less effective against mouse pneumonitis in hamsters, in which host as in cotton rats large doses of the drug possess some activity against feline pneumonitis (99). The difference in response in the mouse and the hamster is not explained by the greater virulence of the feline virus for the mouse or by the level of drug attained in the blood, since this latter is lower in the hamster than in the mouse. Expressed quantitatively, in the hamster ten times as much drug is needed to influence feline pneumonitis as is effective against mouse pneumonitis in the same species, but in the mouse more than two hundred times the dose fails to produce an effect. In the yolk-sac of the chick embryo also, sulphamerazine does not inhibit the growth of feline pneumonitis, whereas it is very active against mouse pneumonitis (99). Simultaneous exhibition of *p*-aminobenzoic acid abolishes the action of sulphadiazine on mouse pneumonitis (265).

Several groups of workers (49, 204, 364) have found the sulphonamides devoid of useful action against various strains of psittacosis or psittacosis-like virus, but apparently two classical American strains (Gleason and 6BC) respond to therapy with sulphadiazine in both eggs and mice (90, 289, 466), though considerable multiplication of virus occurs in the presence of the drug (147). Here again host differences are apparent in the lower blood levels needed for successful treatment in the mouse as compared with the chick embryo. Morgan (306) found that *p*-aminobenzoic acid and several other substances inhibit this therapeutic effect of sulphadiazine against psittacosis (strain 6BC) in the yolk-sac. Thus, with a standard dose of 2.5 mg. of the sulphonamide, the following substances were antagonistic in the amounts stated: *p*-aminobenzoic acid 0.005 mg. (inhibition of competitive type), pteroylglutamic acid 0.05 mg. (inhibition not of competitive type), pteroic acid 0.05 mg., pteroyldiglutamic acid 0.1 mg., pteroyl-γ-diglutamic acid 0.1 mg., pteroyltriglutamic acid 0.1 mg., pteroylaspartic acid 0.5 mg., N-methyl-pteroic acid 5 mg. (possibly attributable to contaminating *p*-aminobenzoic acid). Glutamic and *p*-aminohippuric acids were inert. The therapeutic action of penicillin is not thus inhibited. Morgan suggested that the sulphonamides may prevent growth of psittacosis virus by interfering with its use of *p*-aminobenzoic acid for the synthesis of pteroylglutamic acid, and that pteroic acid may be an intermediate step in the synthesis. He further showed (307, 308) that while vitamin B_{12} does not inhibit the action of sulphadiazine, 1,000,000 units of citrovorum factor (equivalent to about 0.05 mg. pteroylglutamic acid) does. Adenine, guanine, xanthine, hypoxanthine, thymine, thymidine, cytidylic acid and an enzymatic digest of desoxyribosenucleic acid all fail to do so. Golub (147) needed rather larger amounts of *p*-aminobenzoic and pteroylglutamic acids to neutralise the effect of sulphadiazine.

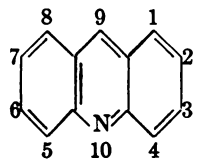
Neitz (314, 315) reported that Uleron (N^1,N^1-dimethyl-N^4-sulphanilylsulphanilamide) possesses some activity against the organism responsible for heartwater in sheep, and Francis (130) that sulphathiazole is slightly active against that of ewe-abortion. Rake and Hamre (346) found sulphamerazine to be without action against the endotoxins produced by agents of the psittacosis-lymphogranuloma group.

We have noted that strains of lymphogranuloma recovered after treatment with sulphonamide may possess various degrees of drug resistance. Golub (147) obtained complete resistance of psittacosis virus to 20 mg. sulphadiazine in the chick embryo after 10 passages in the presence of the drug. Resistance persisted through 18 further drug-free passages and was manifest also to sulphathiazole and sulphamerazine. The resistant virus was morphologically identical with the parent strain by electron microscopy. Loosli *et al.* (265) easily developed sulphadiazine-resistant strains of mouse pneumonitis; resistance persisted through 11 passages in untreated mice and was evident also against sulphathiazole, sulphamezathine, sulphanilamide and sulphaguanidine. Sulphazoxidine had no effect on either resistant or non-resistant strains of the virus.

Other synthetic substances. In addition to the sulphonamides, other synthetic chemical substances exist with therapeutic action against the largest viruses; over the years we ourselves have detected activity, seldom of high order, in a number of wholly different chemical types. Usually the substances in question have possessed both anti-bacterial and anti-viral properties, but in at least one instance the anti-viral compound has been innocuous for bacteria alike *in vitro* and *in vivo*.

Among these other substances are various acridines. Using in mice a strain of psittacosis virus isolated from man and apparently of fair virulence, Mauer (276) obtained good results with trypaflavin (acriflavine) sometimes even when treatment was delayed until the onset of symptoms of disease. In most of his experiments, however, intraperitoneal administration of drug followed closely upon that of virus by the same route. The treatment of intranasal infection does not appear to have been quite as successful. Working independently, Eaton *et al.* (96) and Hurst (201) noted activity in various nitroacridines. The latter reported that "Nitroakridin 3582", 9-(3-diethylamino-2-hydroxypropylamino)-2:3-dimethoxy-6-nitroacridine dihydrochloride,[3] developed in Germany as an anti-rickettsial agent, was less effective than penicillin and considerably more active than sulphadiazine or sulphamezathine against the very virulent M.O.H. 154 strain of psittacosis virus in mice; it was less effective against intranasal than

[3] The system of numbering the acridine nucleus in this review is as follows:



where in other papers a different method has been followed, the appropriate change has been made.

against intraperitoneal or intravenous infections. It also prolonged the survival of eggs inoculated with lymphogranuloma. A concentration of 1:1000 did not inactivate psittacosis virus in 1 hour *in vitro*. Eaton *et al.* found that the above-mentioned nitroacridine together with the corresponding butylamino compound and acriflavine inhibited yolk-sac infections with the viruses of feline pneumonitis, lymphogranuloma and meningo-pneumonitis; the first also had some effect on mouse pneumonitis. Respiratory infections caused by the feline pneumonitis virus in mice were retarded by the two nitroacridines, which, however, had little or no effect against mouse pneumonitis, lymphogranuloma or meningo-pneumonitis given intransasally; it will be recalled that mouse pneumonitis and lymphogranuloma are beneficially influenced by the sulphonamides, whereas feline pneumonitis in mice is not. Proflavine, atabrine (mepacrine) and drugs closely allied to the nitroacridines except for the substitution of —Cl for —NO_2 had no significant action. Hurst was unable to demonstrate an influence of "Nitroakridin 3582" against smaller viruses such as influenza, equine encephalomyelitis, louping-ill or St. Louis encephalitis; as we shall see later, atabrine, a chloroacridine, and some other acridines show considerable activity against several of these viruses in mice, and it is of present interest to note that we have as yet encountered no compound in which activity against the largest viruses coexists with action against the smaller. The significant structural distinction determining specificity for the larger or for the smaller viruses does not, however, reside in the presence or absence of the —NO_2 group (unpublished observation).

Eaton *et al.* (101) observed similar differences from the activity of the sulphonamides with other nitro compounds. In mice sodium *p*-nitrobenzoate, *p*-nitrobenzamide, *p*-nitrobenzamidine and *p*-nitrobenzenesulphonamide, all were more or less active against the virus of feline pneumonitis, but only the last, presumably because of its sulphonamide moiety, was active against mouse pneumonitis. Chloramphenicol was active against lymphogranuloma and slightly against mouse pneumonitis, but only at very large doses against meningo-pneumonitis and feline pneumonitis. At doses toxic for some mice, four derivatives of 5-nitro-2-furaldehyde exerted an action against all four viruses. The *p*-nitrophenyl compounds reduced the growth of feline pneumonitis virus in the chick embryo (allantoic cavity or yolk-sac), and chloramphenicol was more effective in the allantoic cavity than in the mouse (Hurst *et al.* below). "Nitroakridin 3582" was more effective than the nitrofurans against meningo-pneumonitis in the allantoic cavity, but the reverse obtained in mice.

To summarise: while highly sensitive to sulphonamides the agent of mouse pneumonitis is relatively resistant to most nitro compounds, while of feline pneumonitis, meningo-pneumonitis and some strains of psittacosis virus the opposite is true. Lymphogranuloma responds to therapy both with sulphonamides and with at least some nitro compounds.

With a fifth nitrofuran Oddo and Eaton (316) found that the virustatic effect on meningo-pneumonitis virus in the allantoic sac is reversed by cysteine given as long as ninety-six hours after the drug. Cysteine did not reverse the action of chloramphenicol, or *p*-hydroxybenzoic acid the action of either substance.

Eaton *et al.* (102) further demonstrated an inhibitory action of *p*-arsenobenzamide and its dithioglycollate (arsenamide) against mouse pneumonitis and feline pneumonitis in the lungs of mice, and of the latter compound against meningo-pneumonitis and feline pneumonitis in the allantoic sac.

In the category of substances active in eggs but not appreciably active in mice fall some aromatic diamidines (103). Propamidine and pentamidine, but not stilbamidine, inhibit the growth of feline pneumonitis, and less effectively that of meningo-pneumonitis in the chick-allantois; in mice, however, the remedies are but indifferently active against these infections and mouse pneumonitis. In eggs pentamidine almost equals nitroacridines in its efficacy.

To date, the synthetic compounds most highly active against the largest viruses are probably the quinoxaline-1:4-dioxides (202). Although inactive *in vitro*, in the mouse infected intraperitoneally, intranasally or intracerebrally, they evoke an excellent response even though treatment is deferred until some animals are moribund. The therapeutic effect is associated with greatly restricted growth of virus, and often during the period of therapy none can be demonstrated. Nevertheless, a majority of mice remain carriers, almost certainly for life, without however conveying infection to others; the exact percentage depends partly on dosage. The drugs are effective against massive infecting doses of virus, on occasion even more so than against minimal doses, a fact probably explained by the greater antigenic stimulus provided by the larger doses of virus during the period when its growth is largely suppressed by the drug. Of ninety-three substituted quinoxaline oxides examined, the best were approximately equal to chlortetracycline in the therapy of lymphogranuloma in the mouse, but less effective against this infection in the chick embryo or against psittacosis in the mouse. Individual compounds did not always exhibit the same relative order of activity against these infections. Drug resistance to these compounds easily develops, without cross-resistance to penicillin or chlortetracycline. Their therapeutic effect is not abolished by simultaneous exhibition of vitamin K, as potential antagonists to which McIlwain (281) prepared quinoxaline oxides.

Alergant (13) confirmed the clinical activity of the quinoxaline-oxides in man, in which subject, however, they manifest toxic properties precluding their clinical use.

The antibiotics. The synthetic chemist has indeed been unfortunate in the attempted chemotherapy of diseases caused by the largest viruses, for in the post-sulphonamide era each discovery of appreciable activity in one of his products has been forestalled or accompanied by the emergence of a new and more powerful antibiotic. Of those currently available, chloramphenicol, penicillin, the tetracyclines, erythromycin and carbomycin all exhibit major activity.

Heilman and Herrell (182, 183), Parker and Diefendorf (319), Bedson and May (32) and Meyer and Eddie (291) reported the activity of penicillin against various strains of psittacosis, ornithosis[4] or meningo-pneumonitis virus in chick embryos, mice or rice-birds, and Meiklejohn *et al.* (289) and Wiseman *et al.*

[4] Ornithosis is the name suggested by Meyer *et al.* (295) for psittacosis-like viruses isolated from birds other than psittacines.

(466) compared its effects on ten different viruses of the psittacosis-lymphogranuloma group. In the yolk-sac or allantoic cavity large doses of the antibiotic (250–2500 units) were needed to combat the 6BC and Gleason strains of psittacosis virus and the Borg and S-F viruses isolated from outbreaks of a psittacosis-like disease in man; smaller doses the pigeon ornithosis, the feline, mouse or hamster pneumonitis, and the lymphogranuloma viruses; and very small doses (10 units) the Cal.10 meningo-pneumonitis virus. The antibiotic was effective also against such of these strains as, by reason of their pathogenicity, were capable of being tested in mice. Early and Morgan (90, 91) demonstrated an effect in tissue cultures, as well as in eggs and mice, and showed that in the last much depends on the route of inoculation of virus. Against large doses of 6BC virus injected intravenously, sulphadiazine or penicillin (up to 8,000 units daily orally or subcutaneously) were capable of protecting all or nearly all the mice; the sulphonamide was slightly the more efficacious (up to 100 per cent and 83–96 per cent survival, respectively). Against intranasal infection with large amounts of virus, sulphadiazine greatly surpassed penicillin (100 per cent and 18 per cent survival, respectively). Against even small doses of virus introduced into the brain sulphadiazine protected only 11 per cent, penicillin none.

Similar relative behaviour on the part of penicillin has been noted by others (204). The lack of influence on cerebral infections is due, no doubt, to the inability of the antibiotic easily to pass the blood-brain barrier, and when it does do so after inflammation has been established it frequently causes convulsions (345); the highly favourable results reported by Levaditi and Vaisman (252, 253) against intracerebrally injected lymphogranuloma must be considered exceptional.

Contrary to the findings with the 6BC strain of psittacosis virus, against non-American strains penicillin is vastly more active than are the sulphonamides (32, 204). Hamre and Rake (173) found the agent of lymphogranuloma more sensitive than that of feline pneumonitis; growth of both viruses in chick embryos was restricted over the period during which penicillin could be detected. Eaton *et al.* (98) estimated that about twenty times as much penicillin is needed to increase the mean survival time of embryos infected with feline pneumonitis and meningo-pneumonitis as is necessary with mouse pneumonitis. The amount permitting survival of all embryos for twelve days is four to fifteen times that needed to produce a recognisably increased survival-time. To counteract a 300-fold increase in the inoculum of virus, about ten times the amount of drug is required. From this, as from earlier work, it is also clear that larger doses of antibiotic are needed to produce equivalent effects if treatment is delayed (or with the same dose a lesser effect is produced), and that many surviving animals or embryos remain carriers of virus. Sterilisation of the infection is more easily attained with the more susceptible organisms and with enhanced dosage of the antibiotic. Pure crystalline penicillin does not inactivate virus *in vitro*.

In the hands of Loosli *et al.* (266) penicillin appeared to be less effective than sulphadiazine or the newer antibiotics against air-borne infections with mouse pneumonitis virus.

Smadel and Jackson (396) used the 6BC psittacosis virus, a pigeon ornithosis virus, and lymphogranuloma virus to demonstrate the therapeutic activity of chloramphenicol (chloromycetin). In the yolk-sac doses of 0.06 mg. upwards gave a statistically significant prolongation of life with all three viruses, and with larger doses there was a direct relation between dose and activity. Distinctly better results followed treatment delayed for twenty-four hours, and an effect was seen against even large doses of virus. These authors also obtained excellent results in mice infected intraperitoneally (but not intracerebrally), even when treatment did not begin for six days. Daily oral doses of 5 mg. begun a day before infection, or daily intraperitoneal amounts of 0.75 to 1.5 mg. begun a day after, protected all mice given 6BC virus over the period of observation of twenty-one days. During therapy virus was restricted in its growth, but it was not eradicated, and with delayed treatment all animals showed signs of disease. The antibiotic had little virucidal action *in vitro*. The synthetic compound is identical in its properties with the natural product (397). Smadel and Jackson equated chloramphenicol with penicillin and sulphadiazine in the treatment of these virus infections, but Eaton *et al.* (101) did not consider it greatly superior to other nitrocompounds, unless on the ground of lower toxicity. Hurst *et al.* (204), while finding it superior to penicillin in the treatment of lymphogranuloma in chick embryos, obtained disappointing results against this disease and psittacosis in mice if the period of clinical observation were sufficiently prolonged; unlike animals treated with penicillin or with the tetracyclines, those given chloramphenicol often tend to relapse and die at a late stage. The drug is also unsatisfactory in the treatment of feline pneumonitis evoked by intranasal infection of mice (237), but highly effective even in delayed treatment of air-borne infections with mouse pneumonitis (266).

Undoubtedly, the most effective present remedies against the group of infective agents under consideration are the tetracyclines. Wong and Cox (468) reported that, although inactive *in vitro*, chlortetracycline (aureomycin) in amounts of 1 mg. protected chick embryos against massive doses of 6BC virus, and that similar results obtained with lymphogranuloma, S-F human pneumonitis, mouse pneumonitis, feline pneumonitis and meningo-pneumonitis. In mice, as few as three daily doses, each of 1 mg. subcutaneously, protect against a moderate dose of psittacosis virus given intraperitoneally twenty-four hours previously. The antibiotic is equally active against intracerebral infections with psittacosis or lymphogranuloma. It is effective against large inocula of virus, and after considerable delay in starting treatment. With sufficiently large doses the mice never exhibit any signs of illness. Wagner (455) and Wagner *et al.* (456) demonstrated activity against ten strains of viruses of the psittacosis-lymphogranuloma group. Wells and Finland (463) showed that, on a molecular basis, chlortetracycline is five times as active as is chloramphenicol against 6BC virus in the yolk-sac. Loosli *et al.* (266) proved the tetracyclines to be very efficacious against air-borne infections with mouse pneumonitis virus.

Injecting lymphogranuloma into the yolk-sac, Hurst *et al.* (204) arranged the active antibiotics in the following descending order of activity: oxytetracycline

(terramycin), chlortetracycline, chloramphenicol, penicillin. Using the organisms of sheep-abortion (shown to be susceptible to the tetracyclines and to chloramphenicol by Francis (130)) and mouse pneumonitis on the chorio-allantoic membrane and administering drug into the yolk-sac, Inkley (208) listed the antibiotics in the same order; penicillin is inactive against the former virus but active against that of mouse pneumonitis. Against lymphogranuloma and two strains of psittacosis injected intraperitoneally in the mouse, however, oxytetracycline and chlortetracycline appeared approximately equal in activity and clearly superior to procaine penicillin, which in turn is better than chloramphenicol (204). Chlortetracycline (oxytetracycline was not tested on this point) has the further advantage of being equally active against intraperitoneal, intranasal and intracerebral infections. The foregoing differences in therapeutic efficacy in the mouse are reflected day by day in the curves of viral growth, which during therapy is very markedly suppressed by chlortetracycline (even to the point of virus being undetectable on the seventh day), less so by penicillin, and only retarded in reaching its maximum by chloramphenicol.

After therapy is discontinued a modest but not unrestricted increase in virus may take place. Examining individually the spleens of very large numbers of mice surviving as a result of treatment, Hurst and his associates (204) found that despite the superior therapeutic action of chlortetracycline, the percentage of carriers after its use is much higher than among animals given penicillin; this somewhat unexpected discovery may partly be explained by assuming that it is the more susceptible animals which remain carriers—since nearly all mice survive therapy with chlortetracycline, the more susceptible animals live to swell the total of carriers, whereas with a higher mortality in the penicillin-treated groups some of these susceptibles will have succumbed. The detailed analysis, however, suggested that this is not a complete explanation of the facts, and that there exists a genuine difference in the "sterilising" capacity of the two drugs. The carrier-rate with both drugs is also higher among those animals in which treatment began early, *i.e.*, among those with the highest proportion of survivors, and here it seemed that elimination of the more susceptible mice from the groups treated late might well be the whole explanation. There was some suggestion that treatment of carriers naturally recovered from infection might reduce their numbers, though this observation did not accord with the earlier findings of Quan *et al.* (340) that neither chlortetracycline nor penicillin diminished the carrier-rate in parakeets. However, Schmidt and Sprockhoff (379) by suitably large doses of chlortetracycline administered parenterally during the active stages of infection were able to eradicate virus completely from their mice, and more recently Meyer and Eddie (293, 294) have shown that conscientious and prolonged treatment (fourteen to twenty-five days) with large doses of the tetracyclines, preferably tetracycline itself, may free infected birds from psittacosis or ornithosis virus.

Manire and Meyer (272) were unable to influence the immediate toxicity of large intravenous doses of Louisiana (Borg), S-F and feline pneumonitis viruses by treatment with penicillin or chlortetracycline, but they reduced that of certain strains of psittacosis and ornithosis of which the toxins are less rapidly lethal

possibly through being more firmly bound to the virus particle. Here toxicity would depend on proliferation of the virus, which is of course restricted by the drug.

The effect of chlortetracycline on meningo-pneumonitis virus is not reversed by cysteine (316).

Like James *et al.* (209) who used the virus of feline pneumonitis, Hurst *et al.* (202) failed to engender drug resistance in mice infected with lymphogranuloma and psittacosis viruses and treated with subcurative doses of chlortetracycline or penicillin; indeed, in the presence of these antibiotics, it is difficult to maintain the viruses serially, as after a number of passages they frequently die out suddenly. Loosli *et al.* (265) maintained the mouse pneumonitis virus in penicillin-treated mice for 83 passages without engendering resistance. However, by passing feline pneumonitis virus serially in the yolk-sac in the presence of increasing quantities of penicillin, Moulder *et al.* (311) induced drug resistance which attained a maximum after 33 passages and persisted during 20 drugless passages. In the presence of the drug, the altered virus grew at half the normal rate but it killed all the embryos. In the absence of penicillin it was equally virulent as the parent strain for chick embryos but far less so for mice. Parent and resistant strains were equally susceptible to the tetracyclines, but the latter had acquired greater sensitivity to chloramphenicol. During the earlier drugless passages the resistant strain grew in plaque form, as does a normal strain when exposed to penicillin (see below).

Three more recently discovered antibiotics influence infections caused by the psittacosis-lymphogranuloma group of viruses. Erythromycin (ilotycin) is active against meningo-pneumonitis and lymphogranuloma viruses (280, 334); against the former given intranasally to mice its activity equals that of chlortetracycline, but against lymphogranuloma similarly introduced the drug is less successful. It also protects mice against air-borne mouse pneumonitis virus (266).

Tanner *et al.* (427) stated without further amplification that carbomycin (magnamycin) is active against psittacosis. Wong *et al.* (469) found orally or intraperitoneally administered carbomycin to be highly effective against psittacosis virus injected intraperitoneally into mice, even when the infecting dose was very large and treatment delayed until symptoms of disease appeared. A single intraperitoneal dose of 1 mg. protected against 125 LD_{50} virus administered twenty-four hours previously. The drug is several times more effective than chloramphenicol, but like that antibiotic and erythromycin, and unlike the tetracyclines, it does not benefit intracerebral infections with psittacosis or lymphogranuloma.

The latest antibiotic, D-4-amino-3-isoxazolidone (oxamycin, cycloserine), lengthens the survival time of eggs infected with feline pneumonitis, but is far inferior in efficacy to chlortetracycline (74).

Mention may be made of another microbial product, xerosin, capable of transiently suppressing the pulmonary lesions of mouse pneumonitis without decreasing the infective titre of the lungs (161). This general phenomenon will be considered in detail later, in connection with influenza. Xerosin was said to en-

hance the effect of chlor- and oxytetracycline and of chloramphenicol on mouse pneumonitis.

Observations on the mode of action of active substances. Confirming the therapeutic effect of penicillin and of chlortetracycline on infections of the yolk-sac with the viruses of feline and murine pneumonitis, Weiss (462) and Gogolak and Weiss (145) followed the morphological changes in the virus accompanying the action of the drugs, and Hurst *et al.* (202) later published similar findings for lymphogranuloma treated with these antibiotics or with quinoxaline-1:4-dioxide. Under the influence of penicillin administered soon after infection, the viral particles continue to grow but not to divide, and viral plaques up to 6 μ in diameter may result. During the period in which penicillin persists in the embryonic fluids, infection of new cells occurs far less readily than usually, and advanced infection of the yolk-sac is delayed for from five to seven days. Given at a later stage (462), the drug is capable of affording protection up to forty-eight hours before the expected death of the embryo, *i.e.*, up to the beginning of the last complete developmental cycle of the virus. Weiss believes that the enlarged forms exert their usual toxic action on the embryo. Loosli *et al.* (266) noted similar changes in mouse pneumonitis virus treated with penicillin in the mouse; the virus reverted to its normal form within forty-eight to seventy-two hours of discontinuing the drug. Chlortetracycline and quinoxaline oxide greatly retard the development of the virus; the former prevents division of the initial bodies (145), *i.e.*, of the first developmental stage of the virus, and can produce an effect even if administration is deferred to within twenty-four hours of embryonic death. In our experiments the giant plaques characteristic of the action of penicillin did not occur with chlortetracycline or quinoxaline oxide. These observations furnish visual evidence that none of the three drugs is virucidal but that they only modify infection.

The morphological appearances agree well with the studies made by Allen *et al.* (14) on the development of infectivity in the presence of chlortetracycline. The antibiotic does not affect extracellular (centrifuged and washed) Cal.10 meningo-pneumonitis virus. When both are applied to the allantoic membrane, the antibiotic does not interfere with adsorption of virus, but acts by causing an extension of the latent period of viral growth. Administered within the first six or eight hours, it completely inhibits multiplication during the interval of time corresponding to the first cycle of growth, but after eight hours viral synthesis has passed beyond the stage at which it can be blocked completely. With falling concentration of chlortetracycline in the membrane virus resumes its growth. The times of appearance (in hours) of virus in various embryonic structures were as follows:

	Membrane	Liver	Brain
Untreated embryos	24	48	72
Treated embryos	120	144	None at 192

Combined therapy with active substances. The simultaneous exhibition of more than one therapeutically active substance is not necessarily advantageous. In detailed observations on several bacteria, *in vitro* or *in vivo*, Jawetz and his col-

leagues (163, 211, 212, 213, 405) demonstrated that chlor- and oxytetracycline and chloramphenicol may interfere with the action of streptomycin or of penicillin, and sulphadiazine with that of penicillin. Price *et al.* (338) had already shown that *in vitro* antagonism or synergism between a pair of antibiotics might be evident only within certain narrow limits of drug concentration, and that sometimes antagonism might occur at certain relative concentrations, additive or synergistic effects at others. Spicer (406) also noted the various effects of different pairs of antibiotics. Since Jawetz *et al.* (210) further observed that the precise effect obtained depended on the bacterial species under test, and even on the strain of organism within a single species, their results do not automatically apply to viruses, and few definitive observations are on record in this field. However, Early and Morgan (91) found a combination of sulphadiazine and penicillin no more effective than either agent separately in reducing the carrier-rate in mice infected with 6BC psittacosis virus. Again, in lymphogranuloma Hurst *et al.* (202, 204) obtained worse results by combining therapy with procaine penicillin and chlortetracycline than by employing the latter alone, while the combination of quinoxaline-1:4-dioxide with either of the antibiotics was less effective than any of the agents given separately.

Summary. Experimentally, viruses of the psittacosis-lymphogranuloma group are susceptible to chemotherapy with a variety of chemical substances of synthetic or natural origin. To any one substance the different members of the group are not equally susceptible, and the order of relative susceptibility varies according to the substance under test. Moreover, the active substances themselves are of very unequal potency; the best available at present are the antibiotics of the tetracycline group. The pattern of therapeutic behaviour with even the most potent drugs is similar to that observed initially with the sulphonamides. The very active quinoxaline-oxides and the purest preparations of the antibiotics have little or no effect on the viruses *in vitro*, that is to say when the viruses are not actively multiplying. During therapy of infections in the experimental animal the titre of virus in the organs drops, perhaps to the point where virus is undetectable. Nevertheless, unless therapy is very intensive, and greatly in excess of that necessary to produce an excellent clinical result, when dosing ceases virus reappears and many animals remain carriers indefinitely. The exact proportion carrying virus depends partly on the level of dosage, partly on the time of starting treatment, and partly on the particular drug employed.

B. Chemotherapy in Clinical Practice

The facts that individual viruses of the psittacosis-lymphogranuloma group behave differently towards the various chemotherapeutic remedies, that the identity of the host may to some extent influence the outcome of therapy, at least with the less effective agents, and that two of the diseases caused by viruses of the group, namely trachoma and inclusion blennorrhoea, are difficult to study experimentally and to evaluate clinically, all combined to render it anything but a foregone conclusion that the experimental results would consistently be reproducible in man. It is the more gratifying therefore to record a fair measure of agreement between the experimental data and reports from the clinics.

Lymphogranuloma venereum. Gjurić (144) first reported that sulphonamides (the prontosils and uliron), administered with or without antimonials which experimentally have never been shown to possess activity against the causative agent, acted beneficially in lymphogranuloma. Many similar reports followed rapidly (165, 244, 304, 385, 391). The consensus of opinion seems to be that the more acute lesions, inguinal adenitis, ocular infection, etc., respond to therapy, although the drugs may have to be administered for weeks to avoid the risk of recurrence. Improvement also occurs in some cases of longer duration (esthiomène and ano-rectal complications), whether because of an effect on secondary invaders or on the lymphogranulomatous process itself, or on both. Obviously, a dense fibrous stricture cannot be thus removed, and the chronic cases may require months of treatment and the assistance of surgery; it was largely in such cases that Wright *et al.* (475) were not impressed with the action of the sulphonamides, or of penicillin either. Nevertheless, it would appear from the review of Koteen (240) and the papers of Tucker (452) and Costello and D'Avanzo (72) that treatment in the era of sulphonamides on the whole yielded much more favourable results than did the palliative measures available earlier, especially in the earlier stages of the disease. Heyman *et al.* (185) isolated the causative agent from the inguinal lymph nodes of two untreated cases for as long as ninety-five days after the onset of illness, while in nine cases treated with sulphathiazole they failed to do so after the second or third week of therapy. In a further patient, in whom a relapse followed a Frei test six months after the initial infection and four months after treatment with 120 g. sulphathiazole, virus was identified; thus, as in the experimental animal, the sulphonamides do not certainly sterilise the infection.

Willcox (465) found that in small doses penicillin was no more effective than the sulphonamides, but with larger doses (1 mega unit in three days) rapidly obtained a clinical cure in early cases. Woodward (472) used chloramphenicol with similar advantage and disappearance of the characteristic viral inclusions. Robinson (357), however, from the results in three patients thought chloramphenicol disappointing. Wright and his colleagues (339, 476) noted very rapid improvement in acute cases treated with chlortetracycline, and while the antibiotic did not reduce the fibrosis in cases of rectal stricture it nevertheless descreased the pain, discharge and bleeding. Runyan *et al.* (365) showed that virus, previously isolated repeatedly in mice and eggs, disappeared from the buboes of two cases after the second day of treatment. Fletcher *et al.* (121) obtained their best results in acute inguinal adenitis and early rectal lesions. Robinson (357), while admitting a degree of improvement in his series of acute cases, stated that "the results . . . lend a tempering influence to the enthusiasms which might be engendered by Wright's group", and Schamberg *et al.* (376), also treating acute cases, assessed the antibiotic given for up to sixteen days to be about as effective as sulphonamide given for a much longer period. Wammock *et al.* (457) considered chlortetracycline more valuable in chronic than in acute cases; combined with daily manual dilatation during the course of therapy, it produced marked improvement in rectal stricture, in spite of a high proportion of toxic manifestations

at the dosage employed (2 g. daily, total 20–40 g.). Cases of inguinal bubo responded variously and ulcerative lesions poorly. Wright *et al.* (477) treated twenty cases successfully with oxytetracycline, which evoked a response similar to that of chlortetracycline; they recommended continuation of therapy after disappearance of symptoms in order to avoid the risk of recurrence. Tetracycline was effective in two cases of acute lymphogranuloma (274).

Erythromycin has been reported as active by Banov and Goldberg (25) and Cordice *et al.* (70) but is less effective than either chloramphenicol or the tetracyclines.

Psittacosis and ornithosis. We have seen that, experimentally, different strains of psittacosis virus do not respond equally to therapy, and the clinical reports also are in greater conflict than is the case in lymphogranuloma; generally speaking psittacosis and ornithosis seem more difficult to control by chemotherapeutic measures. While improvement has sometimes been claimed from the use of sulphonamides (*e.g.*, 186), most observers have not demonstrated their value (168, 255, 318, 449). More physicians have found penicillin of use (122, 235, 318, 453), alone or in conjunction with sulphadiazine (361), provided that the dosage is adequate (291); however, this experience has not been universal (43, 167, 168), and the antibiotic failed to eradicate virus from a human carrier years after his initial infection (291, 292). More consistent success has followed administration of chlortetracycline, on several occasions after penicillin had failed to benefit the disease (35, 43, 156, 167, 168, 415, 451, 472), and in a laboratory outbreak with a very virulent virus originating in the turkey Pollard *et al.* (332) found both chlortetracycline and oxytetracycline to be effective therapeutic agents.

Trachoma and inclusion conjunctivitis. Because of the relatively greater importance of secondary infections in the clinical course of trachoma, and of the differences in severity of the disease in different parts of the world, the situation here is less easy to assess. By different observers, the sulphonamides have been considered ineffective in treatment, as useful adjuncts to therapy, or as curative agents in themselves; they have been administered topically or systemically, or by both routes. In the earlier encouraging reports (28, 50, 51, 124, 180, 234, 256, 262, 354, 442) several authors noted the disappearance of the characteristic inclusion bodies as a result of medication. Corneal lesions apparently respond sooner than do the conjunctival, and papillary hypertrophy regresses more rapidly than follicular hypertrophy. Poleff (331) claimed an action both on secondary infection and on the trachomatous follicle if treatment began sufficiently early; intensive therapy resulted in sterilisation of the lesions. By 1943, Thygeson (443) was able to cite many successes of sulphonamide therapy and concluded that adequate dosage over a sufficiently long period could lead to rapid and complete healing of the ocular lesions, a conclusion endorsed by Bellows (33). Julianelle *et al.* (219) and Smith *et al.* (399), on the other hand, believed that while the effect on secondary infection was considerable a true cure did not result. Julianelle and Smith (220) showed that even at a concentration of 1:300 sulphanilamide does not destroy, within a period of five hours at room-temperature, the infectivity of trachomatous material for the monkey, but of course its action

might be exerted only on actively growing virus *in vivo*. Sorsby (401) stated that locally applied sulphacetamide combined with expression of the follicles on one or more occasions, and preferably supplemented by systemic treatment with sulphonamide, will effect a clinical cure, and Siniscal (394), from experience with 3,500 patients, maintained that both because of their intrinsic activity and because of their blandness, the more highly soluble sulphonamides (sulphafurazole, sulphacetamide) and sulphadiazine, etc., constitute the first therapeutic choice and are demonstrably superior to the antibiotics. Inclusion conjunctivitis is also benefited by the sulphonamides (441, 443, 445).

Despite a few favourable results (79, 136, 402, 403) penicillin does not appear to have established its value in the treatment of trachoma or inclusion conjunctivitis (246, 444). Pijoan *et al.* (328) claimed that orally administered chloramphenicol reduced the acute inflammatory process and cleared the pannus in cases of trachoma. Braley and Sanders (44), Bellows *et al.* (34), Raïs and Arroyo (344), Shah (387) and Cat (55) obtained good results with chlortetracycline in trachoma, and Boase (38), Sarkies (371) and Ching (59) considered it superior to sulphonamides or penicillin in ameliorating the acute symptoms, while doubting its action on the trachomatous pannus. Duke-Elder *et al.* (88) found it useful in inclusion conjunctivitis resistant for months to the sulphonamides and to penicillin. Similar reports attended the entry of oxytetracycline into therapeutics (56, 301); early trachoma responds promptly and well, chronic cases are best assisted by expression or curettage combined with oxytetracycline. Applying different local treatments to the two eyes, Mitsui and Tanaka (300) found oxytetracycline superior to chlortetracycline and both to be preferable to chloramphenicol in the treatment of trachoma; the first two were effective also in inclusion blennorrhoea. With treatment started within the first week of infection, trachoma was cured in seven to ten days. Started in one to two months a cure was effected within two to five weeks. Chronic trachoma needed two to three months before the follicles disappeared entirely, but concomitant surgery shortened this period. Not all the cases so treated were contaminated by bacteria, and as viral inclusions began to degenerate within twenty-four hours and disappeared in a week, the observations suggest a direct action on the virus.

Primary atypical pneumonia. Clinically, the disease passing under this name is difficult to distinguish from psittacosis, ornithosis, Q fever, etc., or alternatively these may be regarded as individual examples of a clinical state of diverse aetiology (255, 286, 395, etc.). From cases of primary atypical pneumonia, Eaton *et al.* (105) claimed to have isolated in eggs a further virus capable of evoking lesions in the lungs of cotton rats and hamsters, and Eaton *et al.* (100) that this virus was serologically related to the disease. Eaton (92) reported that growth of the virus could be inhibited by chlortetracycline in cotton rats or eggs. Eaton *et al.* (107) found that its growth could be inhibited in eggs by chloramphenicol, and partially, in eggs or in cotton-rats, by two 5-nitro-2-furaldehyde semicarbazones, *p*-nitrobenzaldehyde semicarbazone and *p*-acetylaminobenzaldehyde thiosemicarbazone, and Eaton (94) that it responds to therapy with the tetracyclines, erythromycin, carbomycin, and streptomycin. Other authors have

failed to detect a virus transmissible to laboratory animals in material from similar cases (75), though the Commission on Acute Respiratory Diseases (68) produced evidence of serial transmission to human volunteers with bacteria-free filtrates of sputum or pharyngeal washings.

Although the various severities of the cases makes assessment of the results of therapy far from simple, many clinical trials, some carried out with great care, have suggested a beneficial action of some of the newer antibiotics. In selecting cases to be treated, one or more of the following diagnostic criteria have often been adopted: (a) the presence of characteristic signs and symptoms, including radiological evidence, (b) the failure to respond to therapy with sulphadiazine or penicillin, (c) the absence at any stage of serological evidence of infection with known viral or rickettsial agents, and (d) the frequent appearance of cold haemagglutinins for human group O erythrocytes, or of agglutinins for certain strains of non-haemolytic streptococci. In larger or smaller series of such cases, Brainerd *et al.* (43), Finland *et al.* (115), Kneeland *et al.* (238), Meiklejohn and Shragg (287), Schoenbach and Bryer (381), Collins *et al.* (67), Schoenbach *et al.* (382), all reported rapid and prompt defervescence and clinical recovery following exhibition of chlortetracycline, even though there might be little change in the radiological picture (184); a few relapses responded to a second course of treatment. Anderson (16) noted similar good results in children in Germany, and Blodgett *et al.* (37) considered that smaller doses than those employed by the foregoing observers were adequate; the last workers used daily doses of 1–1.5 g., that is to say rather less than half those commonly employed. In two patients Finland *et al.* (115) claimed a therapeutic effect of streptomycin. Wood (470) recorded striking improvement within twelve hours in a single case treated with chloramphenicol after sulphadiazine and penicillin had failed, and Cohen and Schwartz (65) also reported a beneficial effect of this substance. Melcher *et al.* (290) obtained excellent results in 7 cases treated with oxytetracycline and thought that the side-effects of this drug were less severe than those of chlortetracycline. Comparing the results with the three antibiotics, Graves and Ball (148) found little to choose on the score of therapeutic activity, but decided in favour of oxytetracycline and chloramphenicol on the ground of lower toxicity.

Schoenbach and his colleagues (382) had clearly recognised the difficulties of evaluating the results in cases treated with chlortetracycline. For one thing, in civilian practice hospitalised patients almost inevitably represent a selected group (namely the more severely affected), and two fully comparable populations are likely to be found only in institutions or in the Armed Forces. Tillotson and Oseasohn (446) dismissed the favourable reports on chlortetracycline as inadequately controlled. Harvey *et al.* (181) in a small series of controlled cases, all of which were mild, had not proved chlortetracycline to be of value, while Peck and Berry (327) studying very completely 141 cases in Servicemen observed no significant influence of chlortetracycline, chloramphenicol, streptomycin or penicillin on the duration of illness; symptomatic improvement could not be evaluated owing to a marked tendency to spontaneous remissions. They also agreed with Blodgett *et al.* that larger doses of the antibiotic do not afford better results than

do smaller. Peck and Berry's cases, like those of Harvey *et al.* were predominantly mild, and the authors are inclined to accept the evidence for a favourable effcct of the antibiotics on the more severe cases treated by others. This opinion aecords with the recent direct observations of Meiklejohn *et al.* (288), that it is the cases with higher temperature and more severe manifestations which when treated with antibiotics pursue a clinical course significantly different from that of untreated control cases; in the belief of these writers chloramphenicol and oxytetracycline are at least as effective therapeutic agents as is chlortetracycline.

III. THE SMALLER VIRUSES

A. General

Early claims that the sulphonamides possess activity against one or other of the smaller viruses have not been substantiated, and the antibiotics which have proved so successful in treating diseases caused by viruses of the psittacosis-lymphogranuloma group have not been shown unequivocally to benefit other virus infections. An exception to this statement concerns the effect of chlortetracycline and oxytetracycline in curing clinically, and eradiacting virus from, mice suffering from "grey lung disease", and cotton-rats from a similar condition (18, 19). Chlortetracycline was effective even in chronic cases of several months duration. Chloramphenicol, procaine penicillin, streptomycin and sulphamerazine were ineffective. Andrewes (personal communication) also finds the virus susceptible to neoarsphenamine and tryparsamide.

Although no substance of practical value against the diseases of man or domestic animals has yet emerged from much work intended to find one, many instances are known of the inhibition of viral growth in particular complexes of host cell and virus. Thus many substances are capable of influencing the growth of bacteriophages, sometimes at concentrations which are not bacteriostatic (42, 58, 66, 78, 83, 85, 86, 116, 117, 118, 128, 129, 193, 214, 398, 407, 408, 474), and at this stage it is worth noting that among them are included various acridines. It is comparatively seldom that these results can be transferred to the avian or mammalian host, so that much of the information obtained appears to be of greater interest to those studying the growth and reproduction of bacteriophage than to those engaged in attempted chemotherapy. As will be seen shortly, in tissue cultures also it is relatively easy to interfere with the multiplication of viruses; this work is yielding valuable information regarding the metabolic requirements for viral growth in a cellular environment rather more closely resembling that in the diseased animal. Once again, however, but little of the knowledge accruing has yet led to advances towards effective chemotherapy. By contrast with the foregoing experimental systems, it is relatively difficult to influence the growth of viruses in the chick embryo, and still more so in the hatched chick or in the mouse. In this connection an observation of our former colleague, Mr. J. Francis, is pertinent. Francis injected many hundreds of compounds into the yolk-sac of chick embryos and found that a score or so were significantly active in restricting the lesions due to fowl-pox virus on the chorio-allantoic membrane. None of the compounds produced the slightest effect on

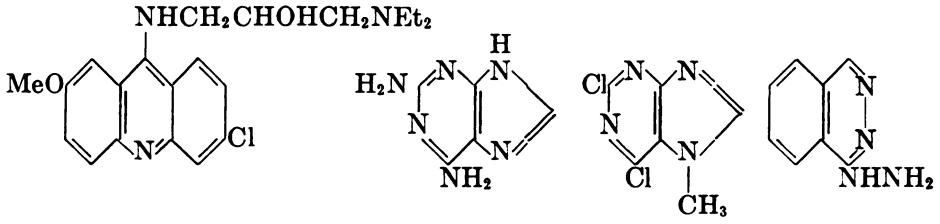
fowl-pox in the hatched bird (personal communication). On the other hand, mepacrine, which in the mouse exhibits marked activity against equine encephalomyelitis, and less activity against several other infections, is inactive against equine encephalomyelitis in the chick embryo (203). In our own experience the only instance in which there is a frequent correlation between results obtained in the chick embryo and those in the mouse is with viruses of the psittacosis-lymphogranuloma group; here we have but rarely failed to reproduce in the mouse positive results obtained in the yolk-sac, and *vice versa*.

The alternative approach to the chemotherapy of virus diseases, that of empirically screening chemical compounds against infections in the mouse, cannot be said to have achieved more than have the studies mentioned above. Coggeshall and Maier (64) examined 67 substances, including many sulphonamides and sulphones, against mouse-adapted poliomyelitis given intracerebrally and influenza A given intranasally to mice. Van den Ende *et al.* (109) screened 115 compounds against intranasally instilled influenza virus and 74 for *in vitro* activity against vaccinia, Krueger *et al.* (243) 26 compounds alone or in combination against influenza, and Kramer *et al.* (242) 190 substances against mouse-adapted poliomyelitis (intracerebrally) and St. Louis encephalitis (intranasally) in mice. All the results were essentially negative. Cutting *et al.* (77) used 150 chemicals against herpes simplex (intraperitoneally), neurovaccinia (intracerebrally) and influenza (intranasally) in mice and against egg-adapted or commercial vaccinia in the yolk-sac or on the chorio-allantoic membrane; 3-methylallantoin, 3-ethylallantoin, 1:3-dimethyluracil and ethyl-*n*-methylcarbamate lengthened the average life of the chick embryos by a fraction of a day. Wooley *et al.* (473) found 22 substances inactive against St. Louis encephalitis (intranasally) and 44 inactive against influenza A. Four of 98, all four dichlorophenoxyacetic or dichlorophenoxypropionic acids, increased the period of survival and/or the number of surviving mice infected intracerebrally with an approximate LD_{75} mouse-adapted poliomyelitis; the effects were not very marked and the authors do not exclude the possibility of a non-specific effect of the drug on the animal. Hotta (194) observed no reduction of mortality when mice infected with dengue were treated with 28 compounds; occasionally the period of survival was somewhat lengthened, but again the specificity of the effect was not established. Screening on a much larger scale has been carried out in various commercial laboratories, and it is certain that the number of compounds found to be devoid of activity against one virus or another totals many thousands.

B. Effects Observed in Tissue Culture

Many different substances have been examined in tissue cultures, with a view either to elucidating the mechanism of their action as chemotherapeutic agents or to discovering new substances with antiviral activity. Some of the advantages of this medium have been outlined by Eaton (93) and Morgan (307). In the course of this work, valuable information has been obtained regarding the energy relationships of viral propagation, but little progress has yet been made towards developing an effective drug.

The activity of a compound in tissue culture may not necessarily be the same as in more complex environments. The chloroacridine (I) inhibited growth of



I II III IV

influenza viruses in tissue culture but not in eggs (97). The amino-(II) and chloropurines (III) retarded multiplication of vaccinia virus in chick embryonic tissue but failed to protect mice inoculated intracerebrally or intranasally from a neurotropic mouse-adapted strain of vaccinia virus (436). 5-Chlorouridine (454) and 1-hydrazinophthalazine (Apresoline) (IV) (322) which inhibited the propagation of Theiler's GD VII strain of murine encephalomyelitis in cultures of mouse brain were inactive against this virus in mice. In contrast, substituted 5-phenoxythiouracils, although only moderately active against vaccinia virus in chick embryonic tissue gave a demonstrable protective effect in mice (437).

Because of the many diverse compounds which have been used in work with tissue cultures, division has been made into their respective chemical groups. As will be seen, the choice of compounds under test has been determined either by (a) their capacity to act as inhibitors of enzyme systems, (b) their structural relationships to known naturally occurring substances such as amino acids, vitamins, etc., or (c) pure empiricism.

Aliphatic compounds. Thompson (431) has shown that sodium iodoacetate, and to a lesser extent sodium malonate prevented the multiplication of vaccinia virus in chick embryonic tissue. Iodoacetate probably acted by combining with, and so rendering unavailable for viral proliferation, vital thiol groups in the tissue enzyme systems (29). Malonate, an enzyme inhibitor (31, 341), also retarded the production of influenza virus in the chorio-allantoic membrane (1). In this instance the inhibition might be related to blockage of the tricarboxylic acid cycle.

Iodoacetate (321), L-lysine and a metabolic product ketoglutaric acid (40) inhibited the propagation of Theiler's GD VII strain of mouse encephalomyelitis virus in mouse brain tissue culture (323).

Amongst a miscellaneous group of compounds, an ester, glycerylmonoacetate, was found to inhibit the growth of poliomyelitis virus in monkey testicular tissue (46).

α-Amino acids. A list of natural and synthetic analogues of α-amino acids ($R.CHCOOH$, NH_2) tested against viruses in tissue culture is shown in Table I.

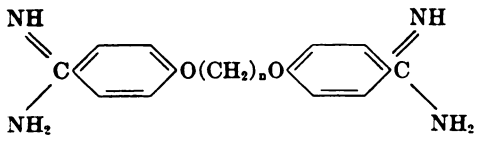
"R" has been varied over a wide range. By antagonising a given acid with a structural analogue information has been obtained of the essential characteristics

of chemical structure which can influence the virus-host metabolism. Thus the importance of methionine has been demonstrated in the biosynthesis of influenza virus in the chorio-allantoic membrane (2, 4), the Lansing strain of poliomyelitis virus in human brain cultures (47), and psittacosis virus (strain 6BC) in minced chick embryonic tissue (310). The inhibitory action of ethionine in each case could be reversed by its lower homologue methionine. Ethionine has also been shown to inhibit the propagation of Theiler's GD VII virus in mouse brain tissue (325); here reversal experiments with methionine were not carried out. Inhibition of influenza B virus in tissue culture by L-canavanine was reversed by the related amino acid, arginine (329).

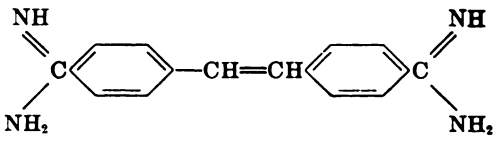
The amphoteric compound α-amino-*p*-methoxyphenylmethanesulphonic acid has been found to interfere with the lag phase of influenza virus multiplication in the chorio-allantoic membrane (8); it has been suggested that the compound interferes with the adsorption of virus or with its penetration of the cellular membrane. There may well be some analogy here with the associated reversible electrostatic attack by phage on the bacterial cell (111).

Aromatic compounds. A number of simple aromatic compounds have been found to interfere with the energy relationships between viruses and their tissue culture medium, in some cases with concomitant inhibition of viral growth. The tissue culture technique has been used in studying the inhibitory action of 2:4-dinitrophenol (DNP) on influenza virus in the chorio-allantoic membrane (93, 106). Inhibition was accompanied by stimulation of respiration, release of phosphate and activation of adenosinetriphosphatase (6). DNP allows metabolic oxidation to proceed but prevents formation of high energy phosphate bonds which are the normal purpose and consequence of metabolic oxidation: it was probably through such an "uncoupling" effect that viral inhibition took place. There was no permanent interference with the metabolic processes required for viral multiplication, nor was DNP virucidal. DNP also inhibited the growth of vaccinia (430, 431) and GD VII mouse encephalomyelitis viruses (321) in tissue cultures.

These results have stimulated interest in other compounds capable of "uncoupling" phosphorylation. Eaton *et al.* (95) have demonstrated that butyl 3:5-diiodo-4-hydroxybenzoate had similar effects to those of DNP and inhibited the growth of influenza virus in chorio-allantoic membrane. Other phenols, and their oxidation products, quinones, have been reported active against psittacosis (53) and vaccinia (430, 431) viruses grown in chick embryonic tissue.



V

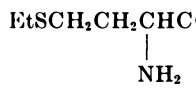
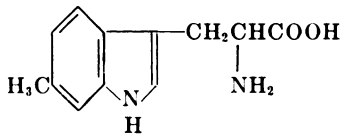
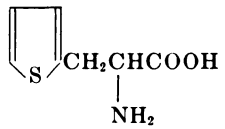
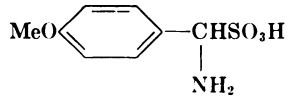
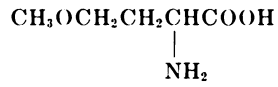


VI

Propamidine (V, n = 3), and to a lesser extent pentamidine (V, n = 5), lowered the mean haemagglutination titres of influenza A virus in de-embryo-

TABLE I

Amino Acids

Compound	Structure	Virus	Tissue culture	Reference
Ethionine		Psittacosis (6BC)	Chick embryonic tissue	310
6-Methyltryptophane				
β-2-Thienylalanine				
L-Arginine DL-Lysine DL-Ornithine		Influenza (Lee) Mumps	Chorio-allantoic membrane	104
α-Amino-*p*-methoxyphenyl-methanesulphonic acid		Early phase in development of influenza (PR8)	Chorio-allantoic membrane	8
DL-Methoxinine DL-Ethionine		Influenza (PR8)	Chorio-allantoic membrane	2
DL-Methoxinine α-Amino-*p*-methoxyphenyl-methanesulphonic acid		Particular phases in development of influenza (PR8)	Chorio-allantoic membrane	9

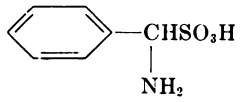
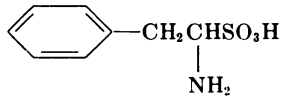
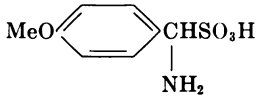
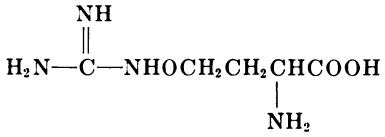
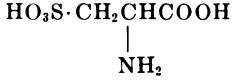
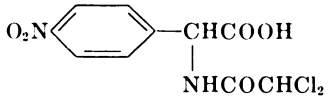
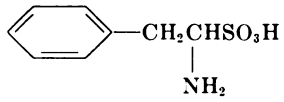
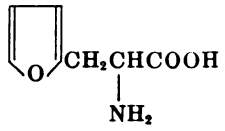
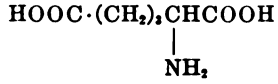
α-Aminophenylmethanesulphonic acid		Influenza (PR8)	Chorio-allantoic membrane	7
α-Amino-β-phenylethanesulphonic acid				
α-Amino-*p*-methoxyphenylmethanesulphonic acid				
Canavanine		Influenza—Lee	Chorio-allantoic membrane	329
DL-Ethionine		Poliomyelitis, Lansing strain	Human embryonic brain tissue	47, cf. 135
Cysteic acid		Poliomyelitis, Lansing strain	Monkey testicular tissue	46, cf. 135
DL-Ethionine				
N-Dichloroacetyl-α-(*p*-nitrophenyl)-glycine				
α-Amino-β-phenylethanesulphonic acid				
β-2-Thienylalanine				

TABLE I—*Continued*

Compound	Structure	Virus	Tissue culture	Reference
L-Lysine hydrochloride DL-Ethionine DL-β-2-Furylalanine DL-β-2-Thienylalanine Glutathione		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	325
Lysine		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	303
L-α-Aminoadipic acid L-Arginine hydrochloride L-Cysteine hydrochloride L-Cystine L-Histidine hydrochloride DL-Ornithine DL-Serine DL-Threonine L-Tryptophane		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	326
L-Lysine L-Histidine L-Tryptophane DL-β-2-Thienylalanine		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	342

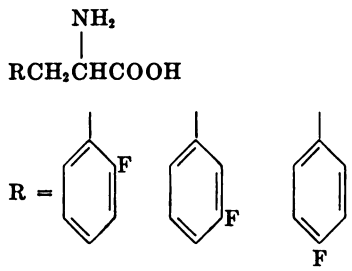
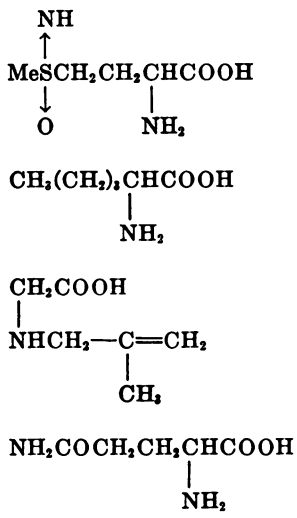
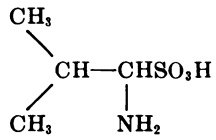
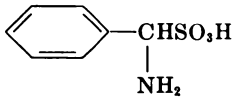
L-Lysine *o*, *m*, and *p*-Fluorophenyl-alanines		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	323
Methoxinine Methionine sulphoximine DL-Norleucine Methallylglycine Glutamine		Theiler's mouse encephalomyelitis GD VII strain	1-day old mouse brain	324

TABLE I—*Continued*

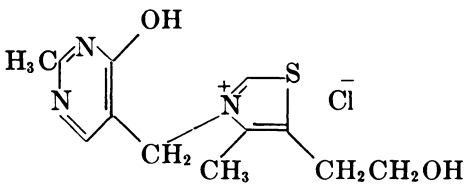
Compound	Structure	Virus	Tissue culture	Reference
Methoxinine		Vaccinia	Chick embryonic tissue	431
Aminomethanesulphonic acid	$NH_2CH_2SO_3H$			
α-Amino*iso*butanesulphonic acid				
α-Aminophenylmethanesulphonic acid				
β-2-Thienylalanine		Vaccinia	Chick embryonic tissue	438

nated allantoic membrane preparations (103). Further work (108) confirmed the action of pentamidine against influenza virus and showed that pentamidine and stilbamidine (VI) also inhibited the growth of mumps virus. Pentamidine retarded oxygen consumption, prolonged the lag-period and interfered with the growth of fibroblasts.

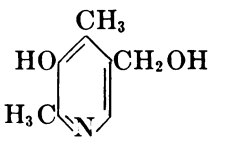
From an early lead in the form of hexylresorcinol, which was found to inhibit type 2 poliomyelitis virus Y-SK strain grown in monkey testicular tissue, further substituted phenols were also found to be effective. Some naturally occurring compounds such as glutathione were found to reverse the inhibition (241).

Thiosemicarbazones. Use of the thiosemicarbazones followed the discovery of their activity against the tubercle bacillus (87). Thompson *et al.* (435) found that benzaldehyde thiosemicarbazones prevented the multiplication of vaccinia virus (CVII strain) in chick embryonic tissue. Contrary to the results obtained against tuberculosis, it was found that viral activity was reduced in compounds containing a substituent at C4 of the benzene nucleus. Later (434) the results with benzaldehyde thiosemicarbazones were confirmed against vaccinia virus (mouse-adapted; IHD strain), and extended to the thiosemicarbazones of pyruvic acid and certain heterocyclic aldehydes.

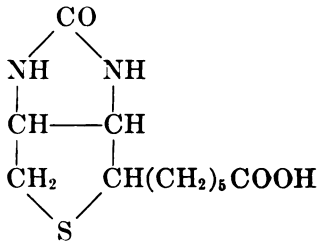
Heterocyclic compounds. Many heterocyclic compounds which have been used in inhibiting viral growth in tissue culture are structurally related to vitamins, components of nucleic acid, and other naturally occurring substances. Oxythia-



VII



VIII



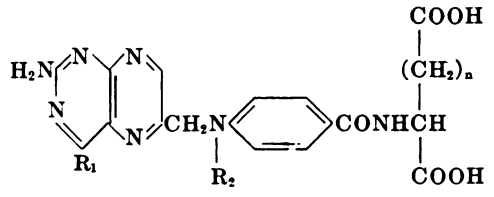
IX

mine (VII) and desoxypyridoxine (VIII), analogues of part of the vitamin B complex, inhibited the multiplication of mumps and influenza A viruses in chick embryonic tissue. Oxythiamine most likely acted indirectly on tissue metabolism by inhibiting the entry of pyruvate into the tricarboxylic acid cycle, and desoxypyridoxine by competing, after phosphorylation, with pyridoxal phosphate (76). Another analogue of the vitamin B complex, homobiotin (IX) inhibited the growth of Lansing type poliomyelitis virus in monkey testicular tissue (46).

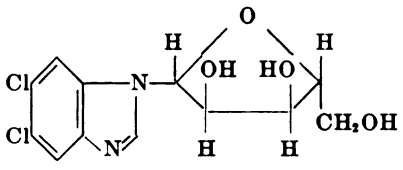
During the course of investigations dealing with possible antiviral effects of analogues of the pyrimidine moieties of nucleic acid, thiouracil was found active against psittacosis virus (6BC) in chick embryonic tissue (309). In a similar culture, a nitroaryl (439) and a number of α-haloacyl (440) derivatives of various 5-aminopyrimidines inhibited proliferation of vaccinia virus. Substitution at

C5 has also been extended to 5-aryloxypyrimidines. Although samples of this series were only moderately active against vaccinia virus in chick embryonic tissue (437), it was of interest that 5-(2:4-dichlorophenoxy)thiouracil was active against vaccinia infection in mice and acted as a synergist with isatin thiosemicarbazone (30). 5-Chlorouridine inhibited the propagation of Theiler's GD VII virus and the uptake of $P^{32}O_4^{\equiv}$ by the ribonucleic acid fraction of minced mouse brain. The analogous naturally occurring nucleoside, uridine, partially reversed the effect (343). This inhibition was probably due to a block in the viral nucleic acid synthesis. Other substituted nucleosides also have inhibitory action (454). Analogues of other basic components of nucleic acid, the purines, interfere with viral proliferation. 2:6-Diaminopurine has shown activity against poliomyelitis (46, c.f. 135), Russian spring-summer encephalitis (132), psittacosis (6BC) (308), vaccinia (436) and Theiler's GD VII strain of murine encephalomyelitis (454) viruses in tissue culture. The inhibitory action could be reversed by adenine but not always by guanine (132, 436). No explanation has been put forward for the reported activity of some natural components of nucleic acid, namely adenine, adenosine, cytidine, guanosine and thymine. 8-Azaguanine, which may be incorporated into nucleic acid (245, 271) exerts an inhibitory action against psittacosis virus (6BC) in minced chick embryonic tissue (308); this effect was reversed by guanine. Halogenated analogues, for example 2:6:8-trichloropurine, were inhibitory against vaccinia virus but their effects were not reversed by adenine (436).

Studies (307, 308) on the pteridines, some of which have been found to counteract the inhibition of psittacosis (6BC) growth by sulfadiazine (306), have lent support to the belief that pteroylglutamic acid (X, R_1 = OH, R_2 = H, n = 2) may be an essential factor for the growth of the virus. 2-Amino-4-hydroxy-6-formylpteridine, xanthopterin and some compounds related to pteroylglutamic acid [4-amino-pteroylglutamic acid (R_1 = NH_2, R_2 = H, n = 2), 4-amino-N^{10}-methylpteroylglutamic acid (R_1 = NH_2, R_2 = CH_3, n = 2), and 4-aminopteroylaspartic acid (R_1 = NH_2, R_2 = H, n = 1)] were inhibitory to psittacosis virus (6BC) in chick embryonic tissue; the last two compounds were antagonised by the citrovorum factor. 4-Aminopteroylaspartic acid also suppressed the growth of meningo-pneumonitis virus in tissue culture.



X



XI

The function of vitamin B_{12} seems to be closely connected with that of the folic acid group; it is not surprising therefore that compounds similar in structure to the benzimidazole portion of the vitamin have been used in attempts to inter-

fere with viral proliferation. Benzimidazole has proved effective as an inhibitor against poliomyelitis (46, c.f. 135), vaccinia (430, 431) and psittacosis viruses (308). Among alkylbenzimidazoles which were found active against influenza B virus in chorio-allantoic membrane cultures, Tamm *et al.* selected 2:5-dimethylbenzimidazole for further study (421, 422, 423). It probably acted by reducing the rate of metabolic processes necessary for viral proliferation. Chemical modifications were made in the benzimidazole nucleus (424) by further substitution and variation of the chain length of the alkyl side-chain. Attempts to correlate the change in structure of the substituted benzimidazole with corresponding enhancement or diminution in activity against virus and microorganisms were not very successful. A closer correlation of the benzimidazole moiety with the naturally occurring benzimidazole "nucleoside" in vitamin B_{12} has been made by a study of N-glycosides of the heterocyclic portion (425, 426). Of the various pentosides and hexosides tested 5:6-dichloro-1-β-D-ribofuranosylbenzimidazole (XI) exerted considerable inhibitory action against several strains of influenza A and B virus in chorio-allantoic membrane cultures. Further experiments have been carried out to determine the mode of action of this compound. Tamm (420) has recently found that further substitution of chlorine into the benzenoid ring has increased the activity of XI some eightfold against influenza B virus in the chorio-allantoic membrane.

The acridine enzyme inhibitors atabrine (164) and proflavine (275) were effective against vaccinia (430), and proflavine against poliomyelitis (46) virus. Near the maximum tolerated dose other chloro- and nitroacridines have retarded influenza A and B and mumps viruses in chorio-allantoic or amniotic membrane cultures (97).

Viruses do not appear to be greatly influenced by heterocyclic sulfonamides (vide, *e.g.*, 239). Sometimes their addition to tissue cultures permitted growth of the virus and eliminated secondary contaminants (369). Sodium sulfadiazine was inhibitory towards actively growing psittacosis virus (strain 6BC) in roller tube tissue culture (90). Darvisul, which appeared to act against a mouse poliomyelitis virus by virtue of its reaction with the cellulose substrate was in turn antagonised by *p*-hydroxybenzoic acid (370).

Whilst investigating drugs capable of depressing the activity of the central nervous system, Apresoline (IV) was found active against Theiler's GD VII strain of mouse poliomyelitis in mouse brain tissue culture (322).

Antibiotics. Little antibiotic activity has been recorded against the smaller viruses in tissue cultures. Penicillin, for example, is often included in the cultures to eliminate bacterial contamination (*e.g.*, 1, 135). However, it is not always effective (360).

The proliferation of influenza A virus was inhibited by Antimycin A through its action upon some component of the succinic dehydrogenase system of the tissue cells (1). Pre-treatment of monkey testicular tissue culture with M.8450, another antibiotic of unknown constitution, inhibited the cytopathogenic effect of the three types of poliomyelitis virus but failed to destroy or neutralise the virus (200).

Penicillin inhibited the growth of psittacosis virus in roller tube tissue culture; streptomycin was ineffective (90).

Miscellaneous. Apart from certain extraneous materials which may interfere with viral proliferation other factors have to be taken into consideration. Thus, phosphatases, present in chorio-allantoic membrane, were found to be effective inhibitors of herpes simplex (LF strain); their action was antagonised by phosphatase inhibitors (15). It has also been found (268) that in tissue culture flasks containing a plasma clot composed of fowl plasma and embryo extract there was present, occasionally, a substance capable of inactivating a filtrate of Fujinami sarcoma virus.

Preparations rich in hyaluronic acid with or without the addition of hyaluronidase were found to inactivate vaccine virus grown in Maitland type media (89). Further studies (279) have given some indication that the activity of the preparations was due to a substance diffusible through a cellophane membrane and that it, or one of its components, was glucuronic acid or a glucuronide.

C. Effects Observed in the Chick Embryo

Different workers have introduced virus on to the chorio-allantoic membrane or into the allantoic cavity and have given drug by the same or by a different route, together with, before or after virus. When virus and drug enter by the same route, unless the former precedes the latter by an interval sufficient to allow it to be taken into the susceptible cells, the possibility of simple chemical inactivation of virus exists; moreover, many drugs in direct contact with the chorio-allantois cause damage to its cells and prevent them from responding normally to the virus. In either event the results may not betoken a true chemotherapeutic effect. When virus is introduced on to the chorio-allantois and drug into the yolk-sac, the conditions more nearly simulate those obtaining in chemotherapy in the mouse given drug intraperitoneally and virus by some other route; false positive results are avoided, although undoubtedly the danger exists that macromolecular substances or substances readily destroyed by metabolic or other processes may not reach the required site. Furthermore (208), drug given into the yolk-sac reaches and exerts any toxic action it may have on the embryo before reaching the virus, thus ensuring that an action on the latter is associated with a reasonable therapeutic index. Much of the work in the chick embryo has been done with influenza and other viruses capable of agglutinating red cells, and many workers have taken the haemagglutination titre rather than infectivity as a measure of the inhibition of viral growth.

Among substances shown to affect growth of viruses in the allantoic cavity are various acridines. Given with or before influenza B virus, "Nitroakridin 3582" prevented growth of small inocula (1–10 MID) and reduced the final haemagglutinating titre with larger infecting doses (154). Rasmussen and Stokes (349) noted an effect on both influenza A and influenza B with the nitroacridine, with "Rutenol" an arsenical salt of it, and with 9-amino-3-nitroacridine, even when given as late as twenty-four hours after infection. The effect was, however, particularly evident during the early stages of viral growth. The drugs appeared

to damage the allantoic membrane, which was atrophic in treated eggs, and the authors consider that the effect on virus may have been secondary to this damage. No effect was observed on virus *in vitro* or in mice (cf. 201). Briody and Stannard (45) reported that proflavine administered a few hours before or a few hours after virus reduced the haemagglutination titre of the allantoic fluid of eggs infected with influenza B; with different strains the ID_{50} was reduced by from 1–4 log. units. The drugs exerted no influence on the viruses of influenza A, mumps or Newcastle disease. When applied directly to the chorio-allantoic membrane two hours after vaccinia virus it reduced the number of pocks, but from what we have said earlier it seems likely that this may have been an expression of local toxicity. Eaton *et al.* (97) found that "Nitroakridin 3582" and its 3-methoxy-6-chloro analogue slightly inhibited mumps virus when both were given into the allantoic sac, but only the former inhibited influenza B. Injected into the yolk-sac the drugs were ineffective.

McClelland and van Rooyen (278) noted activity on the part of some aromatic amidines, of which hexamidine was the best, against influenza A virus in the allantoic cavity, even when administered as long as eighteen hours after virus. Sometimes the loss of infectivity amounted to 89–99 per cent. The compound was not active in mice. Stilbamidine has some effect against mumps (103). Pentamidine is active in diminishing degree against mumps, influenza B and influenza A in the allantoic cavity. In de-embryonated eggs the growth of the influenza viruses is slowed down by propamidine and pentamidine.

A number of phenanthridines reduce the haemagglutination titre of eggs receiving a small dose of influenza A (85).

Cobaltous chloride or acetate administered at the time of inoculation of influenza A and B viruses considerably reduces their growth (349, 378); the effect is most marked during the period of rapid multiplication and persists for up to thirty-two hours. When cobalt is injected at the time of infection, the LD_{50} of treated fluids twenty-four hours later may average 3 log. units less than that of control eggs. Cobalt is also effective at one and eighteen but not at twenty-four hours, and three doses at zero, twelve and twenty-four hours prolong the period of inhibition. The effect is much less pronounced with large doses of virus (1000 ID_{50}); it is overcome by histidine, cysteine and sodium thioglycollate, which form complexes with cobalt. It is not seen *in vitro* or in the mouse.

At doses toxic for some of the eggs, N-ethyl-maleimide introduced into the yolk-sac prior to introducing influenza A into the allantoic cavity completely prevents growth of virus for the first twenty-four hours, possibly by its action on —SH groups necessary for protein synthesis (355).

Green and his associates have described the virus-inhibitory activity of a number of synthetic basic polypeptides and a basic polymer. L- and DL-lysine and DL-lysine-DL-valine inhibit influenza A in the allantoic cavity (363), and the first acts also on Newcastle disease virus and a recently isolated strain of infectious bronchitis virus (151). Introduced into the yolk-sac, L-lysine of molecular weight 2400 (in the earlier papers the figure was given as 4900) inhibited mumps in the allantoic cavity, and in the allantoic cavity one of molecular

weight 16000 (20000 in earlier papers) produced significant effects in quantities as small as 1 μg., or against as many as 30000 ID virus, or with delays of up to thirty-six hours in treatment (149). With small infecting doses (6 LD_{50}) the mortality from Newcastle disease was lowered. Given an hour before virus into the allantoic cavity, the synthetic polymer, polyvinylamine caused a nine-fold reduction in the growth of influenza B (150) compared with a twenty-fold reduction with L-lysine. Weight for weight it was also less active against mumps. Nevertheless it was able to protect a proportion of eggs against a small infecting dose of Newcastle disease virus.

L-canavanine, a close structural analogue of arginine and a potent growth inhibitor for *Neurospora*, lactobacilli and *Bact. coli*, markedly inhibits the growth of influenza B introduced into the allantoic cavity one hour later (329). At a sufficiently large dose (20 mg.) it may completely suppress the formation of haemagglutinin. It may also lower the infectivity titre by 1–3 log. units. The effect lasts forty-four but not sixty-eight hours. Effects are also produced by the amino acid given two hours after virus. It does not act by interfering with adsorption of virus by the tissue and is inactive *in vitro* and in the mouse. In tissue cultures its action is reversed by L-arginine but not by lysine or glutamic acid.

A formaldehyde-tyrosine derivative inhibits the growth of influenza A in the allantoic cavity when administered before or up to four hours after virus; the drop in haemagglutination titre is accompanied by a fall in infectivity (84).

Hannoun has found that many substances hinder the propagation of influenza virus in the chick allantois. Thus aminomethanesulphonic acid, an analogue of glycocoll, and sodium malonate, hydroquinone and a mixture of fluoride and phosphate, which inhibit succinic dehydrogenase, all possess this property (175, 176). The action of malonate in tissue culture had previously been demonstrated by Ackermann (1). Very marked inhibition of viral growth occurred with *p*-acetamidobenzaldehyde thiosemicarbazone, which was not directly virucidal (177). The purine analogues benzimidazole and 2:6-diaminopurine and the pyrimidine analogues veronal and thiouracil also were inhibitory (178). Dinitrophenol, already studied in tissue-culture by Ackermann and Johnson (6) and in tissue culture and intact embryos by Eaton and Perry (106), reduced the growth of virus, presumably by its action on oxydative phosphorylation, and sodium azide by its interference with oxydative processes (179); again neither substance was directly viricidal.

Ackermann and Maassab (5, 8, 9) have studied the action of various aminosulphonic acids, and particularly α-amino-α-*p*-methoxyphenylmethanesulphonic acid, on influenza A virus. In doses well below the lethal it reduces both the haemagglutination titre and infectivity when given into the allantoic cavity fifteen minutes after virus. An effect was also claimed when the acid was administered intracerebrally to mice infected with an approximate LD_{85} neurotropic influenza virus. Subsequent work in tissue culture suggested that the acid acts at an early stage in the development of virus, affecting perhaps its adsorption on or penetration of the host cell. Once this stage has been completed replication

of virus takes place even though the acid be present, though release of virus from the cell, a process occurring over many hours and independent of a "burst" phenomenon or destruction of a cellular membrane, is hindered by the acid. Ackermann and Maassab (9) contrast the time of action of the sulphonic acid with that of another inhibitor of viral growth, DL-methoxinine, which apparently acts on a later stage of viral development. Neither compound, however, exerts any influence at a time when mature virus is forming.

Tannic acid introduced into the allantoic sac half-an-hour before a small dose (10–100 LD_{50}) of influenza A virus prevents the appearance of haemagglutinin in the fluid collected forty-eight hours later (152). It is also effective six hours before and one hour after virus, and it inactivates virus *in vitro*. Similar effects resulted from the use of an unidentified substance derived from a watery extract of tea (153).

Apple pectin, a substance capable of interfering with haemagglutination by the influenza virus, also possesses some inhibitory action when given up to one to two hours after virus injected into the allantoic sac (155).

Among antibiotic substances, several appear to exhibit some antiviral activity in the allantois. Ehrlichin (157) retards the growth of influenza B, especially when introduced after rather than before virus. Although the final titre of virus in treated eggs is the same as in untreated, many of the former survived for six days, by which time all the untreated had died. Viscosin (162) protects many eggs subsequently given 100 LD_{50} infectious bronchitis virus; the infective titre of virus in the fluid is reduced by treatment. Both substances slightly reduce the lesions of influenza in the mouse. In toxic or near-toxic doses, cardicin (270) prevents the development of haemagglutinin in eggs infected with influenza A or B when injected twenty to forty minutes prior to virus. Some plant extracts influence the haemagglutination titre in eggs receiving a small dose of influenza A (58).

Hanan (174) showed that alpha-tocopheryl esters given just before influenza A virus slightly but significantly reduced the infectivity titre as assessed at forty-eight hours.

Finally, Hoyle (198) demonstrated an effect of various triphenylmethane dyes on the multiplication of influenza A. Using doses of virus large enough to infect simultaneously all cells of the allantoic cavity, he incubated the eggs for thirty minutes, introduced the dye, incubated for a further five and one-half hours and then removed the chorio-allantoic membranes, which he washed in saline and froze and thawed three times to release the soluble antigen. This he measured by the complement-fixation technique as an indication of the degree of multiplication of virus. At doses as low as one-tenth of the toxic, several triphenylmethanes, and especially dahlia and crystal violets, greatly reduced the amount of soluble antigen. Liberation of virus into the allantoic fluid was also retarded, but reached the same final haemagglutinating titre as in untreated eggs once the dye had disappeared. Hoyle suggested that the effect arose from disturbance of ribosenucleic acid metabolism, since dyes are known to have an affinity for this substance.

A few further substances influencing production of virus in the allantoic cavity receive mention in the next section.

D. Effects Observed in the Mouse

We have remarked that effects noted in tissue culture or in the allantoic cavity are but rarely transferable to the hatched chick or the mouse. From time to time antiviral action has been described in these or other animals, but in the opinion of the reviewers the significance of some of these observations is doubtful. It is common knowledge that an animal weak or sickly from any cause may not respond typically to infection with a virus, and if the impaired state of health results from administration of toxic doses of a chemical substance the modified infection cannot be accepted as evidence of successful chemotherapy. In our own experience, a substance prone to yield such false-positive results is dithiobiuret, described by Astwood *et al.* (22) as the cause of a reversible paralysis of mice; at many levels of dosage, however, the symptomatology includes a considerable element of spasmodic rigidity of the limbs (personal observation). In rabbits given large doses of dithiobiuret, we succeeded in reducing the size of the initial lesion and in almost completely suppressing the exanthem of infectious myxomatosis resulting from intradermal injection of virus, and again in doubling the period of survival of rabbits infected intradermally with the virus of Aujeszky's disease. The dosage was such that discontinuance of the drug at the time of death of these animals allowed uninfected controls to survive. Nevertheless all infected rabbits died and virus was present in the lesions. Under these circumstances we do not accept the modified clinical picture as indicating a true chemotherapeutic response. Our own criteria in choosing doses of chemical substances to minimise the risk of false-positive results have been placed on record (202). With this preliminary caution we may proceed to examine alleged effects in the mouse, etc.

Influenza and other respiratory diseases in the mouse. In the mouse influenza is in many ways an unusual type of infection which, in our experience, does not lend itself very readily to experimental chemotherapy. In the first place the method commonly used for infecting mice, that of intranasal instillation of virus, is grossly inaccurate in respect of the amount of virus introduced (41). Secondly, the cause of death of the mice, or alternatively the score of pulmonary lesions, is not necessarily related directly to the growth of virus. According to the infecting dose, virus reaches a maximum titre in the lungs in from twenty-four to forty-eight hours or slightly later, at a time when only microscopical lesions are present and the mouse exhibits little or no ill effect of the infection. Later when the titre of virus is falling sharply, a peculiar tissue reaction leading to pulmonary consolidation develops and, if the mouse dies, it does so not from the direct effects of the virus but from asphyxia. It is known, moreover, that strains of virus not yet fully adapted to mice may multiply to as great an extent as they ever will without causing pulmonary consolidation (187), and conversely that the infectious particles of the virus of Newcastle disease may, in the mouse, produce extensive pulmonary consolidation in the absence of demonstrable

multiplication (52, 80, 137). In short, as Ginsberg and Horsfall point out (143), multiplication of the virus is not the sole factor responsible for influenzal pulmonary lesions in the mouse. Quite apart then from the possibility of modified lesions resulting from toxicity of a compound, an apparent chemotherapeutic effect may reflect interference with the full development of the tissue reaction rather than a direct action on the growth of virus.

Over the years we have examined several hundred compounds for activity against influenza in the mouse (unpublished observation). A number have caused significantly reduced pulmonary scores on the conventional seventh day of infection. Most of these have merely delayed the appearance of pulmonary consolidation, for the scores of treated and untreated animals at a later stage (eleven to eighteen days) have been identical; in these instances the mean period of survival was increased by treatment but the eventual mortality unaffected. A smaller number of compounds actually reduced the final degree of pulmonary consolidation and, in nearly thirty consecutive experiments, the best of these, diethylaminomalonate, significantly increased the number of animals surviving with doses of virus up to LD_{100}. Daily titrations of pooled lungs, however, revealed no compound which prevented virus from reaching the same titre at forty-eight hours as that in controls; aminomalonate itself had no effect on the growth of virus, but three compounds, including a quinoxaline-1:4-dioxide, slightly retarded the virus in reaching this titre and accelerated its subsequent fall, *i.e.*, the titres at twenty-four hours and four and seven days were rather lower in the treated animals. Among the compounds giving negative results, or even increasing mortality in the mice, were Furacin, tetrahydrofuran, butyrolactone, etc., claimed by Rubin and Giarman (362) to be therapeutically active in influenza in the mouse.

Seeler *et al.* (384) described a slight but consistent retarding effect of quinine on the course of influenza in the mouse, leading to an increased number of survivals on the tenth day, and when given intravenously at near-toxic doses Janus green B and safranine-pyrazolon-sulphonamide apparently show a similar effect (120).

In the category of substances modifying the tissue reaction caused by viruses of the influenza group falls xerosin, a metabolic product of *Achromobacter* sp. and previously designated APM (159, 160). It suppresses the pneumonia produced by non-multiplying Newcastle disease virus and also, though transiently, the lesions of influenza A virus, without influencing the maximal titre attained by the latter. It operates only when administered parenterally during the period of rapid extension of the lesions, and is no more effective against small than against larger doses of virus. It is inactive *in vitro* and in the allantoic cavity. Groupé *et al.* believe that xerosin competes with some cellular constituent which combined with virus causes the pulmonary damage. With the non-multiplying virus of Newcastle disease, a sufficient amount of xerosin enables the cell to rid itself gradually of virus, but with influenza A, which does multiply, continuing viral synthesis overwhelms the xerosin and suppression of the lesions is but transient. Xerosin given subcutaneously also delays the toxic manifestations of

large doses of influenza A or B virus injected intracerebrally but not intravenously. A small intracerebral dose before but not after infection also protects against virus given by the same route (158).

In contrast, a crystalline antibiotic isolated from cultures of *Nocardia formica* appears to have rather different properties (277). Given parenterally or orally it markedly increases the mean period of survival in infections with influenza A or B or with swine influenza, and the lungs at twenty-four and forty-eight hours contain much less virus, as estimated by their haemagglutination titres, than do those of controls. It is active against mumps and Newcastle disease virus in the chick embryo, and against the latter in tissue culture but not in chickens. It does not suppress the pulmonary consolidation evoked by Newcastle disease virus in mice, and is inactive against Col.-SK encephalitis in mice, hog-cholera in pigs, enteritis in mink and infectious hepatitis in dogs.

Sodium monofluoroacetate interferes with the Krebs cycle and doubles the citric acid content of the mouse lung in half-an-hour, trebles it in an hour and raises it ten-fold in eight hours; thereafter the level falls. Ackermann (3) showed that a dose of 2 mg./kg. inhibited by more than 1 log. unit, and 3–5 mg./kg. by more than 2 log. units, the growth of influenza virus when given twelve hours after infection. The effect was seen also at fifteen minutes and six hours, and with a thousand-fold range of infecting doses. Mogabgab and Horsfall (302) found the higher levels of dosage lethal for 10–20 per cent of mice; nevertheless they observed little effect on the titre of influenza A virus at thirteen hours, though the effect with influenza B was rather greater; in neither case was the ultimate titre of virus lowered. In the chick embryo, two and one-half lethal doses injected into the yolk-sac slightly delayed growth of virus in the allantois without influencing its final titre. Similar slight delay occurred in the multiplication of the pneumonia virus of mice in the mouse lung and of mumps virus in the chick embryo. Three daily doses definitely reduced the titre of the pneumonia virus of mice, but animals similarly treated and infected within a few hours of the third dose supported undiminished growth of virus. The authors concluded that the cellular metabolic processes blocked by fluoroacetate are not essential to these viruses.

We may interpolate that Ainslie (10) noted similar delay in reaching maximum titre with mouse-adapted poliomyelitis virus (type 2) and Watanabe *et al.* (458) with Eastern equine encephalomyelitis; the former produced a lesser effect with DL-methionine sulphoximine. Francis *et al.* (131), however, by administering fluoroacetate intravenously at the time of subcutaneous infection of monkeys with type 1 poliomyelitis, or alternatively three days later, greatly shortened the period of viraemia and reduced the incidence of paralysis. As citric acid did not accumulate in the brain, and at the time of administering drug virus could not have reached the central nervous system, Francis *et al.* postulated that the inhibitor acted on some extraneural tissue important in the initiation of the infection.

An extensive series of studies on the activity of 2:5-dimethylbenzimidazole and its derivatives against influenza virus in tissue culture (see previously)

culminated in the demonstration by Tamm *et al.* (425) of similar activity in the chick embryo and mouse. One of their compounds, 5:6-dichloro-1-β-D-ribofuranosylbenzimidazole, administered twice-daily to mice infected with influenza B, beginning two hours after virus, reduced the haemagglutinating titre of the lungs at forty-eight hours to 10 per cent of that of controls. It did not inactivate virus *in vitro*, did not affect virus-erythrocyte interaction, and did not interfere with adsorption of virus by susceptible cells or the release of virus from infected cells. Its action is thus likely to be intracellular, probably by disturbing metabolic processes involving ribofuranosides; "indeed, it seems not improbable that nucleic acid metabolism is affected". The corresponding 4:5:6-trichloro derivative, which was more active in tissue culture, together with the dichloro compound both markedly inhibit the growth of mumps virus in the allantoic cavity (420).

Horsfall and McCarty (192) observed that polysaccharides derived from various bacterial species, and particularly a capsular polysaccharide of Friedländer bacillus, type B, are capable of lessening the severity of the lesions and of restricting viral growth in infections with the pneumonia virus of mice. In this disease, in contradistinction to influenza, the extent of the pneumonia appears to be a function solely of viral multiplication. The polysaccharide inhibits when given during the first two-thirds of the latent period of the cycle of growth, *i.e.*, within the first ten hours, but is not effective, as far as the first cycle is concerned, when given at twelve hours or later. However, compound administered late may inhibit the second or subsequent cycles, so that a single intranasal dose of 0.02 mg. two or three days after infection permits the animals to recover completely when all the controls die (142). Immune serum administered at this time fails to save the animals. The polysaccharide acts therefore not on the viral particle but on some relatively late stage of its formation by the host cell. It is also surprisingly active against mumps virus in the allantoic cavity, both when given into the allantoic sac and into the yolk-sac (138, 139). Under certain conditions an effect may be observed with as little as 5 μg., or when the polysaccharide is injected as long as four days after virus. Again the evidence suggests that the substance acts subsequent to adsorption of virus and involves the metabolic activities of the host cell. Continued passage in the presence of the polysaccharide results in a strain of virus resistant to its action (141). Although pneumonia virus of mice and the influenza viruses probably infect the same cells of the lung, and according to Ginsberg and Horsfall (140) produce indistinguishable lesions, the latter are not inhibited by the polysaccharide; this together with the fact that pneumonia virus or mumps infection does not interfere with growth of influenza A or B in the same tissue is taken as indication of different metabolic pathways to the synthesis of the two pairs of viruses.

Wheeler and Nungester (464) found that atropine sulphate at fifteen minutes to six hours before intranasal instillation of influenza A virus into mice under ether anaesthesia decreased the incidence and degree of infection. Five minutes after virus the drug was of no avail, and it is easy to accept the authors' explanation in terms of restricted secretion of mucus.

Thiosemicarbazones, thiouracils, etc., and viruses of the vaccinia-variola group. Hamre *et al.* (170) observed that *p*-aminobenzaldehyde-3-thiosemicarbazone, and to a lesser degree its *p*-acetamido analogue, are capable of prolonging the period of survival of eggs infected with 85–340 LD_{50} vaccinia virus thirty minutes or four hours previously; occasional eggs survived to the end of the experiment. The time of survival of intranasally infected mice is also lengthened. The former compound is inactive against meningo-pneumonitis and swine influenza viruses. Of thirteen compounds examined subsequently (171), benzaldehyde-3-thiosemicarbazone and its *p*-acetamido, *p*-amino, *p*-methoxy, *p*-propoxy and *p*-ethylsulphonyl analogues were most effective in eggs. In mice, the parent compound, its *p*-acetamido analogue, and the N4 *iso*butyl derivatives of these two substances were most active; with suitably long periods of therapy, and at doses near the maximum tolerated, treatment results in an appreciably decreased mortality.

Thompson *et al.* (435), who, we may recall, prevented multiplication of vaccinia virus in tissue culture by a low concentration (1 μg./ml.) of benzaldehyde thiosemicarbazone, also protected a substantial proportion of mice infected intracerebrally by feeding the drug, but stated that substitution in the *para* position of the benzene nucleus or in the 4-position of the thiosemicarbazone moiety destroys activity. Thiosemicarbazones containing thiophene, pyridine, quinoline or isatin groups also exhibit activity against vaccinia (434), as well as against a recently isolated strain of variola (298); in spite of the good clinical results, the titre of virus in the brains of treated animals is little different from that in controls. A high degree of therapeutic activity appears to be associated with the presence in the molecule of (a) the $=N—NH—CS—NH_2$ group, and (b) a cyclic component, but some aliphatic oxime thiosemicarbazones are also effective (432). High antiviral activity in tissue culture is not necessarily an indication of corresponding behaviour in the mouse, nor do antiviral properties run parallel with antituberculous. Though of value in the mouse, the thiosemicarbazones do not protect rabbits against vaccinia (432, 434). The various authors are agreed that the drugs are inactive against non-multiplying virus *in vitro*.

Thompson *et al.* (437) had also noted that a number of 5-phenoxythiouracils, only modestly potent as inhibitors of vaccinia virus in tissue culture, confer significant protection against intracerebral or intranasal infections in mice. Most favourable results accrued from the use of 5-(2:4-dichlorophenoxy)-4-hydroxy-2-mercaptopyrimidine given either parenterally or in the food. Although medication begun soon after infection does not prevent signs of illness, many treated animals recover, and on the whole appear to harbour a concentration of virus in the brain lower by about one log. unit than that in the controls. The compound has no action on vaccinia virus *in vitro*, and none against influenza, herpes, St. Louis encephalitis, MM or Rift Valley fever viruses in mice.

Bauer (30) considered that isatin thiosemicarbazone is much more active than previously claimed. Using an infecting dose of 100,000 LD_{50} he obtained 99.99 per cent protection of his mice, that is to say in the presence of the drug the

LD_{50} was four (or more) log. units greater than in controls; "an antiviral effect of this magnitude has hitherto only been observed with penicillin and sulphonamides in the psittacosis-lymphogranuloma group of viruses." The compound has a depôt effect, and even a single dose of 0.25 mg. given eighteen hours after infection produces a better than 50 per cent protection. Ten times this dose does not afford complete protection, however, and the titre of virus in the brains of treated animals is lowered by only one log. unit. 5-(2:4-Dichlorophenoxy)thiouracil is less active but acts synergically, so that combined treatment is better than with either drug alone. Some other phenoxypyrimidines (not all of them thiouracils) are also synergic, even when themselves devoid of appreciable antiviral activity. Bauer concluded that the two classes of compound act differently and that a factor contributed by the host may be necessary, since maximum protection is afforded by quite small doses and greatly increased doses produce no better result, as though in the brain there exists a fixed concentration of some substance essential to their action. The absence of a therapeutic effect in rabbits suggests that this factor is species-specific, but it should be mentioned that at least two entirely different chemotherapeutic agents, the antibiotic, netropsin (373) and mepacrine (206), operate against one or other virus disease in mice but not against the corresponding disease in rabbits, and alternative explanations of the phenomenon present themselves. Bauer considered also that isatin thiosemicarbazone exerts a slight beneficial effect on Rift Valley fever.

The antibiotic netropsin, at half the maximum tolerated dose given intraperitoneally twice-daily, beginning one hour after intracerebral infection, is capable of protecting the majority of mice against a small dose of vaccinia (1 LD_{50}–1 LD_{90}). It does not affect the disease in rabbits, nor does it influence feline pneumonitis, influenza A, Western equine encephalomyelitis or mouse-adapted poliomyelitis (373).

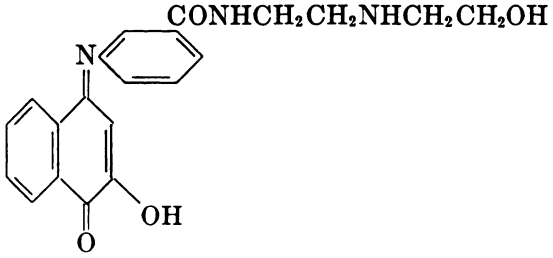
In doses which prevented normal growth of the birds, quinine appeared partially to inhibit or to retard the development of the lesions of fowl-pox in chickens (356).

Manwell and Goldstein (273) and Coulston and Manwell (73) claimed excellent results of topical therapy of canary-pox with alcohol-acetone solutions of mercurochrome.

Dyes, etc., with particular reference to the acridines. Wood and Rusoff (471) noted that intraperitoneal injections of trypan red, and of the closely related Congo red and brilliant vital red, dyes of a class known to diminish the permeability of the blood-brain barrier to convulsant drugs (11, 12, 62), protected many mice against an approximate LD_{60-70} MM virus subsequently administered by the same route. The degree of protection increased with repeated daily doses up to the third, and some protection lasted for at least a month. An effect was obtained also in the cotton rat infected intraperitoneally, but not in either species infected intracerebrally with this virus or with mouse-adapted human poliomyelitis. Trypan red was inactive *in vitro*. Hammon *et al.* (169), in animals dosed repeatedly with trypan red by the subcutaneous route, failed to engender resistance to intraperitoneally injected MM and Russian spring-summer en-

cephalitis viruses, and concluded that the foregoing results were the expression of a non-specific protection afforded by otherwise inert substances injected into the peritoneal cavity prior to the infective agent. Murray *et al.* (313) obtained erratic results in animals given intraperitoneal or oral Congo red and intraperitoneal MM virus, and considered the degree of protection not significant.

Schnitzer *et al.* (380) also could not confirm the claim of Wood and Rusoff. However, they observed activity on the part of sixty-seven of one hundred and sixty naphthoquinonimines against certain neurotropic viruses in mice and, with Jungeblut (225), considered in detail the properties of one (XII). This



XII

compound served to protect a high proportion of mice against multiple paralytic doses of Col.-SK, F and MM viruses, but not against EMC virus which is antigenically related to Col.-SK, when both compound and virus were injected intraperitoneally. When administered intravenously or subcutaneously it was less successful against intraperitoneal virus, and it was ineffective against virus given by the intracerebral, intramuscular, subcutaneous or plantar routes. Some kind of direct interaction between drug and virus was postulated.

Hurst *et al.* (203, 205) on the other hand, obtained results similar to those of Wood and Rusoff in another infection, Eastern equine encephalomyelitis, provided that the virus used was not too "virulent" and that it was introduced intramuscularly rather than intracerebrally. Some other acid bis-azo dyes, together with a diacyldiaminostilbenesulphonic acid (a cotton-substantive whitening agent used in the textile industry) and the cotton-substantive drug suramin ("Antrypol"), produced more or less marked effects which seemed to be related to the number of sulphonic acid groups in the molecule. Continuing investigation disclosed that the basic acridine drug, mepacrine (Atabrine), incidentally also a cotton-substantive dyestuff, is vastly more effective in protecting mice against infection with a limited number of viruses, of which those most influenced are the agents of Eastern and Western equine encephalomyelitis, louping-ill and Rift Valley fever. Inactive *in vitro*, against very large intramuscular inocula of virulent samples of the first two, a single maximum tolerated dose of mepacrine is capable of protecting the majority of mice when given before, together with, or even up to twenty-four hours after virus. We have since found that much smaller doses are nearly as effective. Whereas administration of trypan red is accompanied by only a slightly lowered titre of virus circulating in the blood stream during the systemic phase of infection, mepacrine reduces it greatly,

with small infecting doses even to extinction and subsequent lack of immunity of the animal to reinfection. Histological control of the experimental work demonstrated also the profound effect of mepacrine in Rift Valley fever, in which disease in most treated mice the characteristic massive diffuse necrosis of the liver is replaced by a few small foci of midzonal necrosis. In short, the chemoprophylactic effect of mepacrine in these virus infections in mice is outstanding, and probably without parallel as far as the smaller viruses are concerned. Slighter effects of the drug were noted against equine encephalomyelitis given intracerebrally, herpes febrilis intramuscularly and lymphocytic choriomeningitis, St. Louis encephalitis and louping-ill intracerebrally. No clear beneficial effect was obtained in psittacosis, Russian spring-summer encephalitis, rabies, various forms of mouse encephalomyelitis, mouse-adapted poliomyelitis (type 2), mouse poliomyelitis, Murray Valley encephalitis, grey-lung disease of mice, influenza, infectious myxomatosis, vaccinia, Aujeszky's disease or virus-induced avian tumours. Thompson and Lavender (433) found atabrine useless against Semliki Forest virus.

Since (for different reasons) both trypan red and mepacrine attain high levels in the tissues, Hurst *et al.* examined other substances known to accumulate in the tissues for power to influence equine encephalomyelitis. Some macromolecular substances injected intravenously achieved a limited success; they appeared to operate in a manner different from that of mepacrine, in that they delayed rather than suppressed the rise of viral titre in the bloodstream. The only obvious property in common between trypan red, mepacrine and these macromolecular substances is that they all tend to be concentrated in reticulo-endothelial cells.

The chemotherapeutic action of mepacrine against equine encephalomyelitis may be demonstrated also in the adolescent rat, but not clearly in the guinea-pig, baby chick, rabbit or monkey (206); the drug also does not beneficially influence louping-ill in the sheep (203). As is well known, many animals dosed with mepacrine acquire a very persistent yellow colouration of the skin and other tissues, a colouration which is associated with the widespread deposition in reticulo-endothelial and other cells of basophilic particles having the staining and biological properties of an acid molecule. First described by Siegel and Mushett (393) and Fitzhugh *et al.* (119), they have recently been studied in greater detail by Hurst *et al.* (206). Considerable variation exists between the various species of animals in their capacity to acquire this persistent colouration; for example, except for the kidney, the organs of the guinea-pig do not remain persistently coloured even after very prolonged dosing. Within the range of animal species mentioned above, there exists no correlation between the ability to acquire a yellow colour and to deposit basophilic particles on the one hand and the presence or absence of a chemotherapeutic response to mepacrine on the other. In a single species, the mouse, however, a fairly close correlation exists, in that a number of related acridines possessing antiviral activity are capable of being metabolised or fixed to some tissue constituent in such a way as to lead to the formation of these particles, whereas inactive compounds do not produce them (unpublished observation). Even in the mouse, however, suitable experiments

suggested that the basophilic particles themselves are not therapeutically active (206).

It will be noted that acridines have appeared at many points in this review. In fact, it seems alike from work with bacteriophage, with tissue cultures, with chick embryos and with mice, that many acridines possess antiviral properties; these are seldom evident in the mammalian host and the precise mechanism by which the acridines exert a protective action against certain virus diseases in the mouse still awaits elucidation.

Ciaccio *et al.* (60) noted that certain vital dyes introduced at the site of inoculation of the virus of foot-and-mouth disease in guinea-pigs were able to modify or suppress the customary lesions and in some instances leave the animals fully susceptible to reinoculation. When treatment was first applied one to three minutes after injection of virus, and repeated four times in twenty-four to forty-eight hours, janus green, victoria blue, malachite green, brilliant green, Giemsa solution and nile blue all were more or less active. When the first treatment occurred three hours before or three hours after virus, brilliant green and malachite green afforded the best protection. The authors suggest a direct interaction between the dyes and the virus; the former neutralise the virus *in vitro*, though no complete parallel exists between *in vitro* and *in vivo* effects and some dyes active *in vitro* are ineffective in the guinea-pig.

Attempts to modify the state of reactivity of the central nervous system to neurotropic viruses. It could well be imagined that substances active pharmacologically upon the nervous system might influence, in one direction or other, the growth of viruses which depend for their reproduction upon the metabolism of the affected cellular elements. On various occasions we ourselves have endeavoured without success to influence beneficially a number of neurotropic virus infections (herpes simplex, mouse poliomyelitis, rabies, Eastern equine encephalomyelitis) with drugs such as alcohol, morphine, paraldehyde, chloral hydrate, barbiturates, primidone (Mysoline), chlorpromazine, and so on, as well as with many speculative chemical compounds observed in toxicity tests to give rise to signs of deranged nervous function (unpublished observations). Jungeblut (224) observed no effect of narcotic doses of luminal, or of insulin or metrazol shock, on experimental poliomyelitis of monkeys. Schaeffer *et al.* (375) reported sodium 5-ethyl-5-*iso*amylbarbituric acid (Amytal sodium), paraldehyde, tribromoethanol (Avertin), magnesium sulphate, morphine, cytochrome C, dithiobiuret, dithiocarbamate and prolonged periods of anaesthesia with ether to have no effect in Eastern and Western equine encephalomyelitis, St. Louis encephalitis, poliomyelitis or influenza. Pearson and Lagerborg (322) found that although various barbiturates, salicylic acid derivatives, chloral hydrate, morphine, paraldehyde, urethane, alcohol, etc., inhibited the growth of GD VII mouse encephalomyelitis virus in tissue cultures of mouse brain, the most effective substance, 1-hydrazinophthalazine (Apresoline) failed to alter the infection in mice.

Sulkin *et al.* (418), on the other hand, were more fortunate. By keeping mice anaesthetised with ether for two or three periods, each of four hours, during the

incubation period of Eastern or Western equine encephalomyelitis or St. Louis encephalitis, they greatly reduced mortality in mice receiving intracerebrally a small multiple of the LD_{50}. No such effect occurred with rabies or mouse-adapted poliomyelitis, and Sulkin and Zarafonetis (417) showed that the viruses affected *in vivo* were those which are readily inactivated by ether *in vitro*, albeit at concentrations vastly greater than those likely to obtain in the experimental animal. If in the latter virus is directly inactivated by ether, there must exist considerable local intracellular concentrations of the anaesthetic, or perhaps in the actively multiplying stage virus is more susceptible to its action. The authors, however, believe that the anaesthetic operates indirectly through altered metabolism of the host. As we have seen Schaeffer *et al.* did not confirm these results.

Efforts to influence the reactivity of the nervous tissues have also been made with malononitrile, discovered by Hydén and Hartelius (207) to increase the cytoplasmic nucleic acids and proteins of the large nerve cells. Szanto and Felsenfeld (419) reported that by dosing with malononitrile on the day after infection, and again from the seventh day daily for ten days, they were able to protect 60 per cent mice given 1.3×10^3 MLD mouse-adapted poliomyelitis virus. With much larger infecting doses they obtained only an increased period of survival of the mice, as also with treatment initiated after the onset of paralysis, though in some of these animals the paralysis partly or wholly disappeared before death. Milzer and Adelman (297) could not confirm this action of malononitrile, nor could we ourselves using mouse-adapted poliomyelitis, rabies or louping-ill viruses. It may be of interest to recall that Howe and Bodian (195, 196), by severing the sciatic nerves six to one hundred and eight days before paralysis was due to appear in monkeys infected intranasally with poliomyelitis, were able greatly to diminish the susceptibility of the large anterior horn cells to attack by the virus. Section of the axis cylinders leads, of course, to chromatolysis of the cell, that is to say to considerable *reduction* of the cytoplasmic nucleic acid. Howe and Mellors (197), however, felt that the maximum insusceptibility to virus corresponds more nearly with maximum depletion of cytochrome oxidase activity than with maximum chromatolysis.

Miscellaneous observations. Using Col.-SK encephalitis as the test infection, McKinstry and Reading (284, 285) obtained slight antiviral activity with five of forty-two pyrimidines examined. Whereas no untreated animals survived subcutaneous or intraperitoneal injection of a few multiples of the LD_{50}, a small percentage of the treated mice did so. Three of twenty-two organic arsenicals also manifested some activity against this and related rodent viruses. The best was neoarsphenamine, and its effect was antagonised by cysteine and glutathione.

Moore and Friend (305) observed that 2,6-diaminopurine in maximum tolerated daily doses, begun forty-eight or twenty-four hours before or twenty-four hours after the intraperitoneal or subcutaneous injection of 1–100 LD_{75} Russian spring-summer encephalitis virus, considerably reduced the ensuing mortality from encephalitis. The treatment had little effect upon the titres of virus in the blood, but substantially fewer mice showed virus in the brain. Against virus injected intracerebrally the treatment was without avail, and it also was in-

effective against West Nile, Ilheus encephalitis or louping-ill virus given intraperitoneally or Lansing or Bunyamwera virus given intracerebrally. Thompson *et al.* (436) had already found it useless against intracerebral vaccinia, as were also 2,6-dichloro-7-methylpurine and benzimidazole. Benzimidazole and other purine derivatives tend to decrease the resistance of mice infected with Semliki Forest virus (433), but Brown *et al.* (48) claimed a just significantly reduced mortality in animals infected intracerebrally with mouse-adapted poliomyelitis virus (type 2) when treated with benzimidazole, a depressant of the central nervous system.

Dichlorophenoxy-thiouracil increases the survival of mice infected intraperitoneally with Semliki Forest virus, whereas isatin- and other thiosemicarbazones do not (433).

Powell and his colleagues (337) and Powell and Culbertson (335, 336) have described chemoprophylactic activity on the part of an unpurified and unidentified, thermolabile, macromolecular product elaborated by *Penicillium stolonif-erum*. Given parenterally, but not orally, preferably twenty-four hours before virus rather than shortly after, this or the crude filtrate (M5-8450) protects mice against 100–1000 lethal doses of MM or Semliki Forest virus introduced subcutaneously, intramuscularly or intranasally. The filtrate is inactive against these viruses injected intracerebrally and also in the mouse against mouse-adapted poliomyelitis, type 2, intracerebrally, influenza A or B intranasally, *virus-fixe* intracerebrally or intramuscularly, meningo-pneumonitis intranasally, lymphocytic choriomenigitis intracerebrally and lymphogranuloma venereum intranasally. It was, however, active in mice of 12 g. infected by a peripheral route with hamster-passaged, mouse-adapted poliomyelitis, type 2 (336), while Cochran *et al.* (63) reported that 100 cc. amounts administered to cynomolgus monkeys three times before and a variable number of times after 10 PD_{50} type 1 poliomyelitis virus subcutaneously increased the period of incubation and diminished the incidence of paralysis. This microbial product apparently resembles that described by Shope (388, 389, 390) as helenine and derived from a culture of *Penicillium funiculosum*. Helenine is effective in infections evoked by 10–1000 LD_{100} Col.-SK encephalomyelitis and Semliki Forest viruses, and gave best results when injected before or shortly after virus. Its action appeared to be two-fold, in that on the one hand it delayed the entrance of virus into the nervous tissues and its subsequent increase there, and on the other seemed directly or indirectly to modify the virus and destroy its antigenicity, leaving many treated animals susceptible to reinfection. Maximum therapeutic action was obtained with relatively small doses, and the fact that greatly increased dosage produced no better results suggested to Shope a "triggering" action on some antiviral function of the host. The phenomenon appears to be similar to that observed by Bauer with isatin thiosemicarbazone (see above).

Gebhardt and Bachtold (133) infected monkeys by stomach-tube with a single PD_{50} type 1 poliomyelitis virus. They reduced the incidence of paralysis by dosing, from twenty-four hours before administration of virus, with 4-amino-1-naphthol hydrochloride, *p*-aminophenol and an impurity in gallic acid. The last mentioned had a therapeutic effect when first given five days or more after virus.

Thompson and Lavender (433) increased the number of mice surviving intraperitoneal (but not intracerebral) injection of Semliki Forest virus by feeding D-, L- or DL-ethionine; the effect was not cancelled by simultaneous dosing with methionine.

Of 106 drugs examined by LoGrippo and his colleagues (263, 264), several organic mercurials, of which mercuric α-mercapto-*p*-thiazolylsulphamylacetanilide and mercuric α-mercapto-*p*-sulphamylacetanilide were most effective and least toxic, reduced the excretion of Theiler's mouse-poliomyelitis virus by naturally infected mice. In nearly half the mice virus became undetectable both in the faeces and in the intestinal wall, but in approximately half of these animals virus returned after the drug was discontinued. Much smaller amounts of drug were needed to achieve an antiviral effect *in vivo* than *in vitro*. When fed to mice free from virus the former compound prevented the development of the carrier state when the animals were exposed to infection.

Summary. Although some of the effects described in the preceding pages no doubt arise from a relatively non-specific poisoning of the animals by the compound administered, not all can easily be relegated to this category. While the precise mechanism of none of the more interesting effects has yet been elucidated, their existence suggests at least the possibility that chemical substances may ultimately be used to modify the course of diseases caused by the smaller viruses.

E. The Effect of Dietary, Hormonal and Other Factors in Virus Diseases

We have mentioned in passing that an impaired state of health may considerably modify the response of an infected animal to a virus. There is to-day a growing volume of evidence that changes in the direction either of increased or of decreased susceptibility may follow a variety of procedures which have no direct relevance to current chemotherapy, but which not inconceivably may provide information of value to the chemotherapy of the future. In this section we shall consider briefly the modification of virus diseases by dietary, hormonal and environmental influences.

Dietary factors. Vitamins. Many workers, and particularly Foster and her colleagues and the members of the Wisconsin group, have studied the influence of vitamin deficiencies in virus infections, and have sought to disentangle the effects thus produced from those arising from simple dietary restriction consequent upon the anorexia which often accompanies the deficiency. In these experiments a strictly limited number of test infections have been used, and these chiefly in mice infected with relatively small doses of virus. Although many effects, mainly of prolonged survival rather than of diminished mortality, have been described, no principles capable of general application appear yet to have emerged.

Weaver (461) noted an increased susceptibility of vitamin A-deficient cotton rats to human poliomyelitis virus adapted to this species, when virus was given by intratonsillar, intraperitoneal, subcutaneous or intracardiac injection, or by intracolonic or intranasal instillation. No increase of susceptibility was observed when virus was given intracerebrally, into the bronchi or by feeding, or when it was acquired by contact with an infected animal.

Foster *et al.* (126, 127) increased the resistance of mice infected intracerebrally

with mouse-adapted poliomyelitis virus by restricting the intake of thiamine, and also by general dietary restriction even when additional thiamine and water were added. The effect with thiamine was the greater, suggesting that the deficiency does not operate solely through the anorexia caused. The deficiencies resulted in a lower incidence of paralysis and a lowered mortality, most pronounced at around twelve to seventeen days. Rasmussen *et al.* (350) made similar observations with both mouse-adapted poliomyelitis given intracerebrally and mouse encephalomyelitis (FA strain) given intraperitoneally. They noted that restoration of thiamine might lead to the mice becoming paralysed after a prolonged period of incubation, thus reinforcing the suggestion of Foster *et al.* that the disease might merely be retarded rather than wholly prevented. Similar protection is afforded in mouse-adapted poliomyelitis by feeding oxythiamine (217). Deficiency of thiamine has no influence on poliomyelitis in the monkey (61), and Toomey *et al.* (448) obtained inconstant results with mouse-adapted poliomyelitis in mice. In the cotton rat infected by a variety of routes with adapted human poliomyelitis virus, deficiency of the vitamin B complex and partial inanition are without effect (460).

In infections with the GD VII mouse encephalomyelitis virus, general dietary restriction tends rather to mask the signs of infection (paralysis, etc.) without appreciably modifying the average incubation period, average period of survival or total mortality (82).

In Western equine encephalomyelitis deficiency of thiamine suppresses the clinical manifestations of nervous involvement, but does not prevent virus from multiplying in the brain or evoking characteristic lesions there; it only slightly retards death (230). In chickens infected with avian encephalomyelitis the results are contradictory and vary with the precise experimental conditions (69) while in psittacosis of pigeons the suggestion has been made that deficiency of thiamine may render symptomatic a previously latent infection (330).

Riboflavin deficiency modifies slightly the course of mouse-adapted poliomyelitis but not that of mouse encephalomyelitis (351), while deficiency of pantothenic acid does the opposite (259). Lack of pyridoxine, inositol or biotin leaves unaffected the susceptibility of mice to these infections (260). A chronic "folic acid" deficiency was accompanied by increased resistance of monkeys to poliomyelitis; at the moment of infection, however, the animals were in a far from satisfactory state of general nutrition (257).

Pyridoxine-deficient diets or desoxypridoxine fed *after* infecting mice with the pneumonia virus of mice made the animals more resistant and lowered the titre of virus in the lungs—general dietary restriction was without effect (247). Similar treatment begun eight days or more *before* infection and continued after infection resulted in diminished resistance to infection (299).

Desoxypyridoxine fed to monkeys resulted in susceptibility to paralysis following oral introduction of the Brunhilde strain of poliomyelitis virus, which normally does not cause paralysis when given by this route (39).

The claims of Jungeblut (221, 222, 223) to have reduced the severity of poliomyelitis in monkeys given vitamin C during the incubation period did not receive

confirmation from Sabin (366), and Holden and Molloy (188) did not find the vitamin useful in the treatment of rabbits infected with herpes W virus (more commonly known as Sabin's B virus).

Toomey (447) observed that vitamin D protected *Macacus rhesus* against poliomyelitis virus given by the gastro-intestinal route, and Toomey and Takacs (450) thought that the spread of poliomyelitis virus from a peripheral site of inoculation to the central nervous system of the monkey was favoured by a vitamin D deficiency. However, Sabin *et al.* (368) found no evidence that the deficiency was necessary for a successful result following intrasciatic injection of virus. Such deficiency, coupled with deficient P and Ca in the diet, increases susceptibility of the mouse to mouse-adapted poliomyelitis (125). Weaver (459) obtained no evidence of an influence of avitaminosis D or of partial inanition on poliomyelitis adapted to the cotton rat.

Mice fed little or no vitamin D for twenty-eight days after weaning show an increased susceptibility to swine influenza, as assessed by the conventional mortality-pulmonary score method, and females are more affected than males (478).

A deficiency of food or of essential dietary factors may affect susceptibility to a virus in a rather different manner. Some viruses capable of growth both outside and inside the nervous system invade the latter invariably in newly weaned mice, but less frequently or rarely in fully grown animals. The route of invasion also may vary in young and in maturing animals. Sabin and Duffy (367) observed that defective nutrition might retard or inhibit the development of this "constitutional barrier" to invasion of the nervous system. The deficiency could be brought about by depriving the mother during the period of nursing or by a deficient diet to the weaned offspring. General dietary restriction and specific deficiencies of vitamin E, of the B complex apart from its heat-labile constituents, and of the heat-labile B factors all retarded or inhibited the development of resistance.

Mineral salts. Lichstein *et al.* (258) observed that the amount of Ca, Mg or Cl in the diet made little difference to the susceptibility of mice infected with GD VII mouse encephalomyelitis virus. Na deficiency and still more deficiency of K or P reduced the incidence of paralysis. It should be remarked that the most pronounced results obtained with severe deficiencies in which the general health of the mice was very severely affected.

Proteins and amino acids. In addition to the observations cited in the previous section, Sprunt (409) has shown that a restricted diet increases the rabbit's resistance to intradermal vaccinia, especially if the tissues are hydrated by allowing the animal to consume plenty of water; in the fully hydrated tissues virus particles spread less readily from cell to cell. Adult (but not immature) mice fed on a diet low in protein are slightly more resistant to swine influenza, provided that the deficiency is not prolonged (411, 412). With mouse-adapted poliomyelitis also, a diet low in protein delays the onset of symptoms (218), though apparently the protein level is without influence on GD VII mouse encephalomyelitis (231).

In mouse-adapted poliomyelitis, deficiencies of a number of amino acids prolong the incubation period, decrease the number of animals dying before the

twenty-eighth day, and increase the number dying without showing characteristic symptoms of the disease (81). Deficiency of lysine merely prolongs the period of incubation. The effects of deficiencies of histidine, threonine, methionine and leucine are rather more definite, those of valine and phenylalanine still more so, and those of tryptophane and *iso*leucine pronounced. In spite of the clinical effect the growth of virus is not prevented; in the normally fed mice it grows more rapidly and reaches higher titres, but in the deficient mice it continues to grow for a longer period. The results with GD VII virus are essentially similar; here tryptophane, *iso*leucine, methionine and valine deficiencies are most effective, but none prevent the ultimate death of the mice (333). Lengthened incubation and survival of mice infected with mouse-adapted poliomyelitis also obtain when the diet contains excess methionine, especially if accompanied by a low ration of tryptophane and simultaneous feeding with 6-methyltryptophane (134); both a tryptophane-deficient diet containing 0.4 per cent 6-methyltryptophane and a 9 per cent casein diet containing 3 per cent 6-methyltryptophane considerably prolong survival, the latter in the absence of signs of ill-health or of tryptophane deficiency (348). Low tryptophane diets containing 6-methyltryptophane afford a degree of protection to cynomolgus monkeys receiving poliomyelitis virus orally (352). In mice infected with mouse-adapted poliomyelitis a diet containing 0.02 per cent tryptophane retarded the appearance of nervous symptoms, but at twenty-eight days the incidence of paralysis and of death were approximately the same in deficient and control mice (218). An absolute deficiency of tryptophane retards death from GD VII mouse encephalomyelitis when comparison is made with animals on a diet containing 0.3 per cent tryptophane or an 18 per cent casein optimal diet. However, infected animals with tryptophane deficiency die sooner than do non-infected deficient controls; with absolute deficiency the characteristic clinical signs of infection are suppressed, in spite of the fact that virus multiplies in the brains and evokes histological signs of encephalitis. In such animals the symptoms are those specific for the amino acid deficiency. The accelerated death in infected deficient animals suggests that tryptophane may be a constituent of the virus, which in the course of its growth uses up the scanty tryptophane available thereby precipitating signs of deficiency (231).

Excess leucine, lysine, histidine, phenylalanine and choline do not influence mouse-adapted poliomyelitis (134).

Intraperitoneal injections of methionine enhance the resistance of rabbits to intradermal vaccinia (410), as do also choline and betaine but not glycine. Similar injections into mice on a low protein diet greatly increase their susceptibility to swine influenza (411); cystine has a slight effect in the same direction.

O'Dell *et al.* (317) observed that daily intraperitoneal doses of ribose or desoxyribose nucleic acids, for six to twelve days prior to infection via the pad of the foot with MM virus, prevented paralysis and/or death in many of the mice. A high protein diet afforded protection when combined with a synthetic diet containing not less than 60 per cent casein, but not with a Fox Chow diet. Ribose nucleic acid added to the Fox Chow diet had no effect, but at a concentration

of 1–2 per cent (or yeast at 5 per cent) gave a high degree of protection when added to the 60 per cent casein diet. Ribose nucleic acid also appeared more active intraperitoneally when the animals were fed on the casein diet. Gluten, egg albumen or blood could be substituted for the casein. O'Dell *et al.* explain these results in the following way. The virus, by monopolising the nucleic acid and protein produced by the parasitised cells, leaves little if any available for cellular nutrition. Nucleic acid or protein administered in excess enables the cell to make good this deficiency in spite of the presence of virus.

Hormonal factors. It has long been felt that constitutional factors play a part in the incidence of paralytic poliomyelitis, and that the disease is more frequent in pregnant than in non-pregnant females of the same age-groups. Aycock (23) first offered suggestive evidence that oestrogens administered to castrated immature female monkeys diminish the incidence of paralysis following intranasal infection with the virus. He later (24) confirmed this and showed also that the mean time at which paralysis appears is later in the treated animals. Foley and Aycock (123) observed a similar phenomenon in mice infected intranasally with MM virus, but not if this virus were injected intraperitoneally or mouse-adapted poliomyelitis were injected intracerebrally. Protection evidently depended upon changes in the surface mucosa.

Sprunt *et al.* (414) and Sprunt and McDearman (413) demonstrated a degree of protection by oestrogens or pseudopregnancy against intradermal vaccinia in rabbits. Taylor and Sprunt (428) attributed the effect to increased hydration of the tissues tending to restrict the passage of virus particles to susceptible cells.

Anderson and Bolin (17) fed MM virus to mice in a dose killing 68 per cent of the controls. Administration of progesterone completely abolished mortality, stilboestrol reduced it to 2.5 per cent, testosterone proprionate reduced it to 20 per cent, while desoxycorticosterone was without effect. Desoxycorticosterone, progesterone, testosterone and oestradiol in massive doses did not influence infections with West Nile and Bunyamwera viruses (404).

Kalter and his colleagues (227, 228) noted increased proliferation of influenza A virus in mice receiving pituitary growth hormone or testosterone, and linked it with the increased protein anabolism. Castration, with comparative failure of protein anabolism, or administration of ACTH or cortisone with increased protein catabolism, decreased the rate of viral proliferation. Kilbourne and Horsfall (232) on the other hand, found that in the chick embryo cortisone greatly enhanced the growth of influenza viruses A and B and of mumps virus, in one instance by as much as 688 per cent, in spite of apparent depression of anabolism. They concluded that the evidence was insufficient to justify the assumptions (a) that the concentration of virus is directly related to anabolism, and (b) that cortisone actually does depress anabolism in the chick embryo. However this may be, there are many reports of increased susceptibility to several viral infections following administration of cortisone. The diseases thus influenced include poliomyelitis in mice or hamsters (114, 392), Coxsackie disease (114, 233), West Nile, Ilheus and Bunyamwera infections (404), dermal vaccinia (236), infection with the pneumonia virus of mice (400), and Rift Valley fever and Col.-SK encephali-

tis (114). ACTH has been reported to increase susceptibility to West Nile virus (404) and influenza A (267), but not to pneumonia virus of mice (400), poliomyelitis or Western equine encephalomyelitis (71, 296); it does not reduce the acute toxic effects of influenza virus in mice or rats (229).

Holtman (190) infected mice intracerebrally with poliomyelitis virus. Treatment with thiouracil accelerated paralysis and death, while thyroid extract and thyroactive casein had the opposite effect. Gollan (146), however, detected no action of crystalline thyroxine on MM virus given intraperitoneally.

Environmental factors. The final influence to be considered is that of the environment. Remlinger (353) and McKinley and Acree (283) observed no beneficial effect of interrupted periods of hyperpyrexia in rabbits on the course of rabies and of infectious myxomatosis of rabbits and the Shope fibroma, respectively. Sarracino and Soule (372) found that exposure of mice to an environmental temperature of 37°C for twenty-four hours, and again for ten hours, during the incubation period of influenza did not materially affect the pulmonary lesions. However, Wolf (467) believed that short-wave hyperpyrexia for several hours early in the incubation period of poliomyelitis following intracerebral injection into monkeys could protect the animals from developing the paralytic form of the disease.

Longer periods of raised environmental temperature appear to have a definite effect on the course of certain diseases. Jungeblut *et al.* (226) claimed that, during the summer months, the incubation period in mice infected with Col.-SK virus was lengthened. Lillie *et al.* (261) noted that the average intensity of the cerebral reaction to St. Louis encephalitis in mice was lower in summer and higher in winter, and that these differences could be reproduced experimentally by holding groups of infected mice at different temperatures; however, these different environmental temperatures ranging from the cold room (42°F, 5°C) to the hot room (95°F, 35°C) had little effect on mortality (20).

Armstrong (21) reported that whereas mice given herpes virus subcutaneously, intraperitoneally or by stomach-tube almost always died when kept at 70–80°F (21–26°C), similarly treated mice kept at 98–99°F (36–37°C) almost always survived. Treatment with heat was effective in halting infection even when it had progressed almost to the point of causing symptoms of nervous illness. The virus was not wholly destroyed by the higher temperature because (a) the mice acquired immunity to reinfection, and (b) if subsequently brought back to laboratory temperature some animals developed the disease. Animals were also protected by being kept in the hot-room by day and in the laboratory by night. These results could not be duplicated with St. Louis encephalitis or with mouse-adapted poliomyelitis.

Thompson (429) and Parker and Thompson (320) similarly found it possible partly or wholly to suppress the Shope fibroma and infectious myxomatosis of rabbits by raising the environmental temperature. By contrast, Sulkin (416) observed little effect of temperature on the mortality from influenza A infection in mice, although the pulmonary lesions were less marked at higher temperatures. Schach (374) recorded an increased susceptibility of guinea-pigs to foot-and-

mouth disease at higher environmental temperatures, as did Holtman (190) with poliomyelitis in mice held for some weeks at high temperatures.

Mice acclimatised to a simulated altitude of approximately 20000 ft. (6000m) for three weeks are more resistant to infection with influenza A virus, especially when maintained at this altitude also during the period following infection. The citric acid content of the lungs of the mice was diminished, and it was thought that in consequence the synthesis of virus was restricted (36).

REFERENCES

1. Ackermann, W. W.: Concerning the relation of the Krebs' cycle to virus propagation. J. biol. Chem. **189**: 421–428, 1951.
2. Ackermann, W. W.: The role of L-methionine in virus propagation. J. exp. Med. **93**: 337–343, 1951.
3. Ackermann, W. W.: The relation of the Krebs' cycle to viral synthesis. J. exp. Med. **93**: 635–642, 1951.
4. Ackermann, W. W.: Role of L-methionine in virus propagation. Fed. Proc. **10**: 400, 1951.
5. Ackermann, W. W.: α-Aminosulfonic acids and viral propagation. Proc. Soc. exp. Biol., N. Y. **80**: 362–367, 1952.
6. Ackermann, W. W. and Johnson, R. B.: Some energy relations in a host-virus system. J. exp. Med. **97**: 315–322, 1953.
7. Ackermann, W. W., Kurtz, H., Kleinschmidt, E. F. and Uhlendorf, B. W.: α′-Aminosulfonic acids and viral propagation. Proc. Soc. exp. Biol., N. Y. **80**: 362–367, 1952.
8. Ackermann, W. W. and Maassab, H. F.: Growth characteristics of influenza virus. The influence of a sulphonic acid. J. exp. Med. **99**: 105–117, 1954.
9. Ackermann, W. W. and Maassab, H. F.: Growth characteristics of influenza virus. Biochemical differentiation of stages of development. J. exp. Med. **100**: 329–339, 1954.
10. Ainslie, J. D.: The growth curve of the Lansing strain of poliomyelitis virus in mice: the effect of sodium monofluoroacetate and methionine sulfoximine on the early phase of growth of the virus. J. exp. Med. **95**: 9–18, 1952.
11. Aird, R. B.: Mode of action of brilliant vital red in epilepsy. Arch. Neurol. Psychiat., Chicago **42**: 700–723, 1939.
12. Aird, R. B. and Strait, L.: Protective barriers of the central nervous system. An experimental study with trypan red. Arch. Neurol. Psychiat., Chicago **51**: 54–66, 1944.
13. Alergant, C. D.: Therapy of lymphogranuloma inguinale with 7218. Brit. J. vener. Dis. **29**: 218–221, 1953.
14. Allen, E. G., Girardi, A. J., Sigel, M. M. and Klein, M.: Studies on the psittacosis-lymphogranuloma group. III. The effect of aureomycin on the propagation of virus in the chick embryo. J. exp. Med. **97**: 783–795, 1953.
15. Amos, H.: Inactivation of herpes simplex virus by phosphatase enzymes. J. exp. Med. **98**: 365–372, 1953.
16. Anderson, C. E.: Treatment of primary atypical pneumonia in children with aureomycin. Report of nineteen cases. Amer. J. Dis. Child. **80**: 533–540, 1950.
17. Anderson, J. A. and Bolin, V.: The influence of various hormones on the resistance of Swiss mice to adapted poliomyelitis virus. J. clin. Endocrin. **6**: 466–467, 1946.
18. Andrewes, C. H. and Niven, J. S. F.: Chemotherapeutic experiments with grey lung virus. Brit. J. exp. Path. **31**: 767–772, 1950.
19. Andrewes, C. H. and Niven, J. S. F.: A virus from cotton rats: its relation to grey lung virus. Brit. J. exp. Path. **31**: 773–778, 1950.
20. Armstrong, C.: Studies on the mechanism of experimental intranasal infection in mice. Publ. Hlth. Rep., Wash. **53**: 2004–2012, 1938.
21. Armstrong, C.: Some recent research in the field of neurotropic viruses with especial reference to lymphocytic choriomeningitis and herpes simplex. Milit. Surg. **91**: 129–146, 1942.
22. Astwood, E. B., Hughes, A. M., Lubin, M., Vanderlaan, W. P. and Adams, R. D.: Reversible paralysis of motor function in rats from chronic administration of dithiobiuret. Science **102**: 196–197, 1945.
23. Aycock, W. L.: Alterations in autarceologic susceptibility to experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. **34**: 573–574, 1936.
24. Aycock, W. L.: A subclinical endocrinopathy as a factor in autarceologic susceptibility to poliomyelitis. Endocrinology **27**: 49–57, 1940.
25. Banov, L. and Goldberg, J.: Erythromycin treatment of lymphogranuloma venereum. Antibiotics Annual 1953–1954, pp. 475–479. Medical Encyclopedia, New York 1953.
26. Bär, F.: Chemotherapeutische Versuche bei der experimentellen Infektion der Maus mit Lymphogranuloma inguinale. Klin. Wschr. **17**: 588–590, 1938.
27. Bär, F.: Erfahrungen und Ergebnisse über die chemotherapeutische Beeinflussbarkeit des Lymphogranuloma inguinale und anderer Viruskrankheiten. Z. ImmunForsch **97**: 344–363, 1939–1940.
28. Barrat, P.: Essai de traitement collectif du trachôme par un composé azoïque sulfamidé. Arch. Inst. Pasteur Tunis **30**: 237–244, 1941.
29. Barron, E. S. G. and Singer, T. P.: Studies on biological oxidations. XIX. Sulfhydryl enzymes in carbohydrate metabolism. J. biol. Chem. **157**: 221–240, 1945.
30. Bauer, D. J.: The antiviral and synergic actions of isatin thiosemicarbazone and certain phenoxypyrimidines in vaccinia infection in mice. Brit. J. exp. Path. **36**: 105–114, 1955.
31. Baumann, C. A. and Stare, F. J.: The effect of malonate on tissue respiration. J. biol. Chem. **133**: 183–191, 1940.

32. Bedson, S. P. and May, H. B.: Penicillin in experimental psittacosis of mice. Lancet 2: 394–397, 1945.
33. Bellows, J. G.: Chemotherapy in ophthalmology. Arch. Ophthal., N. Y. 29: 888–903, 1943.
34. Bellows, J. G., Richardson, V. M. and Farmer, C. J.: Aureomycin in ophthalmology. Amer. J. Ophthal. 33: 273–283, 1950.
35. Bergsdorf, M. and Brinkmann, E.: Über einige Psittakosiserkrankungen in Braunschweig und ihre Behandlung mit Aureomycin. Z. ges. inn. Med. 9: 98–100, 1954.
36. Berry, L. J., Mitchell, R. B. and Rubenstein, D.: Effect of acclimatization to altitude on susceptibility of mice to influenza A virus infection. Proc. Soc. exp. Biol., N. Y. 88: 543–548, 1955.
37. Blodgett, W. A., Keating, J. H. and Coffin, G. J.: Dosage of aureomycin in primary atypical pneumonia. J. Amer. med. Ass. 143: 878–879, 1950.
38. Boase, A. J.: Aureomycin in trachoma. Brit. J. Ophthal. 34: 627–632, 1950.
39. Bodian, D.: Poliomyelitis in an uninoculated rhesus monkey, and in orally inoculated monkeys, receiving desoxypyridoxine. Amer. J. Hyg. 48: 87–93, 1948.
40. Borsook, H., Deasy, C. L., Haagen-Smit, A. J., Keighley, G. and Lowy, P. H.: The degradation of α'-aminoadipic acid in guinea pig liver homogenate. J. biol. Chem. 176: 1395–1400, 1948.
41. Bowers, R. H., Davies, O. L. and Hurst, E. W.: A comparison between intranasal instillation and natural inhalation as means of infecting mice with influenza virus. Brit. J. exp. Path. 33: 601–609, 1952.
42. Boyd, J. S. K. and Bradley, P. L.: On the assessment of the influence of chemical compounds on bacteriophage multiplication. Brit. J. exp. Path. 32: 397–407, 1951.
43. Brainerd, H., Lennette, E. H., Meiklejohn, G., Bruyn, H. B. and Clark, W. H.: The clinical evaluation of aureomycin. J. clin. Invest. 28: 992–1005, 1949.
44. Braley, A. E. and Sanders, M.: Aureomycin in ocular infections. Amer. J. Ophthal. 32 (Suppl.): 119–126, 1949.
45. Briody, B. A. and Stannard, C.: The effect of proflavine on the growth of viruses in the chick embryo. J. Immunol. 67: 423–430, 1951.
46. Brown, G. C.: The influence of chemicals on the propagation of poliomyelitis virus in tissue culture. J. Immunol. 69: 441–450, 1952.
47. Brown, G. C. and Ackermann, W. W.: Effect of DL-ethionine on poliomyelitis virus growth in tissue culture. Proc. Soc. exp. Biol., N. Y. 77: 367–369, 1951.
48. Brown, G. C., Craig, D. E. and Kandel, A.: Effect of benzimidazole on experimental poliomyelitis in mice and monkeys. Proc. Soc. exp. Biol., N. Y. 83: 408–411, 1953.
49. Burgh, P., de, Jackson, A. V. and Williams, S. E.: Spontaneous infection of laboratory mice with a psittacosis-like organism. Aust. J. exp. Biol. med. Sci. 23: 107–110, 1945.
50. Burnet, E., Cuénod, A. and Nataf, R.: Chimiothérapie du trachôme par l'azoïque sulfamidé no. 33. Bull. Acad. Méd., Paris 122: 330–342, 1939.
51. Burnet, E., Cuénod, E. and Nataf, R.: Essai de chimiothérapie du trachôme par un derivé glucosé du «4:4'-diaminodiphénylsulfone»; efficacité sur le pannus trachomateux. Bull. Acad. Méd., Paris 121: 317–324, 1939.
52. Burnet, F. M.: The affinity of Newcastle disease virus to the influenza virus group. Aust. J. exp. Biol. med. Sci. 20: 81–88, 1942.
53. Burney, T. E. and Golub, O. J.: The effect of certain enzyme inhibitors on the activity and growth of psittacosis virus. J. Immunol. 60: 213–221, 1948.
54. Calloman, F. T. and Brown, H.: Chemotherapy of experimental lymphogranuloma venereum in mice. Amer. J. Syph. 27: 590–600, 1943.
55. Cat, N. D.: Comments on the treatment of trachoma with aureomycin. Amer. J. trop. Med. 1: 796–798, 1952.
56. Cat, N. D.: Terramycin in the treatment of trachoma. Amer. J. trop. Med. 1: 799–803, 1952.
57. Cerutti, P.: Ricerche di chemioterapia con preparati sulfoamidici e di reinfezione nella malattia di Nicolas e Favre sperimentale. G. ital. Derm. Sif. 81: 1031–1042, 1940.
58. Chantrill, B. H., Coulthard, C. E., Dickinson, L., Inkley, G. W., Morris, W. and Pyle, A. H.: The action of plant extracts on a bacteriophage of *Pseudomonas pyocyanea* and on influenza A virus. J. gen. Microbiol. 6: 74–84, 1952.
59. Ching, R.: Aureomycin in the treatment of trachoma. Arch. Ophthal., N. Y. 45: 657–665, 1951.
60. Ciaccio, G., Gasparini, G. and Ercoli, N.: The effects of vital dyes upon experimental foot and mouth virus infection of guinea pigs. J. Immunol. 72: 299–306, 1954.
61. Clark, P. F., Waisman, H. A., Lichstein, H. C. and Jones, E. S.: Influence of thiamine deficiency in *Macaca mulatta* on susceptibility to experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 58: 42–45, 1945.
62. Cobb, S., Cohen, M. E. and Ney, J.: Anticonvulsive action of vital dyes. Arch. Neurol. Psychiat., Chicago 40: 1156–1177, 1938.
63. Cochran, K. W., Brown, G. C. and Francis, T.: Antiviral action of a mold filtrate on experimental poliomyelitis in cynomolgus monkeys. Proc. Soc. exp. Biol., N. Y. 85: 104–106, 1954.
64. Coggeshall, L. T. and Maier, J.: Effect of various sulfonamides, sulfones, and other compounds against experimental influenza and poliomyelitis infections in white mice. J. Pharmacol. 76: 161–166, 1942.
65. Cohen, P. and Schwartz, R.: Use of chloromycetin in infections. I. In non-bacterial (atypical undifferentiated respiratory infections). J. Pediat. 37: 23–36, 1950.
66. Cohen, S. S. and Fowler, C. B.: Chemical studies on host-virus interactions. III. Tryptophane requirements in the stages of virus multiplication in the *Escherichia coli*-T_2 bacteriophage system. J. exp. Med. 85: 771–784, 1947.
67. Collins, H. S., Wells, E. B., Gocke, T. M. and Finland, M.: Treatment of primary atypical pneumonia with aureomycin. Amer. J. Med. 8: 4–20, 1950.

68. Commission on Acute Respiratory Diseases: The transmission of primary atypical pneumonia to human volunteers. Johns Hopk. Hosp. Bull. 79: 97–167, 1946.
69. Cooperman, J. M., Lichstein, H. C., Clark, P. F. and Elvehjem, C. A.: The influence of thiamine on the susceptibility of chicks to avian encephalomyelitis. J. Bact. 52: 467–470, 1946.
70. Cordice, J. W. V., Avecilla, M., Marmell, M., Shidlovsky, B. A. and Prigot, A.: Erythromycin: a preliminary report on its use in certain venereal diseases. Antibiotics Annual 1: 480–484, 1953.
71. Coriell, L. L., Siegel, A. C., Cook, C. D., Murphy, L. and Stokes, J.: Use of pituitary adrenocorticotropic hormone (ACTH) in poliomyelitis. J. Amer. med. Ass. 142: 1279–1281, 1950.
72. Costello, M. J. and D'Avanzo, C. S.: Lymphogranuloma venereum. Observations on three hundred and eighty-eight patients at Bellevue Hospital. Arch. Derm. Syph., N. Y. 57: 112–121, 1948.
73. Coulston, F. and Manwell, R. D.: Successful chemotherapy of a virus disease of the canary. Amer. J. vet. Res. 2: 101–107, 1941.
74. Cuckler, A. C., Frost, B. M., McClelland, L. and Solotorovsky, M.: The antimicrobial evaluation of oxamycin (D-1-amino-3-isoxazolidone), a new broad-spectrum antibiotic. Antibiot. and Chemother. 5: 191–197, 1955.
75. Curnen, E. C., Mirick, G. S., Ziegler, J. E., Thomas, L. and Horsfall, F. L.: Studies on primary atypical pneumonia. I. Clinical features and results of laboratory investigations. J. clin. Invest. 24: 209–226, 1945.
76. Cushing, R. T. and Morgan, H. R.: Effects of some metabolic analogues on growth of mumps and influenza viruses in tissue cultures. Proc. Soc. exp. Biol., N. Y. 79: 497–500, 1952.
77. Cutting, W. C., Dreisbach, R. H., Halpern, R. M., Irwin, E. A., Jenkins, D. W., Proescher, F. and Tripi, H. B.: Chemotherapy of virus infections. J. Immunol. 57: 379–390, 1947.
78. Czekalowski, J. W.: Studies on the reproduction of bacterial viruses. II. Effect of enzyme-inhibitors on the multiplication of the coliphage T_2. Brit. J. exp. Path. 33: 57–66, 1952.
79. Darius, D. J.: Penicillin treatment of trachoma. A preliminary report. Amer. J. Ophthal. 28: 1007–1009, 1945.
80. Davenport, F. M.: Toxicity of NDV for mouse lungs. J. Immunol. 69: 461–470, 1952.
81. Davies, W. L., Pond, W. L., Smith, S. C., Rasmussen, A. F., Elvehjem, C. A. and Clark, P. F.: The effect of certain amino acid deficiencies on Lansing poliomyelitis in mice. J. Bact. 64: 571–582, 1952.
82. Davies, W. L., Smith, S. C., Pond, W. L., Rasmussen, A. F. and Clark, P. F.: Effect of dietary restriction on susceptibility of mice to infection with Theiler's GD VII virus. Proc. Soc. exp. Biol., N. Y. 72: 528–531, 1949.
82a. De Ritis, F., Coltorti, M. and Giusti, G.: Gli aspetti metabolici delle malattie da virus. VII Congresso della Società Italiana per lo Studio della Malattie Infettive e Parassitarie, pp. 1–192. Torino 1955.
83. Dickinson, L.: The bacteriophages of *Pseudomonas pyocyanea*. I. The effect of various substances upon their development. J. gen. Microbiol. 2: 154–161, 1948.
84. Dickinson, L.: The formaldehyde derivatives of amino acids and the mode of action of a formaldehyde-tyrosine derivative against influenza A virus *in ovo*. Brit. J. Pharmacol. 10: 56–60, 1955.
85. Dickinson, L., Chantrill, B. H., Inkley, G. W. and Thompson, M. J.: The antiviral action of phenanthridinium compounds. Brit. J. Pharmacol. 8: 139–142, 1953.
86. Dolby, D. E.: The effect of enzyme inhibitors on the multiplication of T_2 bacteriophage. J. gen. Microbiol. 12: 406–418, 1955.
87. Domagk, G., Behnisch, R., Mietzsch, F. and Schmidt, H.: Über eine neue, gegen Tuberkelbazillen *in vitro* wirksame Verbindungsklasse. Naturwissenschaften 33: 315, 1946.
88. Duke-Elder, S., Ainslie, D. and Boase, A. J.: Aureomycin in ophthalmology. A preliminary report. Brit. J. Ophthal. 34: 30–37, 1950.
89. Duran-Reynals, F. and Duran-Reynals, M. L.: Inactivation of vaccine virus by preparations of hyaluronic acid with or without hyaluronidase: Experiments on cell cultures. Science 115: 40–41, 1952.
90. Early, R. L. and Morgan, H. R.: Studies on the chemotherapy of viruses in the psittacosis-lymphogranuloma group. III. Effect of certain chemotherapeutic agents on the growth of psittacosis virus (6BC strain) in tissue cultures and eggs. J. Immunol. 53: 151–156, 1946.
91. Early, R. L. and Morgan, H. R.: Studies on the chemotherapy of viruses in the psittacosis-lymphogranuloma group. IV. Effect of certain chemotherapeutic agents on psittacosis virus (6BC strain) infections in mice. J. Immunol. 53: 251–257, 1946.
92. Eaton, M. D.: Action of aureomycin and chloromycetin on the virus of primary atypical pneumonia. Proc. Soc. exp. Biol., N. Y. 73: 24–29, 1950.
93. Eaton, M. D.: Observations on growth of virus and the energy-yielding activities of the host cell. Arch. ges. Virusforsch. 5: 53–72, 1952.
94. Eaton, M. D.: Effect of some newer antibiotics on the agent of primary atypical pneumonia. Antibiotics Annual 1954–1955, pp. 1046–1049. Medical Encyclopedia, New York 1955.
95. Eaton, M. D., Adler, L. T. and Perry, M. E.: Virus growth and cellular energy production: effect of substances chemically related to thyroxin on influenza virus. Proc. Soc. exp. Biol., N. Y. 84: 57–60, 1953.
96. Eaton, M. D., Allen, A. van and Wiener, A.: Action of acridines on agents of the psittacosis-lymphogranuloma group. Proc. Soc. exp. Biol., N. Y. 66: 141–146, 1947.
97. Eaton, M. D., Cheever, F. S. and Levenson, C. G.: Further observations of the effect of acridines on the growth of viruses. J. Immunol. 66: 463–476, 1951.
98. Eaton, M. D., Dozois, T. F., Allen, A. van, Parish, V. L. and Schwalm, S.: Studies on inhibition of the agents of murine and feline pneumonitis by penicillin. J. Immunol. 58: 251–267, 1948.
99. Eaton, M. D. and Hanford, V. L.: Effect of the host in action of sulfonamides on elementary-body agents of murine and feline pneumonitis. Proc. Soc. exp. Biol., N. Y. 59: 63–66, 1945.

100. EATON, M. D., HERICK, W. VAN AND MEIKLEJOHN, G.: Studies on the etiology of primary atypical pneumonia. III. Specific neutralization of the virus by human serum. J. exp. Med. 82: 329–342, 1945.
101. EATON, M. D., HUANG, C. AND LEVENSON, C. G.: Effect of nitrocompounds on viruses of the psittacosis-lymphogranuloma group. Proc. Soc. exp. Biol., N. Y. 71: 501–507, 1949.
102. EATON, M. D., LEVENSON, C. G. AND HANKS, C.: Inhibition of agents of the psittacosis-lymphogranuloma group by *p*-arsenobenzamide. Proc. Soc. exp. Biol., N. Y. 71: 508–509, 1949.
103. EATON, M. D., LEVENSON, C. G. AND PERRY, M.: Inhibition of the growth of viruses in the chick embryo by aromatic diamidines. J. Immunol. 68: 1–9, 1952.
104. EATON, M. D., MAGASANIK, B., PERRY, M. E. AND KARIBIAN, D.: Inhibition of influenza and mumps viruses in tissue culture by basic amino acids. Proc. Soc. exp. Biol., N. Y. 77: 505–508, 1951.
105. EATON, M. D., MEIKLEJOHN, G. AND HERICK, W. VAN: Studies on the etiology of primary atypical pneumonia. A filterable agent transmissible to cotton rats, hamsters, and chick embryos. J. exp. Med. 79: 649–668, 1944.
106. EATON, M. D. AND PERRY, M. E.: Further observations on the effect of 2,4-dinitrophenol on the growth of influenza virus. J. infect. Dis. 93: 269–277, 1953.
107. EATON, M. D., PERRY, M. E. AND GOCKE, I. M.: Effect of nitrocompounds and aldehyde semicarbazones on virus of primary atypical pneumonia. Proc. Soc. exp. Biol., N. Y. 77: 422–425, 1951.
108. EATON, M. D., PERRY, M. E., LEVENSON, C. G. AND GOCKE, I. M.: Studies on the mode of action of aromatic diamidines on influenza and mumps virus in tissue culture. J. Immunol. 68: 321–334, 1952.
109. ENDE, M. VAN DEN, ANDREWES, C. H. AND KING, H.: Chemotherapeutic experiments with the viruses of influenza A, lymphogranuloma venereum and vaccinia. J. Path. Bact. 55: 173–181, 1943.
110. ENDE, M. VAN DEN AND LUSH, D.: Experiments with the pneumotropic strain of lymphogranuloma venereum virus. J. Path. Bact. 55: 81–92, 1943.
111. EVANS, E. A., JR.: Bacterial viruses. With particular reference to the synthesis of. Annu. Rev. Microbiol. 8: 239–256, 1954.
112. FINDLAY, G. M.: Chemotherapeutic investigations on the virus of lymphogranuloma venereum. Lancet 2: 682–683, 1940.
113. FINDLAY, G. M.: The action of sulphanilamide on the virus of lymphogranuloma venereum. Brit. J. exp. Path. 21: 356–360, 1940.
114. FINDLAY, G. M. AND HOWARD, E. M.: The effects of cortisone and adrenocorticotrophic hormone on poliomyelitis and on other virus infections. J. Pharm., Lond. 4: 37–42, 1952.
115. FINLAND, M., COLLINS, H. S. AND WELLS, E. B.: Aureomycin in the treatment of primary atypical pneumonia. New Engl. J. Med. 240: 241–246, 1949.
116. FISCHER, G.: A phagicidal and virucidal agent in maple fruit (*Acer platanoides L.*) preparations. Acta path. microbiol. scand. 31: 433–447, 1952.
117. FITZGERALD, R. J. AND BABBITT, D.: Studies on bacterial viruses. I. The effect of certain compounds on the lysis of *Escherichia coli* by bacteriophage. J. Immunol. 52: 121–125, 1946.
118. FITZGERALD, R. J. AND LEE, M. E.: Studies on bacterial viruses. II. Observations on the mode of action of acridines in inhibiting lysis of virus-infected bacteria. J. Immunol. 52: 127–135, 1946.
119. FITZHUGH, O. G., NELSON, A. A. AND CALVERY, H. O.: The chronic toxicity of quinacrine (atabrine). J. Pharmacol. 85: 207–221, 1945.
120. FLEISHER, M. S.: The effect of various dyes *in vitro* and *in vivo* upon influenza infection in mice. J. Immunol 62: 245–255, 1949.
121. FLETCHER, A., SIGEL, M. M. AND ZINTEL, H. A.: Aureomycin therapy in lymphogranuloma venereum. Arch. Surg., Lond. 62: 239–250, 1951.
122. FLIPPEN, H. F., GAYDOSH, M. J. AND FITTIPOLDI, W. V.: Treatment of human psittacosis with penicillin. J. Amer. med. Ass. 128: 280–281, 1945.
123. FOLEY, G. E. AND AYCOCK, W. L.: Alterations in the autarceologic susceptibility of the mouse to experimental poliomyelitis by estrogenic substances. Endocrinology 37: 245–251, 1945.
124. FORSTER, W. G.: Treatment of trachoma with sulfanilamide. Amer. J. Ophthal. 23: 532–534, 1940.
125. FOSTER, C., JONES, J. H., HENLE, W. AND BRENNER, S. A.: Nutrition and poliomyelitis. The effects of deficiencies of phosphorus, calcium and vitamin D on the response of mice to the Lansing strain of poliomyelitis virus. J. infect. Dis. 85: 173–179, 1949.
126. FOSTER, C., JONES, J. H., HENLE, W. AND DORFMAN, F.: The effect of vitamin B_1 deficiency and of restricted food intake on the response of mice to the Lansing strain of poliomyelitis virus. J. exp. Med. 79: 221–234, 1944.
127. FOSTER, C., JONES, J. H., HENLE, W. AND DORFMAN, F.: The comparative effects of vitamin B_1 deficiency and restriction of food intake on the response of mice to the Lansing strain of poliomyelitis virus, as determined by the paired feeding technique. J. exp. Med. 80: 257–264, 1944.
128. FOSTER, R. A. C.: An analysis of the action of proflavine on bacteriophage growth. J. Bact. 56: 795–809, 1948.
129. FOWLER, C. B. AND COHEN, S. S.: Chemical studies in host-virus interactions. IV. A method of determining nutritional requirements for bacterial virus multiplication. J. exp. Med. 87: 259–274, 1948.
130. FRANCIS, J.: Chemotherapeutic response of the organism causing enzootic abortion in ewes. J. comp. Path. 62: 214–219, 1952.
131. FRANCIS, T., BROWN, G. C. AND KANDEL, A.: Effect of fluoroacetate upon poliomyelitis in monkeys. Proc. Soc. exp. Biol., N. Y. 85: 83–85, 1954.
132. FRIEND, C.: Effect of 2,6-diaminopurine on virus of Russian spring-summer encephalitis in tissue culture. Proc. Soc. exp. Biol., N. Y. 78: 150–153, 1951.
133. GEBHARDT, L. P. AND BACHTOLD, J. G.: Chemoprophylaxis and chemotherapy of experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 88: 103–107, 1955.

134. GERSHOFF, S. N., RASMUSSEN, A. F., ELVEHJEM, C. A. AND CLARK, P. F.: Effect of amino acid imbalance on course of Lansing poliomyelitis in mice. Proc. Soc. exp. Biol., N. Y. 81: 484–486, 1952.
135. GIFFORD, G. E., ROBERTSON, H. E. AND SYVERTON, J. T.: Application of manometric method to testing chemical agents *in vitro* for interference with poliomyelitis virus synthesis. Proc. Soc. exp. Biol., N. Y. 86: 515–522, 1954.
136. GILFORD, G. H.: Treatment of trachoma with penicillin. Brit. med. J. 1: 232–233, 1945.
137. GINSBERG, H. S.: Mechanism of production of pulmonary lesions in mice by Newcastle disease virus (NDV). J. exp. Med. 94: 191–211, 1951.
138. GINSBERG, H. S., GOEBEL, W. F. AND HORSFALL, F. L.: Inhibition of mumps virus multiplication by a polysaccharide. Proc. Soc. exp. Biol., N. Y. 66: 99–100, 1947.
139. GINSBERG, H. S., GOEBEL, W. F. AND HORSFALL, F. L.: The inhibitory effect of polysaccharide on mumps virus multiplication. J. exp. Med. 87: 385–410, 1948.
140. GINSBERG, H. S. AND HORSFALL, F. L.: Concurrent infection with influenza virus and mumps virus or pneumonia virus of mice (PVM) as bearing on the inhibition of virus multiplication by bacterial polysaccharides. J. exp. Med. 89: 37–52, 1949.
141. GINSBERG, H. S. AND HORSFALL, F. L.: A resistant variant of mumps virus. Multiplication of the variant in the presence of inhibitory quantities of Friedländer bacillus polysaccharide. J. exp. Med. 90: 393–407, 1949.
142. GINSBERG, H. S. AND HORSFALL, F. L.: Therapy of infection with pneumonia virus of mice (PVM). Effect of a polysaccharide on the multiplication cycles of the virus and on the course of the viral pneumonia. J. exp. Med. 93: 161–171, 1951.
143. GINSBERG, H. S. AND HORSFALL, F. L.: Quantitative aspects of the multiplication of influenza A virus in the mouse lung. Relation between the degree of viral multiplication and the extent of pneumonia. J. exp. Med. 95: 135–145, 1952.
144. GJURIĆ, N. J.: Neue Wege in der Behandlung des Lymphogranuloma inguinale. Münch med. Wschr. 85: 335–337, 1938.
145. GOGOLAK, F. M. AND WEISS, E.: The effect of antibiotics on agents of the psittacosis-lymphogranuloma group. II. The effect of aureomycin. J. infect. Dis. 87: 264–274, 1950.
146. GOLLAN, F.: Effect of thyroxin on mouse susceptibility to polioencephalitis. Proc. Soc. exp. Biol., N. Y. 67: 362–363, 1948.
147. GOLUB, O. J.: Acquired resistance of psittacosis virus to sulfadiazine and effects of chemical antagonists on sulfonamide activity. J. Lab. clin. Med. 33: 1241–1248, 1948.
148. GRAVES, F. B. AND BALL, W. O.: Evaluation of the treatment of primary atypical pneumonia with aureomycin, chloromycetin and terramycin. J. Pediat. 39: 155–167, 1951.
149. GREEN, M. AND STAHMANN, M. A.: Inhibition of mumps virus multiplication by a synthetic polypeptide. Proc. Soc. exp. Biol., N. Y. 83: 852–858, 1953.
150. GREEN, M. AND STAHMANN, M. A.: Virus inhibitory action of polyvinylamine. Proc. Soc. exp. Biol., N. Y. 87: 507–509, 1954
151. GREEN, M., STAHMANN, M. A. AND RASMUSSEN, A. F.: Protection of embryonated eggs infected with infectious bronchitis or Newcastle disease virus by polypeptides. Proc. Soc. exp. Biol., N. Y. 83: 641–643, 1953.
152. GREEN, R. H.: Inhibition of multiplication of influenza virus by tannic acid. Proc. Soc. exp. Biol., N. Y. 67: 483–484, 1948.
153. GREEN, R. H.: Inhibition of multiplication of influenza virus by extracts of tea. Proc. Soc. exp. Biol., N. Y. 71: 84–85, 1949.
154. GREEN, R. H., RASMUSSEN, A. F. AND SMADEL, J. E.: Chemoprophylaxis of experimental influenza infection in eggs. Publ. Hlth. Rep., Wash. 61: 1401–1403, 1946.
155. GREEN, R. H. AND WOOLLEY, D. W.: Inhibition by certain polysaccharides of hemagglutination and of multiplication of influenza virus. J. exp. Med. 86: 55–64, 1947.
156. GREEN, T. W.: Aureomycin therapy of human psittacosis. J. Amer. med. Ass. 144: 237–238, 1950.
157. GROUPÉ, V., FRANKEL, J. W., LECHEVALIER, M. P. AND WAKSMAN, S. A.: Antiviral properties of Ehrlichin, an antibiotic produced by *Streptomyces lavendulae*. J. Immunol. 67: 471–482, 1951.
158. GROUPÉ, V. AND HERRMANN, E. C.: Modification of the neurotoxic effect of influenza virus in mice by xerosin. J. Immunol. 74: 249–254, 1955.
159. GROUPÉ, V., PUGH, L. H. AND LEVINE, A. S.: Suppression of viral pneumonia in mice by a microbial product (APM). Proc. Soc. exp. Biol., N. Y. 80: 710–714, 1952.
160. GROUPÉ, V., PUGH, L. H. AND LEVINE, A. S.: Mechanism of suppression of non-transmissible pneumonia in mice induced by Newcastle disease virus. Science 118: 187–191, 1953.
161. GROUPÉ, V., PUGH, L. H., LEVINE, A. S. AND HERRMANN, E. C.: Suppression of certain viral lesions by a microbial product, xerosin, lacking in demonstrable antiviral properties and produced by *Achromobacter xerosis* N. Sp. J. Bact. 68: 10–18, 1954.
162. GROUPÉ, V., PUGH, L. H., WEISS, D. AND KOCHI, M.: Observations on antiviral activity of viscosin. Proc. Soc. exp. Biol., N. Y. 78: 354–358, 1951.
163. GUNNISON, J. B., SPECK, R. S., JAWETZ, E. AND BRUFF, J. A.: Studies on antibiotic synergism and antagonism. The effect of sulfadiazine on the action of penicillin *in vitro* and *in vivo*. Antibiot. and Chemother. 1: 259–265, 1951.
164. HAAS, E.: The effect of atabrine and quinine on isolated respiratory enzymes. J. biol. Chem. 155: 321–331, 1944.
165. HAMILTON, G. R.: Treatment of venereal lymphogranuloma with sulfanilamide. Milit. Surg. 83: 431–438, 1938.

166. HAMILTON, H. L.: Effect of *p*-aminobenzoic acid on growth of rickettsiae and elementary bodies, with observations on mode of action. Proc. Soc. exp. Biol., N. Y. **59**: 220–226, 1945.
167. HAMKE, H.: Über Psittakosis und ihre Behandlung mit Aureomycin. Dtsch. med. Wschr. **76**: 246–247, 1951.
168. HAMKE, H. AND RISSE, C.: Eine neue Psittakoseepidemie und wirksame Psittakosebehandlung. Klin. Wschr. **28**: 422, 1950.
169. HAMMON, W. MCD., AIRD, R. B. AND SATHER, G.: Failure of trypan red to protect against certain neurotropic viruses ("M.M." and Russian spring-summer encephalitis). Proc. Soc. exp. Biol., N. Y. **69**: 511–513, 1948.
170. HAMRE, D., BERNSTEIN, J. AND DONOVICK, R.: Activity of *p*-aminobenzaldehyde, 3-thiosemicarbazone on vaccinia virus in the chick embryo and in the mouse. Proc. Soc. exp. Biol., N. Y. **73**: 275–278, 1950.
171. HAMRE, D., BROWNLEE, K. A. AND DONOVICK, R.: Studies on the chemotherapy of vaccinia virus. J. Immunol. **67**: 305–312, 1951.
172. HAMRE, D. AND RAKE, G.: Feline pneumonitis (Baker), a new member of the lymphogranuloma-psittacosis group of agents. J. infect. Dis. **74**: 206–211, 1944.
173. HAMRE, D. AND RAKE, G.: Studies on lymphogranuloma venereum. V. The action of some antibiotic substances and sulfonamides *in vitro* and *in vivo* upon the agents of feline pneumonitis and lymphogranuloma venereum. J. infect. Dis. **81**: 175–190, 1947.
174. HANAN, R.: The effect of tocopheryl esters on influenza virus. Proc. Soc. exp. Biol., N. Y. **75**: 440–444, 1950.
175. HANNOUN, C.: Action inhibitrice d'analogues du glycocolle et de l'adénine sur la multiplication du virus de la grippe. C. R. Acad. Sci., Paris **235**: 1340–1342, 1952.
176. HANNOUN, C.: Action de certains inhibiteurs enzymatiques sur la multiplication du virus de la grippe. C. R. Acad. Sci., Paris **235**: 1445–1446, 1952.
177. HANNOUN, C.: Activité de la thiosemicarbazone de la *p*-acétamidobenzaldéhyde sur le virus de la grippe cultivé sur embryon de Poulet. C. R. Acad. Sci., Paris **236**: 864–865, 1953.
178. HANNOUN, C.: Action des analogues puriques et pyrimidiques sur la multiplication du virus de la grippe dans l'embryon de Poulet. Atti VI Congr. Internaz. Microbiol. **1**: 431–432, 1953.
179. HANNOUN, C.: Effets du 2-4-dinitrophénol et du nitrure de sodium sur le système embryon de Poulet—virus grippal. C. R. Acad. Sci., Paris **238**: 1172–1174, 1954.
180. HARLEY, R. D., BROWN, A. E. AND HERRELL, W. E.: Sulfanilamide and neoprontosil in the treatment of trachoma. Proc. Mayo Clin. **14**: 641–645, 1939.
181. HARVEY, J. C., MIRICK, G. S. AND SCHAUB, I. G.: Clinical experience with aureomycin. J. clin. Invest. **28**: 987–991, 1949.
182. HEILMAN, F. R. AND HERRELL, W. E.: Penicillin in the treatment of experimental ornithosis. Proc. Mayo Clin. **19**: 57–65, 1944.
183. HEILMAN, F. R. AND HERRELL, W. E.: Penicillin in the treatment of experimental psittacosis. Proc. Mayo Clin. **19**: 204–207, 1944.
184. HERRELL, W. E.: Observations on the clinical use of aureomycin. Proc. Mayo Clin. **24**: 612–618, 1949.
185. HEYMAN, A., WALL, M. J. AND BEESON, P. B.: The effect of sulfonamide therapy on the persistence of the virus of lymphogranuloma in buboes. Amer. J. Syph. **31**: 81–86, 1947.
186. HINSHAW, H. C.: Psittacosis: possible response to sulfapyridine. Proc. Mayo Clin. **15**: 657–662, 1940.
187. HIRST, G. K.: Studies on the mechanism of adaptation of influenza virus to mice. J. exp. Med. **86**: 357–381, 1947.
188. HOLDEN, M. AND MOLLOY, E.: Further experiments on the inactivation of herpes virus by vitamin C (l-ascorbic acid). J. Immunol. **33**: 251–257, 1937.
189. HOLDER, E. C., LEVINE, S. AND BULLOWA, J. G. M.: *In vitro* action of sulfonamides on lymphogranuloma venereum virus. J. Pharmacol. **74**: 99–105, 1942.
190. HOLTMAN, D. F.: The effect of environmental temperature on mouse susceptibility to poliomyelitis virus. Science **103**: 137–138, 1946.
191. HOLTMAN, D. F.: The effect of thiouracil and thyroactive substances on mouse susceptibility to poliomyelitis virus. Science **104**: 50–51, 1946.
192. HORSFALL, F. L. AND MCCARTY, M.: The modifying effects of certain substances of bacterial origin on the course of infection with pneumonia virus of mice (PVM). J. exp. Med. **85**: 623–646, 1947.
193. HOTCHIN, J. E.: The influence of acridines on the interaction of *Staphylococcus aureus* and staphylococcus K phage. J. gen. Microbiol. **5**: 611–618, 1951.
194. HOTTA, S.: Therapeutic experiments on dengue infections in mice. Ann. trop. Med. Parasit. **47**: 1–8, 1953.
195. HOWE, H. A. AND BODIAN, D.: Production of immunity to poliomyelitis virus in motor cells of the monkey's spinal cord. Proc. Soc. exp. Biol., N. Y. **42**: 346–349, 1939.
196. HOWE, H. A. AND BODIAN, D.: Refractoriness of nerve cells to poliomyelitis virus after interruption of their axones. Johns Hopk. Hosp. Bull. **69**: 92–134, 1941.
197. HOWE, H. A. AND MELLORS, R. C.: Cytochrome oxidase in normal and regenerating neurons. J. exp. Med. **81**: 489–500, 1945.
198. HOYLE, L.: The effect of triphenylmethane dyes on the intracellular growth of influenza virus A. Brit. J. exp. Path. **30**: 123–129, 1949.
199. HUANG, C. AND EATON, M. D.: The reversal by PABA of sulfonamide inhibition of the viruses of lymphogranuloma venereum and mouse pneumonitis. J. Bact. **58**: 73–88, 1949.
200. HULL, R. N. AND LAVELLE, J. M.: Inhibition of cytopathogenic effect of poliomyelitis viruses in tissue culture by antibiotic M. 8450. Proc. Soc. exp. Biol., N. Y. **83**: 787–790, 1953.
201. HURST, E. W.: Nitroakridin 3582: a compound possessing chemotherapeutic activity against the viruses of psittacosis and lymphogranuloma venereum. Brit. J. Pharmacol. **3**: 181–186, 1948.

202. HURST, E. W., LANDQUIST, J. K., MELVIN, P., PETERS, J. M., SENIOR, N., SILK, J. A. AND STACEY, G. J.: The therapy of experimental psittacosis and lymphogranuloma venereum (inguinale) II. The activity of quinoxaline-1:4-dioxide and substituted and related compounds, with a note on the morphological changes induced by lymphogranuloma virus by these compounds and by antibiotics. Brit. J. Pharmacol. 8: 297–305, 1953.

203. HURST, E. W., MELVIN, P. AND PETERS, J. M.: The prevention of encephalitis due to the viruses of Eastern equine encephalomyelitis and louping-ill: experiments with trypan red, mepacrine and many other substances. Brit. J. Pharmacol. 7: 455–472, 1952.

204. HURST, E. W., PETERS, J. M. AND MELVIN, P.: The therapy of experimental psittacosis and lymphogranuloma venereum (inguinale). I. The comparative efficacy of penicillin, chloramphenicol, aureomycin and terramycin. Brit. J. Pharmacol. 5: 611–624, 1950.

205. HURST, E. W., PETERS, J. M. AND MELVIN, P.: The action of mepacrine and trypan red in a number of virus diseases. Brit. J. Pharmacol. 7: 473–481, 1952.

206. HURST, E. W., SNOW, G. A. AND ROBERTS, D. C.: The antiviral activity of mepacrine in relation to morphological changes produced by the drug. Brit. J. exp. Path. 36: 215–225, 1955.

207. HYDÉN, H. AND HARTELIUS, H.: Stimulation of the nucleoprotein-production in the nerve cells by malononitrile and its effect on psychic functions in mental disorders. Acta psychiat., Kbh. Suppl. 48: pp. 1–117, 1948.

208. INKLEY, G. W.: Chemotherapeutic studies on the viruses of sheep abortion and mouse pneumonitis (Nigg) with special reference to an embryonated egg method. Brit. J. Pharmacol. 8: 448–453, 1953.

209. JAMES, D. G., PRICE, K. M. AND KNEELAND, Y.: Effect of small amounts of aureomycin and terramycin on virus of feline pneumonitis. Proc. Soc. exp. Biol., N. Y. 77: 431–434, 1951.

210. JAWETZ, E., GUNNISON, J. B., BRUFF, J. B. AND COLEMAN, V. R.: Studies on antibiotic synergism and antagonism. Synergism among seven antibiotics against various bacteria *in vitro*. J. Bact. 64: 29–39, 1952.

211. JAWETZ, E., GUNNISON, J. B. AND SPECK, R. S.: Studies on antibiotic synergism and antagonism: the interference of aureomycin, chloramphenicol and terramycin with the action of streptomycin. Amer. J. med. Sci. 222: 404–412, 1951.

212. JAWETZ, E., GUNNISON, J. B., SPECK, R. S. AND COLEMAN, V. R.: Studies on antibiotic synergism and antagonism. The interference of chloramphenicol with the action of penicillin. Arch. intern. Med. 87: 349–359, 1951.

213. JAWETZ, E. AND SPECK, R. S.: Joint action of penicillin with chloramphenicol on an experimental streptococcal infection of mice. Proc. Soc. exp. Biol., N. Y. 74: 93–96, 1950.

214. JONES, D.: The effect of antibiotic substances upon bacteriophage. J. Bact. 50: 341–348, 1945.

215. JONES, H., RAKE, G. AND STEARNS, B.: Studies on lymphogranuloma venereum. III. The action of the sulfonamides on the agent of lymphogranuloma venereum. J. infect. Dis. 76: 55–69, 1945.

216. JONES, H. P., RAKE, G. AND MCKEE, C. M.: Chemotherapy of lymphogranuloma venereum with sulfonamide drugs. Proc. Soc. exp. Biol., N. Y. 48: 318–323, 1941.

217. JONES, J. H., FOSTER, C. AND HENLE, W.: Effect of oxythiamine on infection of mice with the Lansing strain of poliomyelitis virus. Proc. Soc. exp. Biol., N. Y. 69: 454–458, 1948.

218. JONES, J. H., FOSTER, C., HENLE, W. AND ALEXANDER, D.: Dietary deficiencies and poliomyelitis. Effects of low protein and of low tryptophan diets on the response of mice to the Lansing strain of poliomyelitis virus. Arch. Biochem. 11: 481–487, 1946.

219. JULIANELLE, L. A., LANE, J. F. AND WHITTED, W. P.: The effect of sulfanilamide on the course of trachoma. Amer. J. Ophthal. 22: 1244–1252, 1939.

220. JULIANELLE, L. A. AND SMITH, J. E.: Studies on the infectivity of trachoma. XI. The effect of sulfanilamide on the virus. Amer. J. Ophthal. 25: 317–321, 1942.

221. JUNGEBLUT, C. W.: Vitamin C therapy and prophylaxis in experimental poliomyelitis. J. exp. Med. 65: 127–146, 1937.

222. JUNGEBLUT, C. W.: Further observations on vitamin C therapy in experimental poliomyelitis. J. exp Med. 66: 459–477, 1937.

223. JUNGEBLUT, C. W.: A further contribution to vitamin C therapy in experimental poliomyelitis. J. exp. Med. 70: 315–332, 1939.

224. JUNGEBLUT, C. W.: Failure of hypnotic and convulsive agents to alter the course of experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 43: 464–468, 1940.

225. JUNGEBLUT, C. W.: Chemotherapeutic effects of a naphthoquinonimine on infection of mice with Columbia-SK group of viruses. Proc. Soc. exp. Biol., N. Y. 77: 176–182, 1951.

226. JUNGEBLUT, C. W., SANDERS, M. AND FEINER, R. R.: Studies in rodent poliomyelitis. I. Further experiments with the murine strain of SK poliomyelitis virus. J. exp. Med. 75: 611–629, 1942.

227. KALTER, S. S., SMOLIN, H. J., MCELHANEY, J. M. AND TEPPERMAN, J.: Endocrines and their relation to influenza virus infection. J. exp. Med. 93: 529–538, 1951.

228. KALTER, S. S., STUART, D. C. AND TEPPERMAN, J.: Alterations in rate of influenza virus proliferation produced by growth hormone and testosterone. Proc. Soc. exp. Biol., N. Y. 74: 605–607, 1950.

229. KASS, E. H., NEVA, F. A. AND FINLAND, M.: Failure of ACTH to protect against acutely lethal toxins of influenza virus and rickettsiae. Proc. Soc. exp. Biol., N. Y. 76: 560–563, 1951.

230. KEARNEY, E. B., POND, W. L., PLASS, B. A., MADDY, K. H., ELVEHJEM, C. A. AND CLARK, P. F.: Effect of thiamine deficiency on Western equine encephalomyelitis in mice. J. infect. Dis. 82: 177–186, 1948.

231. KEARNEY, E. B., POND, W. L., PLASS, B. A., MADDY, K. H., ELVEHJEM, C. A. AND CLARK, P. F.: The influence of varied protein intake and of tryptophane deficiency on Theiler's encephalomyelitis of mice. J. Bact. 55: 89–111, 1948.

232. KILBOURNE, E. D. AND HORSFALL, F. L.: Increased virus in eggs injected with cortisone. Proc. Soc. exp. Biol., N. Y. 76: 116–118, 1951.

233. KILBOURNE, E. D. AND HORSFALL, F. L.: Lethal infection with Coxsackie virus of adult mice given cortisone. Proc. Soc. exp. Biol., N. Y. 77: 135–138, 1951.
234. KIRK, R., MCKELVIE, A. R. AND HUSSEIN, H. A.: Sulphanilamide in the treatment of trachoma. Lancet 2: 994–995, 1938.
235. KIRKWOOD, T.: Human ornithosis. Report of a case treated with penicillin. Illinois med. J. 90: 193–196, 1946.
236. KLIGMAN, A. M., BALDRIDGE, G. D., REBELL, G. AND PILLSBURY, D. M.: The effect of cortisone on the pathologic responses of guinea pigs infected cutaneously with fungi, viruses and bacteria. J. Lab. clin. Med. 37: 615–620, 1951.
237. KNEELAND, Y. AND PRICE, K. M.: Treatment with chloramphenicol, aureomycin, and terramycin of the pneumonia of mice caused by feline pneumonitis virus. J. Immunol. 65: 653–660, 1950.
238. KNEELAND, Y., ROSE, H. M. AND GIBSON, C. D.: Aureomycin in the treatment of primary atypical pneumonia. Amer. J. Med. 6: 41–50, 1949.
239. KOPROWSKI, H. AND LENNETTE, E. H.: Propagation of yellow fever virus in tissue cultures containing sulphonamides. Amer. J. Hyg. 40: 1–13, 1944.
240. KOTEEN, H.: Lymphogranuloma venereum. Medicine, Baltimore 24: 1–69, 1945.
241. KRAMER, P. E., ROBBINS, M. L. AND SMITH, P. L.: Phenolic compounds as chemotherapeutic agents against poliomyelitis in tissue culture. J. Pharmacol 113: 262–271, 1955.
242. KRAMER, S. D., GEER, H. A. AND SZOBEL, D. A.: The chemoprophylactic and therapeutic action of a wide variety of chemical compounds on two neurotropic virus infections in mice. J. Immunol. 49: 273–314, 1944.
243. KRUEGER, A. P., *et al.*: Attempts to protect against influenza virus with various sulfonamides, acridines and antibiotics. Science 98: 348–349, 1943
244. LAIRD, S. M.: Sulphanilamide in climatic bubo. Brit. med. J. 2: 1043–1044, 1938.
245. LASNITZKI, I., MATTHEWS, R. E. F. AND SMITH, J. D.: Incorporation of 8-azaguanine into nucleic acids. Nature, Lond. 173: 346–348, 1954.
246. LAVERY, F. S.: Sulphonamides and penicillin in the treatment of trachoma. Brit. J. Ophthal. 30: 591–594, 1946.
247. LEFTWICH, W. B. AND MIRICK, G. S.: The effect of diet on the susceptibility of the mouse to pneumonia virus of mice (PVM). I. Influence of pyridoxine in the period after the inoculation of virus. J. exp. Med. 89: 155–173, 1949.
248. LEVADITI, C.: L'activité thérapeutique des dérivés benzéniques sulfurés dans les maladies provoquées par les ultravirus. C. R. Soc. Biol., Paris 127: 958–960, 1938.
249. LEVADITI, C.: Chimiothérapie de la lymphogranulomatose inguinale expérimentale. C. R. Soc. Biol., Paris 128: 138–140, 1938.
250. LEVADITI, C.: Chimiothérapie de la maladie de Nicolas-Favre expérimentale. C. R. Soc. Biol., Paris 128: 875–877, 1938.
251. LEVADITI, C.: Chimiothérapie expérimentale de la lymphogranulomatose inguinale (maladie de Nicolas-Favre). C. R. Soc. Biol., Paris 129: 490–492, 1938.
252. LEVADITI, C. AND VAISMAN, A.: Action thérapeutique de la pénicilline dans la syphilis cliniquement inapparente et la maladie de Nicolas-Favre chez la souris. Bull. Acad. Méd., Paris 128: 699–701, 1944.
253. LEVADITI, C. AND VAISMAN, A.: Effet curatif de la pénicilline dans la maladie de Nicolas-Favre de la souris. Bull. Acad. Méd., Paris 129: 253–255, 1945.
254. LEVADITI, C., VAISMAN, A. AND REINIÉ, L.: Chimiothérapie de la lymphogranulomatose inguinale (maladie de Nicolas et Favre). C. R. Soc. Biol., Paris 131: 40–42, 1939.
255. LEVINSON, D. C., GIBBS, J. AND BEARDWOOD, J. T.: Ornithosis as a cause of sporadic atypical pneumonia. J. Amer. med. Ass. 126: 1079–1084, 1944.
256. LIAN, S. B.: Prontosiltherapie bij trachoom. Geneesk. Tijdschr. Ned.-Ind. 78: 1058–1065, 1938.
257. LICHSTEIN, H. C., MCCALL, K. B., ELVEHJEM, C. A. AND CLARK, P. F.: The influence of "folic acid" deficiency in *Macaca mulatta* on susceptibility to experimental poliomyelitis. J. Bact. 52: 105–110, 1946.
258. LICHSTEIN, H. C., MCCALL, K. B., KEARNEY, E. B., ELVEHJEM, C. A. AND CLARK, P. F.: Effect of minerals on susceptibility of Swiss mice to Theiler's virus. Proc. Soc. exp. Biol., N. Y. 62: 279–284, 1946.
259. LICHSTEIN, H. C., WAISMAN, H. A., ELVEJHEM, C. A. AND CLARK, P. F.: Influence of pantothenic acid deficiency on resistance of mice to experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 56: 3–5, 1944.
260. LICHSTEIN, H. C., WAISMAN, H. A., MCCALL, K. B., ELVEHJEM, C. A. AND CLARK, P. F.: Influence of pyridoxine, inositol and biotin on susceptibility of Swiss white mice to experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 60: 279–287, 1945.
261. LILLIE, R. D., DYER, R. E., ARMSTRONG, C. AND PASTERNACK, J. G.: Seasonal variation in intensity of brain reaction of the St. Louis encephalitis in mice and of endemic typhus in guinea pigs. Publ. Hlth. Rep., Wash. 52: 1805–1822, 1937.
262. LOE, F.: Sulfanilamide treatment of trachoma. J. Amer. med. Ass. 111: 1371–1372, 1938.
263. LOGRIPPO, G. A., EARLE, D. P., BRODIE, B. B., GRAEF, I., BOWMAN, R. AND WARD, R.: The effect of drugs on the excretion of Theiler's virus (TO) by mice. Amer. J. Hyg. 55: 55–69, 1952.
264. LOGRIPPO, G. A., EARLE, D. P., GRAEF, I. AND WARD, R.: Effect of a mercurial compound in suppressing intestinal carriage of Theiler's virus (TO) in mice. Amer. J. Hyg. 55: 70–73, 1952.
265. LOOSLI, C. G., HAMRE, D., GRAYSTON, J. T. AND ALEXANDER, E. R.: Experimental air-borne mouse pneumonitis virus (MPV) infections in mice. III. The development of a strain of MPV resistant to sulfadiazine and related compounds. Antibiotics Annual 1954–1955, pp. 490–503. Medical Encyclopedia, New York 1955.
266. LOOSLI, C. G., HAMRE, D., RITTER, G. AND BERLIN, B. S.: Experimental air-borne mouse pneumonitis virus (MPV) infections in mice. II. The prophylactic and therapeutic effect of sulfadiazine and antibiotics. Antibiotics Annual 1954–1955, pp. 474–489. Medical Encyclopedia, New York 1955.

267. Loosli, C. G., Hull, R. B., Berlin, B. S. and Alexander, E. R.: The influence of ACTH on the course of experimental influenza type A virus infection. J. Lab. clin. Med. 37: 464–476, 1951.
268. Ludford, R. J.: The occasional neutralisation of the active agent of filterable fowl tumours by fluid media from tissue cultures. Amer. J. Cancer 35: 63–71, 1939.
269. MacCallum, F. O. and Findlay, G. M.: Chemotherapeutic experiments on the virus of lymphogranuloma inguinale in the mouse. Lancet 2: 136–138, 1938.
270. Machlowitz, R. A., Charney, J., Gibson, O., Fisher, W. P., Roberts, W. S. and Asheshov, I. N.: Cardicin, an antibiotic having antimicrobial and antiviral properties. Antibiot. and Chemother. 3: 966–970, 1953.
271. Mandel, H. G., Carlo, P. E. and Smith, P. K.: The incorporation of 8-azaguanine into nucleic acids of tumour-bearing mice. J. biol. Chem. 206: 181–189, 1954.
272. Manire, G. P. and Meyer, K. F.: The toxins of the psittacosis-lymphogranuloma group of agents. II. Effect of aureomycin and penicillin upon the toxins of psittacosis viruses. J. infect. Dis. 86: 233–240, 1950.
273. Manwell, R. D. and Goldstein, F.: A new and effective method of treating canary-pox. Proc. Soc. exp. Biol., N. Y. 41: 554–555, 1939.
274. Marmell, M. and Prigot, A.: Tetracycline in the treatment of certain venereal diseases. Antibiot. and Chemother. 4: 1117–1121, 1954.
275. Martin, G. J. and Fisher, C. V.: Nutritional status of Staphylococcus aureus as influenced by proflavine. J. Lab. clin. Med. 29: 383–389, 1944.
275a. Matthews, R. E. F. and Smith, J. D.: The chemotherapy of viruses. In: Advances in Virus Research, ed. K. M. Smith and M. A. Lauffer, 3: 49–148. Academic Press, New York 1955.
276. Mauer, G.: Die Wirkung des Trypaflavins bei psittakoseinfizierten Mäusen. Zbl. Bakt., Abt. I 142: 279–286, 1938.
277. McClelland, L.: A crystalline antiviral agent produced by a new species of *Nocardia*. II. Antiviral activity in animals. Antibiotics Annual 1953–1954, pp. 615–621. Medical Encyclopedia, New York 1953.
278. McClelland, L. and van Rooyen, C. E.: Studies on the effect of some aromatic amidines and other chemical compounds on the growth of influenza virus in the embryonated egg. Canad. J. Res. 27: Sect. E: 177–185, 1949.
279. McCrea, J. F. and Duran-Reynals, F.: Inactivation of vaccinia virus by a diffusible component from hydrolysed hyaluronic acid. Science 118: 93–95, 1953.
280. McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M. and Smith, J. W.: "Ilotycin", a new antibiotic. Antibiot. and Chemother. 2: 281–283, 1952.
281. McIlwain, H.: Bacterial inhibition by metabolite analogues. Part V. Reactions and antibacterial properties of *p*-diazine di-N-oxides. J. chem. Soc. 1943: 322–325.
282. McKee, C. M., Rake, G., Greep, R. O. and van Dyke, H. B.: Therapeutic effect of sulfathiazole and sulfapyridine. Proc. Soc. exp. Biol., N. Y. 42: 417–421, 1939.
283. McKinley, E. B. and Acree, E. G.: Experimental fever therapy in myxomatosis and fibroma of rabbits. Proc. Soc. exp. Biol., N. Y. 36: 414–416, 1937.
284. McKinstry, D. W. and Reading, E. H.: Studies on the chemotherapy of experimental virus infections. I. The effect of certain pyrimidine derivatives on experimental murine poliomyelitis. J. Franklin Inst. 237: 422–431, 1944.
285. McKinstry, D. W. and Reading, E. H.: Studies on the chemotherapy of experimental virus infections. II. The effect of certain organic arsenicals on the course of experimental murine poliomyelitis. J. Franklin Inst. 240: 422–429, 1945.
286. Meiklejohn, G., Beck, M. D. and Eaton, M. D.: Atypical pneumonia caused by psittacosis-like viruses. J. clin. Invest. 23: 167–175, 1944.
287. Meiklejohn, G. and Shragg, R. I.: Aureomycin in primary atypical pneumonia. J. Amer. med. Ass. 140: 391–396, 1949.
288. Meiklejohn, G., Thalman, W. G., Waligora, D. J., Kempe, C. H. and Lennette, E. H.: Chemotherapy in primary atypical pneumonia. J. Amer. med. Ass. 154: 553–557, 1954.
289. Meiklejohn, G., Wagner, J. C. and Beveridge, G. W.: Studies on the chemotherapy of viruses in the psittacosis-lymphogranuloma group. I. Effect of penicillin and sulfadiazine on ten strains in chick embryos. J. Immunol. 54: 1–8, 1946.
290. Melcher, G. W., Gibson, C. D., Rose, H. M. and Kneeland, Y.: Terramycin in the treatment of pneumococcic and primary atypical pneumonia. J. Amer. med. Ass. 143: 1303–1308, 1950.
291. Meyer, K. F. and Eddie, B.: The knowledge of human virus infections of animal origin. J. Amer. med. Ass. 133: 822–828, 1947.
292. Meyer, K. F. and Eddie, B.: Human carrier of the psittacosis virus. J. infect. Dis. 88: 109–125, 1951.
293. Meyer, K. F. and Eddie, B.: Chemotherapy of natural psittacosis and ornithosis. Field trial of tetracycline (polyotic hydrochloride), chlortetracycline and oxytetracycline. Antibiotics Annual 1954–1955, pp. 544–555. Medical Encyclopedia, New York 1955.
294. Meyer, K. F. and Eddie, B.: Chemotherapy of natural psittacosis and ornithosis. Field trial of tetracycline, chlortetracycline, and oxytetracycline. Antibiot. and Chemother. 5: 289–299, 1955.
295. Meyer, K. F., Eddie, B. and Yanamura, H. Y.: Ornithosis (psittacosis) in pigeons and its relation to human pneumonitis. Proc. Soc. exp. Biol., N. Y. 49: 609–615, 1942.
296. Milzer, A.: Effect of pituitary adrenocorticotrophic hormone (ACTH) on experimental poliomyelitis and equine encephalomyelitis. J. infect. Dis. 88: 54–55, 1951.
297. Milzer, A. and Adelman, P.: Failure of malononitrile in therapy of experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 74: 134–135, 1950.

298. MINTON, S. A., OFFICER, J. E. AND THOMPSON, R. L., Effect of thiosemicarbazones and dichlorophenoxy thiouracil on multiplication of a recently isolated strain of variola-vaccinia virus in the brain of the mouse. J. Immunol. 70: 222–228, 1953.
299. MIRICK, G. S. AND LEFTWICH, W. B.: The effect of diet on the susceptibility of the mouse to pneumonia virus of mice (PVM). II. Influence of pyridoxine administered in the period before as well as after the inoculation of virus. J. exp. Med. 89: 175–184, 1949.
300. MITSUI, Y. AND TANAKA, C.: Terramycin, aureomycin and chloramphenicol in the treatment of trachoma. Antibiot. and Chemother. 1: 146–157, 1951.
301. MITSUI, Y., TANAKA, C., TOYA, H., IWASHIGE, Y. AND YAMASHITA, K.: Terramycin in the treatment of trachoma. Arch. Ophthal., N. Y. 46: 235–244, 1951.
302. MOGABGAB, W. J. AND HORSFALL, F. L.: Effect of sodium monofluoroacetate on the multiplication of influenza viruses, mumps virus and pneumonia virus of mice (PVM). J. exp. Med. 96: 531–548, 1952.
303. MOLDAVE, K., WINZLER, R. J. AND PEARSON, H. E.: Effect of lysine on metabolism of minced one-day-old mouse brain and propagation of Theiler's GD VII virus. Fed. Proc. 10: 225, 1951.
304. MONTEL, L.-R. AND NGUYEN-VAN-THO: Traitement de la maladie de Nicolas-Favre par les dérivés sulfamidés (rubiazol-septasine). Bull. Soc. franç. Derm. Syph. 45: 652–655, 1938.
305. MOORE, A. E. AND FRIEND, C.: Effect of 2,6-diaminopurine on the course of Russian spring-summer encephalitis infection in the mouse. Proc. Soc. exp. Biol., N. Y. 78: 153–157, 1951.
306. MORGAN, H. R.: Studies on the relationship of pteroylglutamic acid to the growth of psittacosis virus. J. exp. Med. 88: 285–294, 1948.
307. MORGAN, H. R.: Factors related to the growth of psittacosis virus (strain 6BC). I. Pteroylglutamic acid, vitamin B_{12}, and citrovorum factor. J. exp. Med. 95: 269–276, 1952.
308. MORGAN, H. R.: Factors related to the growth of psittacosis virus (strain 6BC). II. Purines, pyrimidines, and other components related to nucleic acid. J. exp. Med. 95: 277–283, 1952.
309. MORGAN, H. R.: Factors related to growth of psittacosis virus (strain 6BC). III. Uracil and related compounds. Proc. Soc. exp. Biol., N. Y. 81: 448–450, 1952.
310. MORGAN, H. R.: Factors related to the growth of psittacosis virus (strain 6BC). IV. Certain amino acids, vitamins and other substances. J. exp. Med. 99: 451–460, 1954.
311. MOULDER, J. W., MCCORMACK, B. R. S., GOGOLAK, F. M., ZEBOVITZ, M. M. AND ITATANI, M. K.: Production and properties of a penicillin-resistant strain of feline pneumonitis virus. J. infect. Dis. 96: 57–74, 1955.
312. MUDROW, L. AND BOCK, M.: Der Antagonismus von Sulfonamiden und Para-Aminobenzosäure bei experimentellen Spirochäten-, Spirillen- und Virusinfektionen. Z. ImmunForsch. 104: 463–473, 1943.
313. MURRAY, F. J., SCRUGHAM, J. F. AND FOTER, M. J.: Effect of Congo red on the "MM" virus. Proc. Soc. exp. Biol., N. Y. 72: 275–276, 1949.
314. NEITZ, W. O.: Die Wirkung von Uliron auf das Herzwasser (*Rickettsia ruminantium*) der Schafe. Berl. Münch. tierärztl. Wschr. 1939: 134–136.
315. NEITZ, W. O.: Uleron in the treatment of heartwater. J. S. Afr. vet. med. Ass. 11: 15, 1940.
316. ODDO, F. G. AND EATON, M. D.: *In vivo* reversal by cysteine of the virustatic effect of a nitrofuran. Proc. Soc. exp. Biol., N. Y. 81: 197–200, 1952.
317. O'DELL, T. B., WRIGHT, H. N. AND BIETER, R. N.: Chemotherapeutic activity of nucleic acids and high protein diets against the infection caused by the MM virus in mice. J. Pharmacol. 107: 232–240, 1953.
318. PARKER, R. F.: Psittacosis as a cause of atypical pneumonia. Penicillin therapy. Ohio St. med. J. 41: 1097–1098, 1945.
319. PARKER, R. F. AND DIEFENDORF, H. W.: Effect of penicillin on certain viruses. Proc. Soc. exp. Biol., N. Y. 57: 351–354, 1944.
320. PARKER, R. F. AND THOMPSON, R. L.: The effect of external temperature on the course of infectious myxomatosis of rabbits. J. exp. Med. 75: 567–573, 1942.
321. PEARSON, H. E.: Factors affecting the propagation of Theiler's GD VII mouse encephalomyelitis virus in tissue cultures. J. Immunol. 64: 447–454, 1950.
322. PEARSON, H. E. AND LAGERBORG, D. L.: Effects of CNS depressant drugs on mouse encephalomyelitis virus. J. Bact. 69: 193–194, 1955.
323. PEARSON, H. E., LAGERBORG, D. L. AND WINZLER, R. J.: Effects of certain amino acids and related compounds on propagation of mouse encephalomyelitis virus. Proc. Soc. exp. Biol., N. Y. 79: 409–411, 1952.
324. PEARSON, H. E., LAGERBORG, D. L., WINZLER, R. J. AND VISSER, D. W.: Methionine compounds and growth of mouse encephalomyelitis virus in tissue culture. J. Bact. 69: 225, 1955.
325. PEARSON, H. E. AND WINZLER, R. J.: Amino acids, analogues and the propagation of Theiler's GD VII Virus in mouse brain tissue culture. Fed Proc. 8: 409, 1949.
326. PEARSON, H. E. AND WINZLER, R. J.: Amino acid inhibition of Theiler's GD VII virus in mouse brain tissue. Fed. Proc 9: 389, 1950.
327. PECK, G. A. AND BERRY, J. W.: Antibiotic therapy in primary atypical pneumonia. The use of aureomycin, chloromycetin, streptomycin and penicillin in controlled studies. Antibiot. and Chemother. 1: 291–298, 1951.
328. PIJOAN, M. J., PAYNE, E. H. AND DINEEN, J.: Progress in the treatment of trachoma with chloromycetin (chloramphenicol). Amer. J. trop. Med. 30: 677–680, 1951.
329. PILCHER, K. S., SOIKE, K. F., SMITH, V. H., TROSPER, F. AND FOLSTON, B.: Inhibition of multiplication of Lee influenza virus by canavanine. Proc. Soc. exp. Biol., N. Y. 88: 79–86, 1955.
330. PINKERTON, H. AND SWANK, R. L.: Recovery of virus morphologically identical with psittacosis from thiamin-deficient pigeons. Proc. Soc. exp. Biol., N. Y. 45: 704–706, 1940.

331. POLEFF, L.: Der wirkliche Wert der Sulfamidotherapie bei Trachom. Ophthalmologica, Basel 105: 156–174, 1943.
332. POLLARD, M., BUSSELL, R. H., BENEDICT, A. A. AND WILSON, R.: The response of three human infections of psittacosis to antibiotic therapy. Antibiot. and Chemother. 4: 138–140, 1954.
333. POND, W. L., DAVIES, W. L., SMITH, S. C., ELVEHJEM, C. A., RASMUSSEN, A. F. AND CLARK, P. F.: The influence of amino acid deficiencies on Theiler's GD VII encephalomyelitis of mice. J. Bact. 64: 583–592, 1952.
334. POWELL, H. M., BONIECE, W. S., PITTENGER, R. C., STONE, R. L. AND CULBERTSON, C. G.: Laboratory studies on "Ilotycin". Antibiot. and Chemother. 3: 165–182, 1953.
335. POWELL, H. M. AND CULBERTSON, C. G.: Further studies on chemoprophylaxis and chemotherapy of small virus infections in white mice. Antibiotics Annual 1953–1954, pp. 147–156. Medical Encyclopedia, New York 1953.
336. POWELL, H. M. AND CULBERTSON, C. G.: Action of an antiviral mold filtrate against MEF 1 poliomyelitis virus in mice. Proc. Soc. exp. Biol., N. Y. 83: 161–163, 1953.
337. POWELL, H. M., CULBERTSON, C. G., MCGUIRE, J. M., HOEHN, M. M. AND BAKER, L. A.: A filtrate with chemoprophylactic and chemotherapeutic action against MM and Semliki Forest viruses in mice. Antibiot. and Chemother. 2: 432–434, 1952.
338. PRICE, C. W., RANDALL, W. A., WELCH, H. AND CHANDLER, V. L.: Studies of the combined action of antibiotics and sulfonamides. Amer. J. Publ. Hlth. 39: 340–344, 1949.
339. PRIGOT, A., WRIGHT, L. T., LOGAN, M. A. AND LUCA, F. R. DE: Anorectogenital lymphogranuloma venereum and granuloma inguinale treated with aureomycin. N. Y. St. J. Med. 49: 1911–1917, 1949.
340. QUAN, S. F., MEYER, K. F. AND EDDIE, B.: Attempts to cure parakeet psittacosis carriers with aureomycin and penicillin. J. infect. Dis. 86: 132–135, 1950.
341. QUASTEL, J. H. AND WHEATLEY, A. H. M.: Biological oxidations in the succinic acid series. Biochem. J. 25: 117–128, 1930.
342. RAFELSON, M. E., JR., PEARSON, H. E. AND WINZLER, R. J.: The effects of certain amino acids and metabolic antagonists on propagation of Theiler's GD VII virus and P^{32} uptake by minced one-day-old mouse brain. Arch. Biochem. 29: 69–74, 1950.
343. RAFELSON, M. E., JR., PEARSON, H. E. AND WINZLER, R. J.: *In vitro* inhibition of radiophosphate uptake and growth of a neurotropic virus by 5-chlorouridine. Proc. Soc. exp. Biol., N. Y. 76: 689–692, 1951.
344. RAÍS AND ARROYO: Premiers essais de traitement du trachôme par l'aureomycine. Tunis. méd. 28: 681–687, 1950.
345. RAKE, G.: Chemotherapy of lymphogranuloma venereum. Amer. J. trop. Med. 28: 555–562, 1948.
346. RAKE, G. AND HAMRE, D. M.: Action of sulfonamides on toxins of agents of the lymphogranuloma-psittacosis group. Proc. Soc. exp. Biol., N. Y. 55: 90–91, 1944.
347. RAKE, G., JONES, H. AND NIGG, C.: Sulfonamide chemotherapy of mouse pneumonitis, meningo-pneumonitis and lymphogranuloma venereum. Proc. Soc. exp. Biol., N. Y. 49: 449–452, 1942.
348. RASMUSSEN, A. F., CLARK, P. F., SMITH, S. C. AND ELVEHJEM, C. A.: Effect of 6-methyltryptophan on Lansing poliomyelitis in mice. Bact. Proc. 93–94, 1951.
349. RASMUSSEN, A. F. AND STOKES, J. C.: Chemical inhibition of the growth of the virus of influenza in embryonated eggs. J. Immunol. 66: 237–247, 1951.
350. RASMUSSEN, A. F., WAISMAN, H. A., ELVEHJEM, C. A. AND CLARK, P. F.: Influence of the level of thiamine intake on the susceptibility of mice to poliomyelitis virus. J. infect. Dis. 74: 41–47, 1944.
351. RASMUSSEN, A. F., WAISMAN, H. A. AND LICHSTEIN, H. C.: Influence of riboflavin on susceptibility of mice to experimental poliomyelitis. Proc. Soc. exp. Biol., N. Y. 57: 92–95, 1944.
352. RASMUSSEN, A. F., WEAVER, R. W., ELVEHJEM, C. A. AND CLARK, P. F.: Influence of low tryptophane diets containing 6-methyltryptophane on oral infection with poliomyelitis virus. Proc. Soc. exp. Biol., N. Y. 84: 306–308, 1953.
353. REMLINGER, P.: L'élévation de la température du corps dans le traitement de la rage et des maladies infectieuses. C. R. Soc. Biol., Paris 60: 1030–1031, 1906.
354. RICHARDS, P., FORSTER, W. G. AND THYGESON, P.: Treatment of trachoma with sulfanilamide. Arch. Ophthal., N. Y. 21: 577–580, 1939.
355. RITIS, F. DE, GIUSTI, G. AND VILLARI, V.: Attività della imide dell'acido maleico (n-etyl-maleimide) sulla moltiplicazione virale. Arch. ges. Virusforsch. 5: 432–440, 1954.
356. ROBBINS, B. H.: Effect of quinine upon the course of fowl-pox infection in the chick. J. Pharmacol. 76: 57–63, 1942.
357. ROBINSON, R. C. V.: Newer antibiotics in the treatment of venereal diseases. Amer. J. Syph. 34: 273–288, 1950.
358. RODANICHE, E. C.: Sulfanilylguanidine and sulfanilamide in the treatment of lymphogranuloma venereum infections of mice. J. infect. Dis. 70: 58–61, 1942.
359. RODANICHE, E. C.: The fate of the virus of lymphogranuloma venereum in infected mice receiving sulfonamide therapy. J. infect. Dis. 73: 173–179, 1943.
360. ROSE, H. M., MOLLOY, E. AND O'NEILL, E.: Effect of penicillin on bacterial contamination of eggs and tissue cultures inoculated with unfiltered sputums. Proc. Soc. exp. Biol., N. Y. 60: 23–25, 1945.
361. ROSEBURY, J., ELLINGSON, H. V., MEIKLEJOHN, G. AND SCHABEL, F.: A laboratory infection with psittacosis virus treated with penicillin and sulfadiazine, and experimental data bearing on the mode of infection. J. infect. Dis. 80: 64–77, 1947.
362. RUBIN, B. A. AND GIARMAN, N. J.: The therapy of experimental influenza in mice with antibiotic lactones and related compounds. Yale J. Biol. Med. 19: 1017–1022, 1947.
363. RUBINI, J. R., RASMUSSEN, A. F. AND STAHMANN, M. A.: Inhibitory effect of synthetic lysine polypeptides on the growth of influenza virus in embryonated eggs. Proc. Soc. exp. Biol., N. Y. 76: 662–665, 1951.

364. RUDD, G. V. AND BURNET, F. M.: Intranasal infection of mice with the virus of psittacosis. Aust. J. exp. Biol. med. Sci. 19: 33–38, 1941.
365. RUNYAN, J. W., KRAFT, L. M. AND GORDON, I.: Effect of aureomycin on the survival of virus in lymphogranulomatous buboes. Amer. J. Med. 7: 419–420, 1949.
366. SABIN, A. B.: Vitamin C in relation to experimental poliomyelitis with incidental observations on certain manifestations in *Macacus rhesus* monkeys on a scorbutic diet. J. exp. Med. 69: 507–515, 1939.
367. SABIN, A. B. AND DUFFY, C. E.: Nutrition as a factor in the development of constitutional barriers to involvement of the nervous system by certain viruses. Science 91: 552–554, 1940.
368. SABIN, A. B., WARD, R., RAPOPORT, S. AND GUEST, G. M.: Neuroinvasiveness of poliomyelitis virus in relation to vitamin D nutrition. Proc. Soc. exp. Biol., N. Y. 48: 451–454, 1941.
369. SANDERS, M., HUANG, C. H. AND SIMMS, H. S.: Tissue cultures in virus field work. J. Bact. 45: 81–82, 1943.
370. SANDERS, M., SUBBAROW, Y. AND ALEXANDER, R. C.: An effective antiviral synthetic. Tex. Rep. Biol. Med. 6: 385–395, 1948.
371. SARKIES, J. W. R.: Aureomycin in trachoma. Brit. J. Ophthal. 35: 549–552, 1951.
372. SARRACINO, J. B. AND SOULE, M. H.: Effect of heat, cold, fatigue and alcohol on resistance of mice to human influenza virus. Proc. Soc. exp. Biol., N. Y. 48: 183–186, 1941.
373. SCHABEL, F. M., LASTER, W. R., BROCKMAN, R. W. AND SKIPPER, H. E.: Observations on antiviral activity of netropsin. Proc. Soc. exp. Biol., N. Y. 83: 1–3, 1953.
374. SCHACH, W.: Der Einfluss der "Bodenexposition" und der Lufttemperatur auf den Ablauf der Maul- und Klauenseucheinfektion beim Meerschweinchen. Z. Hyg. InfektKr. 117: 149–152, 1936.
375. SCHAEFFER, M., SILVER, F. F. AND PI, C. C.: Studies on the chemotherapy of virus infections. I. General anaesthetics and other drugs ineffective against experimental virus infections in mice. J. Immunol. 63: 109–115, 1949.
376. SCHAMBERG, I. L., CARROZZINO, O. M. AND BOGER, W. P.: Treatment of early lymphogranuloma venereum with aureomycin. Amer. J. Syph. 35: 370–377, 1951.
377. SCHLOSSBERGER, H. AND BÄR, F.: Untersuchungen über die Wirkungsweise von Sulfonamidverbindungen bei der Infektion von Mäusen mit Streptokokken und Lymphogranuloma inguinale. Zbl. Bakt., Abt. I 144: 228–233, 1939.
378. SCHMIDT, J. R. A. AND RASMUSSEN, A. F.: Inhibitory effect of cobaltous ions on multiplication of influenza virus. Proc. Soc. exp. Biol., N. Y. 81: 244–246, 1952.
379. SCHMIDT, W. AND SPROCKHOFF, H. VON: Aureomycin bei experimenteller Psittakose der Maus. Z. Hyg. InfektKr. 138: 122–131, 1953.
380. SCHNITZER, R. J., BUCK, M. AND STEIGER, N.: Chemotherapeutic effect of 2-hydroxy-1,4-naphthoquinonimine on infections of mice with Col SK virus. Proc. Soc. exp. Biol., N. Y. 77: 182–187, 1951.
381. SCHOENBACH, E. B. AND BRYER, M. S.: Treatment of primary atypical nonbacterial pneumonia with aureomycin. J. Amer. med. Ass. 139: 275–280, 1949.
382. SCHOENBACH, E. B., SWEED, A., TEPPER, B. AND BRYER, M. S.: An evaluation of aureomycin therapy in primary atypical pneumonia. New Engl. J. Med. 243: 799–806, 1950.
383. SEELER, A. O., GRAESSLE, O. AND DUSENBERY, E. D.: The effect of para-aminobenzoic acid on the chemotherapeutic activity of the sulfonamides in lymphogranuloma venereum and in duck malaria. J. Bact. 45: 205–209, 1943.
384. SEELER, A. O., GRAESSLE, O. AND OTT, W. H.: Effect of quinine on influenza virus infections in mice. J. infect. Dis. 79: 156–158, 1946.
385. SHAFFER, L. W. AND ARNOLD, E.: Lymphogranuloma venereum especially its treatment with sulfanilamide. Arch. Derm. Syph., N. Y. 38: 705–712, 1938.
386. SHAFFER, M. F., JONES, H., GRACE, A. W., HAMRE, D. M. AND RAKE, G.: Use of the yolk sac of the developing chicken embryo in the isolation of the agent of lymphogranuloma venereum. J. infect. Dis. 75: 109–112, 1944.
387. SHAH, M. A.: Aureomycin in trachoma. Brit. J. Ophthal. 35: 50–52, 1951.
388. SHOPE, R. E.: An antiviral substance from *Penicillium funiculosum*. I. Effect upon infection in mice with swine influenza virus and Columbia SK encephalomyelitis virus. J. exp. Med. 97: 601–625, 1953.
389. SHOPE, R. E.: An antiviral substance from *Penicillium funiculosum*. II. Effect of helenine upon infection in mice with Semliki Forest virus. J. exp. Med. 97: 627–638, 1953.
390. SHOPE, R. E.: An antiviral substance from *Penicillium funiculosum*. III. General properties and characteristics of helenine. J. exp. Med. 97: 639–650, 1953.
391. SHROPSHEAR, G.: Sulfanilamide in the treatment of strictures of the rectum caused by lymphogranuloma venereum. Illinois med. J. 74: 153–156, 1938.
392. SHWARTZMAN, G.: Enhancing effect of cortisone upon poliomyelitis infection (strain MEF 1) in hamsters and mice. Proc. Soc. exp. Biol. N. Y., 75: 835–838, 1950.
393. SIEGEL, H. AND MUSHETT, C. W.: Structural changes following administration of quinacrine hydrochloride. Arch. Path. (Lab. Med.) 38: 63–70, 1944.
394. SINISCAL, A. A.: The sulfonamides and antibiotics in trachoma. J. Amer. med. Ass. 148: 637–639, 1952.
395. SMADEL, J. E.: Atypical pneumonia and psittacosis. J. clin. Invest. 22: 52–65, 1943.
396. SMADEL, J. E. AND JACKSON, E. B.: Effect of chloromycetin on experimental infection with psittacosis and lymphogranuloma venereum viruses. Proc. Soc. exp. Biol., N. Y. 67: 478–483, 1948.
397. SMADEL, J. E., JACKSON, E. B., LEY, H. L. AND LEWTHWAITE, R.: Comparison of synthetic and fermentation chloramphenicol (chloromycetin) in rickettsial and viral infections. Proc. Soc. exp. Biol., N. Y. 70: 191–194, 1949.
398. SMITH, A. G.: The effect of acriflavine and phosphine GRN on lysis of bacteria by bacteriophage. J. Immunol. 61: 57–63, 1949.

399. SMITH, J. E., JULIANELLE, L. A. AND GAMET, J. H.: Sulfonamide therapy of trachoma. An experimental study with a critical analysis of the literature. Amer. J. Ophthal. **24**: 174–185, 1941.
400. SMITH, J. M., MURPHY, J. S. AND MIRICK, G. S.: Effect of adrenal hormones on infection of mice with pneumonia virus of mice (PVM). Proc. Soc. exp. Biol., N. Y. **78**: 505–510, 1951.
401. SORSBY, A.: The treatment of trachoma with special reference to local sulphonamide therapy. Brit. J. Ophthal. **29**: 98–102, 1945.
402. SORSBY, A.: Penicillin in ophthalmology. An interim review. Brit. J. Ophthal. **29**: 511–536, 1945.
403. SORSBY, A. AND HOFFA, E.: Local penicillin therapy in ophthalmia neonatorum. Brit. med. J. **1**: 114–115, 1945.
404. SOUTHAM, C. M. AND BABCOCK, V. I.: Effect of cortisone, related hormones and adrenalectomy on susceptibility of mice to virus infections. Proc. Soc. exp. Biol., N. Y. **78**: 105–109, 1951.
405. SPECK, R. S., JAWETZ, E. AND GUNNISON, J. B.: Studies on antibiotic synergism and antagonism. The interference of aureomycin or terramycin with the action of penicillin in infections in mice. Arch. intern. Med. **88**: 168–174, 1951.
406. SPICER, S.: Bacteriologic studies of the newer antibiotics: effect of combined drugs on micro-organisms. J. Lab. clin. Med. **36**: 183–191, 1950.
407. SPIZIZEN, J.: Biochemical studies on the phenomenon of virus reproduction. I. Amino acids and the multiplication of bacteriophage. J. infect. Dis. **73**: 212–221, 1943.
408. SPIZIZEN, J.: Biochemical studies on the phenomenon of virus reproduction. II. Studies on the influence of compounds of metabolic significance on the multiplication of bacteriophage. J. infect. Dis. **73**: 222–228, 1943.
409. SPRUNT, D. H.: The effect of undernourishment on the susceptibility of the rabbit to infection with vaccinia. J. exp. Med. **75**: 297–304, 1942.
410. SPRUNT, D. H.: Inhibiting effect of methionine, choline and betaine on rabbit's susceptibility to infection with vaccinia. Proc. Soc. exp. Biol., N. Y. **51**: 226–227, 1942.
411. SPRUNT, D. H.: Increased susceptibility of mice to swine influenza as a result of methionine injections. Proc. Soc. exp. Biol., N. Y. **67**: 319–321, 1948.
412. SPRUNT, D. H.: Effect of malnutrition on the infection of mice with influenza virus. Fed. Proc. **8**: 369, 1949.
413. SPRUNT, D. H. AND MCDEARMAN, S.: Studies on the relationship of sex hormones to infection. III. A quantitative study of the increased resistance to vaccinial infection produced by the estrogenic hormone and pseudopregnancy. J. Immunol. **38**: 81–95, 1940.
414. SPRUNT, D. H., MCDEARMAN, S. AND RAPER, J.: Studies on the relationship of the sex hormones to infection. I. The effect of the estrogenic and gonadotropic hormones on vaccinia and the spreading factor. J. exp. Med. **67**: 159–168, 1938.
415. STROBEL, W.: Beitrag zum Krankheitsbild der Ornithose im Kindesalter. Dtsch. med. Wschr. **79**: 176–178, 1954.
416. SULKIN, S. E.: The effect of environmental temperature on experimental influenza in mice. J. Immunol. **51**: 291–300, 1945.
417. SULKIN, S. E. AND ZARAFONETIS, C.: Influence of anesthesia on experimental neurotropic virus infections. II. *In vitro* studies with the viruses of Western and Eastern equine encephalomyelitis, St. Louis encephalitis, poliomyelitis (Lansing), and rabies. J. exp. Med. **85**: 559–569, 1947.
418. SULKIN, S. E., ZARAFONETIS, C. AND GOTH, A.: Influence of anesthesia on experimental neurotropic virus infections. I. *In vivo* studies with the viruses of Western and Eastern equine encephalomyelitis, St. Louis encephalitis, poliomyelitis (Lansing), and rabies. J. exp. Med. **84**: 277–292, 1946.
419. SZANTO, P. B. AND FELSENFELD, O.: Influence of malononitrile upon poliomyelitis in mice. Proc. Soc. exp. Biol., N. Y. **72**: 15–17, 1949.
420. TAMM, I.: Inhibition of influenza and mumps virus multiplication by 4,5,6- (or 5,6,7-) trichloro-1-β-D-ribofuranosylbenzimidazole. Science **120**: 847–848, 1954.
421. TAMM, I., FOLKERS, K. AND HORSFALL, F. L., JR.: Inhibition of influenza virus multiplication by 2,5-dimethylbenzimidazole. Yale J. Biol. Med. **24**: 559–567, 1952.
422. TAMM, I., FOLKERS, K. AND HORSFALL, F. L., JR.: Inhibition of influenza virus multiplication by alkyl derivatives of benzimidazole. I. Kinetic aspects of inhibition by 2,5-dimethylbenzimidazole as measured by infectivity titrations. J. exp. Med. **98**: 219–227, 1953.
423. TAMM, I., FOLKERS, K. AND HORSFALL, F. L., JR.: Inhibition of influenza virus multiplication by alkyl derivatives of benzimidazole. II. Measurement of inhibitory activity by hemagglutination titrations. J. exp. Med. **98**: 229–243, 1953.
424. TAMM, I., FOLKERS, K., SHUNK, C. H., HEYL, D. AND HORSFALL, F. L., JR.: Inhibition of influenza virus multiplication by alkyl derivatives of benzimidazole. III. Relationship between inhibitory activity and chemical structure. J. exp. Med. **98**: 245–259, 1953.
425. TAMM, I., FOLKERS, K., SHUNK, C. H. AND HORSFALL, F. L., JR.: Inhibition of influenza virus multiplication by N-glycosides of benzimidazoles. J. exp. Med. **99**: 227–250, 1954.
426. TAMM, I. AND TYRRELL, D. A.: Influenza virus multiplication in the chorio-allantoic membrane in vitro: kinetic aspects of inhibition by 5:6-dichloro-1-β-D-ribofuranosylbenzimidazole. J. exp. Med. **100**: 541–562, 1954.
427. TANNER, F. W., ENGLISH, A. R., LEES, T. M. AND ROUTIEN, J. B.: Some properties of Magnamycin, a new antibiotic. Antibiot. and Chemother. **2**: 441–443, 1952.
428. TAYLOR, H. M. AND SPRUNT, D. H.: Increased resistance to viral infection as a result of increased fluid in tissues. J. exp. Med. **78**: 91–97, 1943.
429. THOMPSON, R. L.: The influence of temperature upon proliferation of infectious fibroma and infectious myxoma viruses *in vivo*. J. infect. Dis. **62**: 307–312, 1938.
430. THOMPSON, R. L.: The effect of enzyme inhibitors, nutriles and substitution compounds on the growth of vaccinia virus. J. Bact. **51**: 629–630, 1946.

431. THOMPSON, R. L.: The effect of metabolites, metabolite antagonists and enzyme-inhibitors on the growth of the vaccinia virus in Maitland type of tissue cultures. J. Immunol. 55: 345–352, 1947.
432. THOMPSON, R. L., DAVIS, J., RUSSELL, P. B. AND HITCHINGS, G. H.: Effect of aliphatic oxime and isatin thiosemicarbazones on vaccinia infection in the mouse and in the rabbit. Proc. Soc. exp. Biol., N. Y. 84: 496–499, 1953.
433. THOMPSON, R. L. AND LAVENDER, A. R.: Effect of ethionine and other materials on Semliki Forest virus infection in the mouse. Proc. Soc. exp. Biol., N. Y. 84: 483–486, 1953.
434. THOMPSON, R. L., MINTON, S. A., OFFICER, J. E. AND HITCHINGS, G. H.: Effect of heterocyclic and other thiosemicarbazones on vaccinia infection in the mouse. J. Immunol. 70: 229–234, 1953.
435. THOMPSON, R. L., PRICE, M. L. AND MINTON, S. A., JR.: Protection of mice against vaccinia virus by administration of benzaldehyde thiosemicarbazone. Proc. Soc. exp. Biol., N. Y. 78: 11–13, 1951.
436. THOMPSON, R. L., PRICE, M. L., MINTON, S. A., JR., ELION, G. B. AND HITCHINGS, G. H.: Effects of purine derivatives and analogues on multiplication of the vaccinia virus. J. Immunol. 65: 529–534, 1950.
437. THOMPSON, R. L., PRICE, M., MINTON, S. A., FALCO, E. A. AND HITCHINGS, G. H.: Protection of mice against the vaccinia virus by the administration of phenoxythiouracils. J. Immunol. 67: 483–491, 1951.
438. THOMPSON, R. L. AND WILKIN, M. L.: Inhibition of growth of the vaccinia virus by β-2-thienylalanine and its reversal by phenylalanine. Proc. Soc. exp. Biol., N. Y. 68: 434–436, 1948.
439. THOMPSON, R. L., WILKIN, M. L., HITCHINGS, G. H., ELION, G. B., FALCO, E. A. AND RUSSELL, P. B.: The effects of antagonists on the multiplication of vaccinia virus *in vitro*. Science 110: 454, 1949.
440. THOMPSON, R. L., WILKIN, M. L., HITCHINGS, G. H. AND RUSSELL, P. B.: The virostatic and virucidal action of α-haloacylamides on vaccinia virus *in vitro*. Proc. Soc. exp. Biol., N. Y. 72: 169–171, 1949.
441. THYGESON, P.: Sulfanilamide therapy of inclusion conjunctivitis. Amer. J. Ophthal. 22: 179–180, 1939.
442. THYGESON, P.: The treatment of trachoma with sulfanilamide. A report of 31 cases. Amer. J. Ophthal. 23: 679–685, 1940.
443. THYGESON, P.: Sulfonamide compounds in treatment of ocular infections. Arch. Ophthal., N. Y. 29: 1000–1022, 1943.
444. THYGESON, P.: Trachoma and inclusion conjunctivitis. In: "Viral and rickettsial infections of man," ed. by T. M. Rivers, pp. 358–369. Lippincott, Philadelphia 1948.
445. THYGESON, P. AND STONE, W.: Epidemiology of inclusion conjunctivitis. Arch. Ophthal., N. Y. 27: 91–119, 1942.
446. TILLOTSON, I. G. AND OSEASOHN, R. O.: The treatment of primary atypical pneumonia—the need for controls in the evaluation of aureomycin therapy. Ohio St. med. J. 48: 32–33, 1952.
447. TOOMEY, J. A.: Ingestion of vitamins A, B, C and D and poliomyelitis. Amer. J. Dis. Child. 53: 1202–1208, 1937.
448. TOOMEY, J. A., FROHRING, W. O. AND TAKACS, W. S.: Vitamin B_1 deficient animals and poliomyelitis. Yale J. Biol. Med. 16: 477–485, 1943–4.
449. TOOMEY, J. A. AND LOHREY, R. C.: Psittacosis treated with sulfonamide drugs. Amer. J. med. Sci. 211: 163–165, 1946.
450. TOOMEY, J. A. AND TAKACS, W. S.: Poliomyelitis virus and deficiently medullated nerves. J. Bact. 39: 64, 1940.
451. TRÜB, C. L. P.: Wiederauftreten der Papageienkrankheit (Psittakosis). Münch. med. Wschr. 92: 702–706, 1950.
452. TUCKER, H. A.: Inguinal lymphogranuloma venereum in the male. A study of 750 consecutive cases from Panama. Amer. J. Syph. 29: 619–629, 1945.
453. TURGASEN, F. E.: Human ornithosis treated with penicillin. J. Amer. med. Ass. 126: 1150–1151, 1944.
454. VISSER, D. W., LAGERBORG, D. L. AND PEARSON, H. E.: Inhibition of mouse encephalomyelitis virus *in vitro* by certain nucleoprotein derivatives. Proc. Soc. exp. Biol., N. Y. 79: 571–573, 1952.
455. WAGNER, J. C.: Aureomycin studies. I. Effect of aureomycin on ten strains of virus in the psittacosis-LGV group. J. clin. Invest. 28: 1049, 1949.
456. WAGNER, J. C., ANDREWES, V. W. AND WATSON, M. S.: Effect of aureomycin on viruses of the psittacosis-LGV group in embryonated eggs and mice. Proc. Soc. exp. Biol., N. Y. 76: 79–83, 1951.
457. WAMMOCK, V. S., GREENBLATT, R. B., DIENST, R. B., CHEN, C. AND WEST, R. M.: Auroemycin in the treatment of granuloma inguinale and lymphogranuloma inguinale. J. invest. Derm. 14: 427–434, 1950.
458. WATANABE, T., HIGGINBOTHAM, R. D. AND GEBHARDT, L. P.: Effect of sodium monofluoroacetate on multiplication of Eastern equine encephalomyelitis virus. Proc. Soc. exp. Biol., N. Y. 80: 758–761, 1952.
459. WEAVER, H. M.: The effect of rachitogenic diets, partial inanition, and sex on the resistance of cotton-rats to the virus of poliomyelitis. J. Pediat. 24: 88–105, 1944.
460. WEAVER, H. M.: Resistance of cotton-rats to the virus of poliomyelitis as affected by intake of vitamin B complex, partial inanition and sex. Amer. J. Dis. Child. 69: 26–32, 1945.
461. WEAVER, H. M.: Resistance of cotton-rats to the virus of poliomyelitis as affected by intake of vitamin A, partial inanition and sex. J. Pediat. 28: 14–23, 1946.
462. WEISS, E.: The effect of antibiotics on agents of the psittacosis-lymphogranuloma group. I. The effect of penicillin. J. infect. Dis. 87: 249–263, 1950.
463. WELLS, E. B. AND FINLAND, M.: Comparative effect of aureomycin and chloromycetin on psittacosis in chick embryos. Proc. Soc. exp. Biol., N. Y. 72: 365–368, 1949.
464. WHEELER, A. H. AND NUNGESTER, W. J.: The effect of atropine sulfate on the course of influenza virus infection. Science 100: 523–524, 1944.
465. WILLCOX, R. R.: Simplified penicillin treatment of lymphogranuloma inguinale and other venereal diseases in West African troops. Post Grad. med. J. 22: 97–98, 1946.
466. WISEMAN, R. W., MEIKLEJOHN, G., LACKMAN, D. B., WAGNER, J. C. AND BEVERIDGE, G. W.: Studies on the

chemotherapy of viruses in the psittacosis-lymphogranuloma group. II. Effect of penicillin and sulfadiazine on seven strains in mice. J. Immunol. **54**: 9–16, 1946.

467. Wolf, H. F.: Prevention of poliomyelitis in monkeys by means of hyperpyrexia. Proc. Soc. exp. Biol., N. Y. **32**: 1083–1087, 1935.
468. Wong, S. C. and Cox, H. R.: Action of aureomycin against experimental rickettsial and viral infections. Ann. N. Y. Acad. Sci. **51**: 290–303, 1948.
469. Wong, S. C., James, C. G. and Finlay, A.: The action of carbomycin (Magnamycin) on some viral and rickettsial infections. Antibiot. and Chemother. **3**: 741–750, 1953.
470. Wood, E. J.: Atypical pneumonia treated with chloromycetin. Lancet **2**: 55–56, 1949.
471. Wood, H. G. and Rusoff, I. I.: The protective action of trypan red against infection by a neurotropic virus. J. exp. Med. **82**: 297–309, 1945.
472. Woodward, T. E.: Chloromycetin and aureomycin: therapeutic results. Ann. Intern. Med. **31**: 53–82, 1949.
473. Wooley, J. G., Bond, H. W. and Perrine, T. D.: The effect of chemical substances in mice infected with St. Louis encephalitis, PR8 strain of influenza or the Lansing strain of poliomyelitis virus. J. Immunol. **68**: 621–626, 1952.
474. Wooley, J. G., Murphy, M. K., Bond, H. W. and Perrine, T. D.: The effect of certain chemical compounds on the multiplication of T_2 bacteriophage. J. Immunol. **68**: 523–530, 1952.
475. Wright, L. T., Freeman, W. A. and Bolden, J. V.: Lymphogranulomatous strictures of the rectum. A résumé of four hundred and seventy-six cases. Arch. Surg., Chicago **53**: 499–544, 1946.
476. Wright, L. T., Sanders, M., Logan, M. A., Prigot, A. and Hill, L. M.: Aureomycin: a new antibiotic with virucidal properties. J. Amer. med. Ass. **138**: 408–412, 1948.
477. Wright, L. T., Whitaker, J. C., Wilkinson, R. S. and Beinfield, M. S.: The treatment of lymphogranuloma venereum with terramycin. Report of twenty successfully treated cases. Antibiot. and Chemother. **1**: 193–197, 1951.
478. Young, G. A., Underdahl, N. R. and Carpenter, L. E.: Vitamin D intake and susceptibility of mice to experimental swine influenza virus infection. Proc. Soc. exp. Biol., N. Y. **72**: 695–697, 1949.