The management of acute necrotizing encephalitis: a review of 369 cases

MARC RAPPEL

Department of Neurosurgery, St Pierre University Hospital, Free University of Brussels

Introduction

Acute necrotizing encephalitis (ANE) has a highly fatal outcome and the importance of cerebral oedema as a cause of death has been clearly recognized (Pierce *et al.*, 1964; Page, Tyler & Shillito, 1967; Delmas-Marsalet *et al.*, 1968). Signs of brain herniation are common and have been well documented (Haymaker *et al.*, 1958; Bloedhorn *et al.*, 1962). This happens even in the absence of clinical signs of cerebral hypertension.

Van Bogaert, Radermecker & Devos (1955), Brihaye (1958) and Haymaker *et al.* (1958) had already noticed the close similarities between ANE and herpes encephalitis, but ANE was thought to be a mode of reaction against several viral aggressions rather than the unique expression of herpes simplex virus (HSV) infestation (Bergouignan, Julien & Vital, 1968a). Growing evidence for the identity of the two diseases has been brought to light little by little. From 1965 up to 1970, out of thirty-nine cases where electron microscopy was performed, thirty-six showed the typical herpes-like particles (Rappel *et al.*, 1971) and to date more than ten cases must be added to this series (Caulet *et al.*, 1971; Laterre, 1972; Vital, 1972). Virus isolation and especially immunofluorescence techniques (Tomlinson & McCallum, 1969; Liu *et al.*, 1971; Longson, 1973) have brought further evidence so that it can be assumed—with the possible exception of three cases (Duckett, Kelly & Grant, 1963; Scheid & Jochheim, 1956; Heathfield *et al.*, 1967)—that ANE is of herpetic origin.

Therefore a correct therapeutic approach will include on the one hand the relief of the raised intracranial pressure, either surgically or medically or by both means; on the other hand, the inhibition of growth of the virus by cytotoxic compounds and/or interferon-inducers. In the present article, the term 'treatment' includes decompressive therapy and antiviral treatment with the exclusion of brain biopsy performed through a burr hole; as well as all the supportive treatments such as antibiotics and cardio-respiratory support.

Decompressive therapy

The presenting symptoms of ANE are often those

of a temporal lobe mass (Pierce *et al.*, 1964; Carmon, Behar & Beller, 1965; Potter 1969) and/or of raised intracranial pressure (Haymaker *et al.*, 1958; Drachman & Adams, 1962; Castleman & McNeely, 1964; Blackwood *et al.*, 1966). In similar situations, i.e. glioblastoma (Hitchcock & Sato, 1964) or acute hemorrhagic leukoencephalitis (Coxe & Luse, 1963) decompressive therapy followed or not by lobectomy will be performed.

Recently, Long *et al.* (1972a) have observed that in experimental brain oedema, early excision of the lesion prevented the development of swelling. Surgery performed later was as good as steroids, whereas after 24 hr, excision had no effect. However, in clinical situations, decompressive therapy itself can be a harmful procedure, allowing a sudden 'mushroom-like' billowing out of the cerebral matter through the opened skull. Such swelling will impair even more the local cerebral circulation and break down further the blood-brain barrier, increasing as a result the pre-existing oedema and leading to necrosis of the herniated brain (Fox, 1964).

Therefore medical decompression by hypertonic solutions of urea or mannitol, or by steroids are used pre- and per-operatively. Hypertonic solutions act rapidly and briefly (Goldstein *et al.*, 1964; McQueen & Jeanes, 1964) whereas steroids show a slower but more sustained action (Kofman, *et al.*, 1957). Therefore, the first ones are used in acute situations, whereas the latter are preferred in more chronic conditions. Hydrocortisone, prednisolone and dexamethasone are clinically active at initial dosage of 100, 50 and 10 mg respectively, to be repeated (Fox, 1964).

The benefit gained from steroid therapy does not seem to depend upon their anti-oedema properties; ubiquitous effects are more likely, through their protective action on cell membranes (Long, Maxwell & French, 1972b; Demopoulos *et al.*, 1972). Some experimental work suggests that the beneficial effect of dexamethasone does not appear to be mediated by its effects on oedema (Lewin, Pappius & Hansebout, 1972; Pappius, 1972). However, Clasen *et al.* (1972) suggest that in inflammatory and necrotic lesions the response to dexamethasone might not be as good as in oedema of other origin.

On the other hand, the deleterious effect of steroids in viral infections has often been stressed (Findley & Howard, 1952; Kilbourne, 1955a; Immam & Hammon 1957a; Kilbourne, 1957; Coid, Tobin & Beswick, 1960; Weinstein, 1962; Rook, Wilkinson & Ebling, 1968; Toole & McCall, 1969; Longson & Beswick, 1971) and especially in herpes simplex keratitis (Jawetz, Okumoto & Sonne, 1959; Baron, Le Bourhis & Gouray, 1959; McCoy & Leopold, 1960; Bonamour, 1962; Kaufman & Maloney, 1962; Kaufman, Martola & Dohlman, 1963; Neuberger & Schneeweis, 1963; Schneeweis, Neuberger & Meyer, 1963; Crompton, 1964; Duke-Elder, 1965; Maloney & Kaufman, 1965; Patterson & Jones, 1967).

In experimental herpes encephalitis, hydrocortisone did not have a beneficial effect in guinea-pigs (Tokumaru, 1967) neither did prednisolone have any effect in ninety-two cases of viral encephalitis (Hohenegger, 1967). On the other hand, Crompton & Teare (1965) reported two cases of herpes encephalitis after the reduction of steroid maintenance therapy in chronic diseases.

Antiviral therapy

Idoxuridine

Idoxuridine (5-iodo-2'-deoxyuridine; IUDR, IDU, SKF 14-287) a pyrimidine analogue was, like other halogenated derivatives (FUDR, BUDR), primarily prepared for studies on cancer therapy, but has shown only moderate tumour-inhibitory effect (Calabresi *et al.*, 1961). On the other hand halogenated pyrimidines were found to be—in *vitro*—good inhibitors of DNA-containing viruses (Herrmann, 1961; Lerman, Doyle & Doyle, 1962; Rapp, 1964; Buthala, 1964).

This was confirmed in animals (Perkins *et al.*, 1962; Kaufman, 1962; Calabresi, McCollum & Welch, 1962, 1963a, b; Kaufman & Maloney, 1963). In man good results have been obtained in herpetic keratitis (Maxwell, 1963; Thomas, Purnell & Rosenthal, 1965), in severe cutaneous herpes (Longson, 1970) and in stomatitis (Douglas, Condemi & Balduzzi, 1971). IDU was also found active against vaccinia-zoster virus (Juel-Jensen *et al.*, 1970).

In encephalitis, the systemic route must be used. Idoxuridine is poorly soluble in water, unless the solution is alkalized at pH 8.5–9. The compound acts as a false thymidine and blocks the duplication of the virus, but has in counterpart a toxic effect on a variety of rapidly proliferating tissues such as hair-follicles, bone-marrow and epithelial cells of the oral mucosa. The effects are often mild and transient at the usual dosage of 400–600 mg/kg body weight (Calabresi *et al.*, 1961), although severe side-effects have been reported (Dayan & Lewis, 1969).

IDU can reverse the deleterious effects of corti-

coids in herpes keratitis, but this reversal is only relative (Kaufman & Maloney, 1962; Kaufman *et al.*, 1963).

IDU-resistant viruses have been observed (Buthala, 1964).

Cytosine-arabinoside

Cytosine-arabinoside (1-β-D-arabinofuranosylcytosine, cytarabine, cytosar, Ara-C, C-A, U-19-220A) was also first used in cancer therapy (Evans *et al.*, 1961; Talley & Vaitkevicius, 1963) but its antiviral activity was rapidly recognized (Underwood, 1962; Rapp, 1964; Buthala, 1964; Butel & Rapp, 1965) and its use in varicella-zoster and HSV infections advocated (Kaufman & Maloney, 1963; McKelvey & Kwaan, 1969; Hall *et al.*, 1969; Miller, Sloan & Silverman, 1969; Juel-Jensen, 1970a, b; Foerster & Hryniuk, 1971) in spite of some doubts cast about its effectiveness (Seligman & Rosner, 1970; Mann, 1971).

Buthala (1964) has demonstrated that cytarabine and IDU had only additive effect, but Ara-C was able to eliminate even the IDU-resistant viruses (Underwood, Wisner & Weed, 1964).

Because of the high toxicity of the drug when given in continuous perfusion, single daily rapid intravenous injections are now preferred. The schedule proposed by Juel-Jensen (1971), i.e. respectively 10, 8, 8, 8, and 6 mg/kg body weight appears to be safe.

In cell culture infected by HSV, Ara-C was found much more active than IDU (Buthala, 1964) whereas as in rats, inoculated with vaccinia, IDU only was active (Calabresi *et al.*, 1963b). In herpes simplex keratitis in the rabbit, Ara-C was found to be at least as effective as IDU (Underwood, 1962).

Almost all the cases of herpes encephalitis in adults are due to HSV type I (Craig & Nahmias, 1973). Walker *et al.* (1970) have demonstrated that in HSV type I and type II infections, better results were obtained with IUDR and FUDR respectively, whereas Ara-C inhibited both type of viruses. The existence of IDU-resistant strains (Buthala, 1964a), that can be overcome by Ara-C (Underwood *et al.*, 1964), is in favour of the latter drug as well as its simple preparation, compared with the painstaking and time-consuming preparation of IDU solution. However, in the present state of knowledge, there is no definite superiority of one drug over the other which has been demonstrated in herpes encephalitis.

Interferons

Interferons, discovered by Isaacs & Lindenmann (1957), are peptides produced by most animals—including man—and play a significant role in the protection against viral diseases (Isaacs & Hitchcock, 1960; Scientific Committee on Interferon, 1962;

Gresser & Naficy, 1964; Wheelock & Sibley, 1964; Kozaki, 1969; Friedman and Sonnabend, 1970; Grossberg, 1972). The evidence that foreign nucleic acid stimulated interferon production (Isaacs, Cox & Rotem, 1963) had led to the discovery of many interferon-inducers (De Clercq and Merigan, 1970a) among which are the polycarboxylates (Merigan & Finkelstein, 1968; Billiau, Muyembe & De Somer, 1971); polyriboinosinic-polyribocytidylic acid (Poly-I-Poly-C), a synthetic double-stranded RNA (Field *et al.*, 1967; Rabson, Tyrrell & Levy, 1969), and tilorone hydrochloride (bis-DEAE-fluorenone) a low-molecular-weight aromatic amine (Mayer & Kruger, 1970). Poly-I-Poly-C, and to a lesser extent DEAE-dextran, seems to exert a direct inhibitory action on DNA synthesis (Levy, 1970; Serota & Baserga, 1970).

The usefulness of interferon, or of the synthetic inducers, has been demonstrated against many viruses, including herpes (Cantell & Tommila, 1960; Jones, Galbraith & Al-Hussaini, 1962; Park & Baron, 1968; Lindh *et al.*, 1969; De Clercq & Merigan, 1970b; Kruger & Mayer, 1970). Its protective activity in experimental herpes encephalitis has been demonstrated by Catalano & Baron (1969).

Unfortunately repeated exposure to stimulation led to the development of hyporeaction, tolerance or refractoriness of the interferon-forming cells (Ho, 1970). This in turn has to be overcome by other drugs (Grossberg, 1972).

Human cell culture seems not to be affected by Poly-I-Poly-C (Hilleman, 1970a); careful and limited experimentations in man have shown only moderate toxic effects (fever, slight liver changes, disorders of coagulation) (Hilleman, 1970b; Merigan, 1970).

However, the problem of the toxicity/activity ratio of the inducers is still a preoccupying factor which prevents their generalized use (Levy, 1970; Hill *et al.*, 1971) and will perhaps restrict them to the treatment of life-threatening virus infections (Finter, 1970).

Other compounds

In recent years, several compounds have been tested against viruses. Rifampicin has shown antiviral properties (Heller *et al.*, 1969; Subak-Sharpe, Timbury & Williams, 1969) and some derivatives, like rifamycines and aminopiperazines, are active against HSV (Lancini, Cricchio & Thiry, 1971). L-asparaginase has also proved its effectiveness (Maral & Werner, 1971) and extracts of Burkitt's lymphoma cell culture have been successfully used in ocular herpes simplex infection in rabbits (Albert & Rabson, 1971).

It must be pointed out that most of the above antiviral compounds show also some antitumour

activity (Calabresi *et al.*, 1961; Evans *et al.*, 1961; Adamson *et al.*, 1969; Levy *et al.*, 1969; Adamson, 1971; Crowther, 1971) and some of them paradoxically depress both specific (immunologic) and non-specific (interferon system) mechanisms of defence against infection, while their action on chromosomes is still a matter of controversy (Kilbourne, 1955b; Immam and Hammon, 1957b; Kilbourne, Smart & Pokorny, 1961; Holmes, Gilson & Deinhardt, 1964; Kabak, Saksela & Mellman, 1964; Hilleman, 1965; Levy, Axelrod & Baron, 1965; Mitchell *et al.*, 1969; Berenbaum, 1970; Chakrabarty & Friedman, 1970; Ho, 1970).

Results and discussion

369 cases of ANE have been reviewed and the results are summarized in Tables 1 and 2. The figures suggest that any treatment is better than no treatment at all. However, these rough results deserve some comments. Most of the cases—either published

TABLE 1. Outcome of 369 cases of ANE

Treatment	No. of cases	Alive	Dead
Untreated	268	63	205
Treated	101	49	52

TABLE 2. Outcome of 101 treated cases

Treatment	No. of cases	Alive	Dead
Surgery only	28	11	17
IDU only	25	13	12
Ara-C only	8	7	1
Steroids only	19	9	10
Steroids + surgery	2	1	1
IDU or Ara-C + surgery	12	4	8
IDU or Ara-C + steroids	3	2	1
IDU or Ara-C + surgery + steroids	3	2	1
Poly-I-Poly-C	1	0	1

or the subject of personal communications—have been referred to hospital because of the severity of the disease, and indeed coma was one of the most common presenting symptoms. Therefore the high mortality rate observed in ANE may have been biased by a preselection of the worst cases. It must be remembered that ANE was first—and sometimes still remains—a necropsy diagnosis, even though it is now becoming a bedside diagnosis. In 1958, Haymaker *et al.* reviewed all the cases of ANE in adults known at the time; until then thirty-seven cases had been collected. To date more than 400 cases have been reported, and nearly thirty new cases are added every year (see Table 4). This more likely reflects improvement in diagnosis rather than higher

prevalence of the disease, for many cases may have been unrecognized in the past (Nolan, Carruthers & Lerner, 1970; Upton, Barwick & Foster, 1971).

A few authors have published relatively large series of untreated patients with survival (Meyer *et al.*, 1960; Leider *et al.*, 1965; Miller, Hesser & Tompkins, 1966; Olsen *et al.*, 1967). These cases probably represent the less severe form of the disease. Miller *et al.* (1966) points out that in their series ten out of thirteen comatose patients died, whereas only one of the seven non-comatose patients died. A benign form of the disease, presenting like a more or less transient temporal lobe impairment may have been wrongly diagnosed as 'stroke' (Rappel & Violon, 1973). Therefore, if severer cases of ANE have been missed, milder cases may also have been overlooked, so that the true incidence, natural history and mortality rate of the disease remains largely unknown.

On the other hand, the terms 'alive' and 'dead' do not give a full account of the outcome of the disease. Table 3 gives the survival time in 172 deaths. In untreated patients, the death rate amounts to 80% within 3 weeks, 84% within a month and 90% within 2 months. Within 6 months, all but one patient had died. In treated patients, the mortality rates are 57.5, 67.5 and 80% for 3 weeks, 1 and 2 months respectively. At 6 months, 12.5% are still alive. This seems to indicate that treating the patients will increase the survival time.

However, Table 4 shows that 70% of all the treated cases have been reported within the last 5 years. The part played in that period of time by the improvement of supportive treatment, especially

cardio-respiratory, is difficult to assess. One must point out that as far as the presenting symptoms and the severity of the disease are concerned the treated group was in no way different from the untreated group.

However, the patients of the latter group have been usually reported as part of series collected over several years (Haymaker *et al.*, 1958; Bennett, Zurhein & Roberts, 1962; Drachman & Adams, 1962; Flament-Durand, Capon & Coers, 1965; Leider *et al.*, 1965; Miller *et al.*, 1966; Olson *et al.*, 1967; Roy & Wolman, 1969) thus preventing any time/outcome correlation. Until now, no controlled trial has ever been performed, but some reports deserve our interest.

Nolan *et al.* (1970) had better results in the treated than in the untreated patients observed during the same period of time. Two of the three survivors reported by Carmon *et al.* (1965) were treated. The only survivors in the series of Bergouignan *et al.* (1968b) and Delmas-Marsalet *et al.* (1968) were also the only patients operated upon.

Another point in favour of the effectiveness of treatment is that the first signs of recovery often appeared 12-72 hr after therapy was begun (Adams & Jennett, 1967; Evans *et al.*, 1967; Marshall, 1967; Duffy, 1969; Rappel & Brihaye, 1969; Goldman *et al.*, 1970; Masquin, 1970; Nolan *et al.*, 1970; Silk & Roome, 1970; Bellanti, Catalano & Chambers, 1971; Chow *et al.*, 1971; Gurwith, Harman & Merigan, 1971; Habel & Brown, 1972; Upton *et al.*, 1971; Laterre, 1972). This phenomenon was not observed in untreated patients. After initial improvement some patients died several weeks or months later from causes not directly related to ANE (Duffy, 1969; Bellanti *et al.*, 1971; Rappel *et al.*, 1971). In the present review they are considered as treatment-failures. Indeed their increased sensitivity to dramatic and fatal infections can be considered as a remote effect of their initial illness. The quality of survival is discussed elsewhere in this issue (Oxbury & MacCallum, 1973) and will therefore not be commented on in the present study.

In the present state of knowledge no treatment seems to be preferable to the others. In Case A described by Gurwith *et al.* (1971), the patient deteriorated whilst on dexamethasone and recovered shortly after IDU therapy had begun. In Case I of Laterre (1972) IDU was of no help, but external decompression and lobectomy had an obvious beneficial effect. In Case I (J.S.) described by Rappel *et al.* (1971) the situation deteriorated despite surgery, but responded rapidly to IDU.

Today's treatment should not be confined to only one approach to the disease but will include surgery and drug therapy. Surgery has the advantage of allowing a large view of the affected area, often

TABLE 3. Survival time— data available from 172 patients out of 257 deaths

Death within	Untreated patients	Treated patients
1 week	26	5
2 weeks	52	9
3 weeks	27	9
1 month	6	4
2 months	7	5
6 months	13	3
1 year	0	3
1 year	1	2

TABLE 4. Cases of ANE published

Year	Untreated patients		Treated patients	
	Dead	Alive	Dead	Alive
1967	36	18	2	5
1968	13	4	4	3
1969	16	—	5	6
1970	9	5	8	11
1971	2	—	14	13

permitting a per-operative diagnosis. On the other hand the necrotic tissues can be easily removed, and intracranial pressure better controlled. Drug therapy will include medical decompression and virus growth inhibition. The possible usefulness of combined therapy like Ara-C and L-asparaginase, discussed in this issue by Cappel, Thiry & Klastersky (1973), suggest that the future lies in polychemo-therapy. We must also bear in mind that the treatment should be started as early as possible in order to prevent irreversible damage taking place before therapy (Charnock & Cramblett, 1970).

The present review is intended to demonstrate the difficulties, the biases, the loopholes and the limits of a retrospective study. The time has now come to encourage the undertaking of prospective and collaborative studies, for the advancement of our knowledge and for the sake of our patients.

References

- ADAMS, J. H. & JENNETT, W. B. (1967) Acute necrotizing encephalitis: a problem in diagnosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**, 248.
- ADAMSON, R. H. (1971) Antitumour activity of two antiviral drugs. Rifampicin and tilorone. *Lancet*, **i**, 398.
- ADAMSON, R. H., FABRO, S., HOMAN, E. R., O'GARA, R. W. & ZENDZIAN, R. P. (1969) Pharmacology of polyribonucleoside: polyribocytidylic acid, a new antiviral and antitumour agent. *Antimicrobial Agents and Chemotherapy*, **148**.
- ALBERT, D. M. & RABSON, A. S. (1971) Inhibition of ocular herpes simplex infection in rabbits by extracts of Burkitt's lymphoma cell culture (35841). *Proceedings of the Society for Experimental Biology and Medicine*, **138**, 108.
- BARON, A., LE BOURHIS & GOURAY (1959) Action des corticostéroïdes sur les lésions herpétiques de la cornée. *Bulletin de la Société française d'ophtalmologie*, **72**, 647.
- BELLANTI, J. A., CATALANO, L. W. & CHAMBERS, R. W. (1971) Herpes simplex encephalitis. Virologic and serologic study of a patient treated with an interferon inducer. *Journal of Pediatrics*, **78**, 136.
- BENNETT, D. R., ZURHEIN, G. M. & ROBERTS, T. S. (1962) Acute necrotizing encephalitis. *Archives of Neurology*, **6**, 96.
- BERENBAUM, M. C. (1970) Immuno-suppression by L-asparaginase. *Nature*, **225**, 550.
- BERGOUIGNAN, M., JULIEN, J. & VITAL, C. (1968a) Le virus herpétique est-il responsable des encéphalites aiguës nécrosantes? *Presse Médicale*, **76**, 703.
- BERGOUIGNAN, M., JULIEN, J., VITAL, C. & DUVERT, M. (1968b) Notre expérience de l'encéphalite aiguë nécrosante. Mise en évidence du virus herpétique au microscope électronique. *Presse Médicale*, **76**, 709.
- BILLIAU, A., MUYEMBE, J. J. & DE SOMER, P. (1971) Mechanism of antiviral activity *in vivo* of polycarboxylates which induce interferon production. *Nature New Biology*, **232**, 183.
- BLACKWOOD, W., DUDGEON, J. A., NEWNS, G. H. & PHILLIPS, B. M. (1966) Case of encephalitis due to herpes simplex. *British Medical Journal*, **1**, 1519.
- BLOEDHORN, VON H., STAMMLER, A., ACKERMANN, R. & SCHEID, W. (1962) Herpes simplex Enzephalitis des Erwachsenen mit tödlichem Ausgang. *Deutsche medizinische Wochenschrift*, **87**, 1247.
- BONAMOUR, G. (1962) Place de la corticothérapie dans le traitement des kératites herpétiques. *L'Année thérapeutique et clinique en ophtalmologie*, **13**, 283.
- BRIHAYE, J. (1958) *Etude des encéphalites herpétiques et des encéphalites nécrosantes aiguës* (thesis). *Acta medica belgica*, **1**.
- BUTEL, J. S. & RAPP, F. (1965) The effect of arabinofuranosylcytosine on the growth cycle of simian virus 40. *Virology*, **27**, 490.
- BUTHALA, D. A. (1964) Cell culture studies on antiviral agents. I. Action of cytosine arabinoside and some comparisons with 5-iodo-2'-deoxyuridine. *Proceedings of the Society for Experimental Biology and Medicine*, **115**, 69.
- CALABRESI, P., CARDOSO, S. S., FINCH, S. C., KLIEGERMAN, M. M., VON ESSEN, C. F., MING Y CHU & WELCH, A. D. (1961) Initial clinical studies with 5-iodo-2'-deoxyuridine. *Cancer Research*, **21**, 550.
- CALABRESI, P., MCCOLLUM, R. W. & WELCH, A. D. (1962) The inhibitory effects of 5-iodo-2'-deoxyuridine (IUdR) upon infections caused by vaccinia. *Clinical Research*, **10**, 397.
- CALABRESI, P., MCCOLLUM, R. W. & WELCH, A. D. (1963a) Suppression of infections resulting from a deoxyribonucleic acid virus (vaccinia) by systemic administration of 5-iodo-2'-deoxyuridine. *Nature*, **197**, 767.
- CALABRESI, P., MCCOLLUM, R. W. & WELCH, A. D. (1963b) Comparison of the systemic anti-vaccinial activity of analogs of pyrimidine nucleosides. *Proceedings of the American Association for Cancer Research*, **4**, 9.
- CANTELL, K. & TOMMILA, V. (1960). Effect of interferon on experimental vaccinia and herpes-simplex virus infections in rabbit's eyes. *Lancet*, **ii**, 682.
- CAPPEL, R., THIRY, L. & KLASTERSKY, J. (1973) Anti-herpetic activity of L-asparaginase and arabinoside cytosine used in combination *in vitro*. *Postgraduate Medical Journal*, **49**, 428.
- CARMON, A., BEHAR, A. & BELLER, A. J. (1965) Acute necrotizing haemorrhagic encephalitis presenting clinically as a space-occupying lesion. A clinico-pathological study of six cases. *Journal of Neurological Sciences*, **2**, 328.
- CASTLEMAN, B. & MCNEELY, B. U. (1964) Case records of the Massachusetts General Hospital Weekly clinicopathological exercises—case 61. *New England Journal of Medicine*, **271**, 1313.
- CATALANO, L. W. & BARON, S. (1969) Protection against herpes simplex encephalitis by an interferon inducer (abstract 549). Fourth International Congress of Neurological Surgery. *Excerpta Medica International Congress Series*, **193**, 195.
- CAULET, T., VILDE, L., GEOFFROY, H., DUFOUR, M. & PLUOT, M. (1971) Particules virales du groupe de l'herpès à nouveau montrées par l'étude ultrastructurale d'un cas d'encéphalite aiguë nécrosante. *Presse Médicale*, **79**, 14.
- CHAKRABARTY, A. K. & FRIEDMAN, H. (1970) L-asparaginase-induced immunosuppression: effects on antibody forming cells and serum titers. *Science*, **167**, 869.
- CHARNOCK, E. L. & CRAMBLETT, H. G. (1970) 5-iodo-2'-deoxyuridine in neonatal herpes virus homines encephalitis. *Journal of Pediatrics*, **76**, 459.
- CHOW, A., FIALA, M., HRYNIUK, W. & GUZE, L. B. (1971) Cytosine arabinoside (Ara-C) therapy for herpes simplex encephalitis (abstract 56). In: *Proceedings of the 11th Interscience Conference on Antimicrobial Agents and Chemotherapy*, p. 28. American Society of Microbiology.
- CLASEN, P. A., HINDO, W. A., PANDOLFI, S. & LAING, I. (1972) The role of necrosis and inflammation in the response of cerebral edema to steroids. In: *Workshop on the Effects of Steroids on Brain Edema* (Ed. by K. Schürmann and H. J. Reulsen), p. 34. Mainz University Press.

- COID, C. R., TOBIN, J. O'H. & BESWICK, T. S. L. (1960) The sensitivity of monkeys to subcutaneous inoculation of the Brunenders strain of type I poliomyelitis virus. *Journal of Pathology and Bacteriology*, **79**, 325.
- COXE, W. S. & LUSE, S. A. (1963) Acute hemorrhagic leuko-encephalitis—a clinical and electron-microscopic report of two patients treated with surgical decompression. *Journal of Neurosurgery*, **20**, 584.
- CRAIG, C. P. & NAHMIA, A. J. (1973) Different patterns of neurological involvement with herpes simplex type 1 and 2. To be published.
- CROMPTON, D. (1964) Corticosteroids exacerbate ocular herpes simplex. *Medical Journal of Australia*, **2**, 950.
- CROMPTON, M. R. & TEARE, R. D. (1965) Encephalitis after the reduction of steroid maintenance therapy. *Lancet*, **ii**, 1318.
- CROWTHER, P. (1971) L-asparaginase and human malignant disease. *Nature*, **229**, 168.
- DAYAN, A. D. & LEWIS, P. D. (1969) Idoxuridine and jaundice. *Lancet*, **ii**, 1073.
- DE CLERCQ, E. & MERIGAN, T. C. (1970a) Induction of interferon by non-viral agents. *Archives of Internal Medicine*, **126**, 94.
- DE CLERCQ, E. & MERIGAN, T. C. (1970b) Current concepts of interferon and interferon induction. *Annual Review of Medicine*, **21**, 17.
- DELMAS-MARSALET, P. M., BERGOUIGNAN, M., CASTAING, R., DU PASQUIER, P. & VITAL, C. (1968) Fréquence actuelle des encéphalites herpétiques de l'adulte: sur une série personnelle de huit cas confirmés par la microscopie électronique. *Bulletin de l'Académie Nationale de Médecine (Paris)*, **152**, 316.
- DEMOPOULOS, H. B., MILVY, P., KAKARI, S. & RANSOHOFF, J. (1972) Molecular aspects of membrane structure in cerebral edema. In: *Workshop on the Effects of Steroids on Brain Edema* (Ed. by K. Schürman and H. J. Reulen), p. 8. Mainz University Press.
- DOUGLAS, R. G., CONDEMI, J. J. & BALDUZZI, P. (1971) Experience with idoxuridine treatment of herpes simplex stomatis (abstract). In: *Proceedings of the 11th Interscience Conference on Antimicrobial Agents and Chemotherapy*, p. 27. American Society of Microbiology.
- DRACHMAN, D. A. & ADAMS, R. D. (1962) Herpes simplex and acute inclusion-body encephalitis. *Archives of Neurology*, **7**, 45.
- DUCKETT, S., KELLY, R. & GRANT, H. C. (1963) Un cas de méningo-encéphalite nécrasante avec inclusions intracellulaires dû à une infection psittacose possible. *Revue Neurologique*, **108**, 899.
- DUFFY, G. (1969) Herpes simplex encephalitis—neurosurgical implications and treatment. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 634.
- DUKE-ELDER, S. (1965) Viral kerato-conjunctivitis. In: *System of Ophthalmology* (Ed. by St Duke-Elder), Vol. 8, part 1, p. 327. H. Kimpton, London.
- EVANS, A. D., GRAY, O. P., MILLER, M. H., VERRIER-JONES, E. R., WEEKS, R. D. & WELLS, C. E. C. (1967) Herpes simplex encephalitis treated with intravenous idoxuridine. *British Medical Journal*, **2**, 407.
- EVANS, J. S., MUSSER, E. A., MENGEL, G. D., FORSLAD, K. R. & HUNTER, J. H. (1961) Antitumour activity of 1-β-D-arabinofuranosylcytosine hydrochloride. *Proceedings of the Society for Experimental Biology and Medicine*, **106**, 350.
- FIELD, A. K., TYTELL, A. A., LAMPSON, G. P. & HILLEMANN, M. R. (1967) Inducers of interferon and host resistance. II. Multistranded synthetic polynucleotide complexes. *Proceedings of the National Academy of Science*, **58**, 1004.
- FINDLEY, G. M. & HOWARD, E. M. (1952) The effect of cortisone ACTH on poliomyelitis and on other virus infections. *Journal of Pharmacy and Pharmacology*, **4**, 37.
- FINTER, N. B. (1970) Exogenous interferon in animals and its clinical implications. *Archives of Internal Medicine*, **126**, 147.
- FLAMENT-DURAND, J., CAPON, A. & COERS, C. (1965) Etude anatomo-clinique de cinq cas d'encéphalite nécrasante aigüe. *Revue Neurologique*, **113**, 503.
- FOERSTER, J. & HRYNIUK, W. (1971) Cytosine arabinoside and herpes zoster. *Lancet*, **ii**, 712.
- FOX, J. L. (1964) Development of recent thoughts on intracranial pressure and the blood-brain barrier. *Journal of Neurosurgery*, **21**, 909.
- FRIEDMAN, R. M. & SONNABEND, J. A. (1970) Mechanism of action of interferon. *Archives of Internal Medicine*, **126**, 51.
- GOLDMAN, B., NAHOR, A., BRAHAM, J. & PADEH, B. (1970) Herpes encephalitis treated with idoxuridine. *Lancet*, **ii**, 155.
- GOLDSTEIN, S. L., HIMWICH, W. A., KNAPP, F. M. & ROVINE, B. W. (1964) Effect of urea and other dehydrating agents upon dog brain. *Journal of Neurosurgery*, **21**, 672.
- GRESSER, I. & NAFICY, K. (1964) Recovery of an interferon-like substance from cerebrospinal fluid. *Proceedings of the Society for Experimental Biology and Medicine*, **117**, 285.
- GROSSBERG, S. E. (1972) The interferons and their inducers. Molecular and therapeutic considerations. *New England Journal of Medicine*, **287**, 13.
- GURWITH, M. J., HARMAN, C. E. & MERIGAN, T. C. (1971) Approach to diagnosis and treatment of herpes simplex encephalitis. *California Medicine*, **115**, 63.
- HABEL, A. H. & BROWN, J. K. (1972) Dexamethasone in herpes-simplex encephalitis. *Lancet*, **i**, 695.
- HALL, T., WILFERT, C., JAFFE, N., TRAGGIS, D., LUX, S., ROMPF, P. & KATZ, S. (1969) Treatment of varicella-zoster with cytosine arabinoside. *Clinical Research*, **17**, 470.
- HAYMAKER, W., SMITH, M. G., VANBOGAERT, L. & DE CHENAR, C. (1958) Pathology of viral disease in man characterized by nuclear inclusions. In: *Viral Encephalitis* (Ed. by W. S. Fields and R. J. Blatner), p. 95. Charles C. Thomas, Springfield, Illinois.
- HEATHFIELD, K. W. G., PILSWORTH, R., WALL, B. J. & CORSELLIS, J. A. N. (1967) Coxsackie B5 infections in Essex 1965, with particular reference to the nervous system. *Quarterly Journal of Medicine*, **36**, 579.
- HELLER, E., ARGAMAN, M., LEVY, H. & GOLDBLUM, N. (1969) Selective inhibition of vaccinia virus by the antibiotic Rifampicin. *Nature*, **222**, 273.
- HERRMANN, E. C. Jr (1961) Plaque inhibition test for detection of specific inhibitors of DNA containing viruses. *Proceedings of the Society for Experimental Biology and Medicine*, **107**, 142.
- HILL, D. A., BARON, S., LEVY, H. B., BELLANTI, J., BUCKLER, C. E., CANNELLOS, G., CARBONE, P., CHANOCK, R. M., DE VITA, V., GUGGENHEIM, M. A., HOMAN, E., KAPIKIAN, A. Z., KIRSCHSTEIN, R. L., MILLS, J., PERKINS, J. C., VAN KIRK, J. E. & WORTHINGTON, M. (1971) Clinical studies of induction of interferon by polyinosinic-polycytidylic acid. In: *Perspectives in Virology VII. From Molecules to Man* (Ed. by M. Pollard), p. 197. Academic Press, New York.
- HILLEMANN, M. R. (1965) Immunologic, chemotherapeutic and interferon approaches to control of viral infection. *American Journal of Medicine*, **38**, 751.
- HILLEMANN, M. R. (1970a) Double-stranded RNAS (Poly I:C) in the prevention of viral infections. *Archives of Internal Medicine*, **126**, 109.
- HILLEMANN, M. R. (1970b) Prospects for the use of double-stranded ribonucleic acid (Poly I:C) inducers in man. *Journal of Infectious Diseases*, **121**, 196.
- HITCHCOCK, E. & SATO, F. (1964) Treatment of malignant gliomata. *Journal of Neurosurgery*, **21**, 497.
- HO, M. (1970) Factors influencing the interferon response. *Archives of Internal Medicine*, **126**, 135.

- HOHENEGGER, M. (1967) Ist Cortison in der Behandlung der Virusenzephalitis von Wert? *Wiener medizinische Wochenschrift*, **117**, 286.
- HOLMES, A. W., GILSON, J. & DEINHARDT, F. (1964) Inhibition of interferon production by 5-iodo-2-deoxyuridine. *Virology*, **24**, 229.
- IMMAM, I. Z. E. & HAMMON, W. MCD. (1957a) Susceptibility of hamsters to peripherally inoculated Japanese B and St Louis viruses following cortisone, X-ray, trauma. *Proceedings of the Society for Experimental Biology and Medicine*, **95**, 6.
- IMMAM, I. Z. E. & HAMMON, W. MCD. (1957b) Immunologic response and pathogenesis of Japanese B infection in peripherally inoculated normal and cortisone treated hamsters. *Proceedings of the Society for Experimental Biology and Medicine*, **95**, 12.
- ISAACS, A., COX, R. A. & ROTEM, Z. (1963) Foreign nucleic acids as the stimulus to make interferon. *Lancet*, **ii**, 113.
- ISAACS, A. & HITCHCOCK, G. (1960) Role of interferon in recovery from virus infections. *Lancet*, **ii**, 69.
- ISAACS, A. & LINDENMANN, J. (1957) Virus and interference. I. The interferon. *Proceedings of the Society for Experimental Biology and Medicine*, **147**, 258.
- JAWETZ, E., OKUMOTO, M. & SONNE, M. (1959) Studies on herpes simplex. X. The effect of corticosteroids on herpetic keratitis in the rabbit. *Journal of Immunology*, **83**, 486.
- JONES, B. R., GALBRAITH, J. E. K. & AL-HUSSAINI, M. K. (1962) Vaccinal keratitis treated with interferon. *Lancet*, **i**, 875.
- JUEL-JENSEN, B. E. (1970a) Varicella and cytosine-arabinside. *Lancet*, **i**, 572.
- JUEL-JENSEN, B. E. (1970b) Severe generalized primary herpes treated with cytarabine. *British Medical Journal*, **2**, 1954.
- JUEL-JENSEN, B. E. (1971) Personal communication.
- JUEL-JENSEN, B. E., MCCALLUM, F. O., MCKENZIE, A. M. R. & PIKE, M. C. (1970) Treatment of zoster with idoxuridine in dimethylsulphoxide. Results of two double-blind controlled trials. *British Medical Journal*, **4**, 776.
- KABACK, M. M., SAKSELA, E. & MELLMAN, W. J. (1964) The effect of 5-bromo-deoxyuridine on human chromosomes. *Experimental Cell Research*, **34**, 182.
- KAUFMAN, H. E. (1962) Clinical cure of herpes simplex keratitis by 5-iodo-2¹-deoxyuridine. *Proceedings of the Society for Experimental Biology and Medicine*, **109**, 251.
- KAUFMAN, H. E. & MALONEY, E. D. (1962) IDU and hydrocortisone in experimental herpes simplex keratitis. *Archives of Ophthalmology*, **68**, 396.
- KAUFMAN, H. E. & MALONEY, E. D. (1963) IDU and cytosine arabinoside in experimental herpetic keratitis. *Archives of Ophthalmology*, **69**, 226.
- KAUFMAN, H. E., MARTOLA, E. L. & DOHLMAN, C. H. (1963) Herpes simplex treatment with IDU and corticosteroids. *Archives of Ophthalmology*, **69**, 468.
- KILBOURNE, E. D. (1955a) Reactivation of non-infective virus in cortisone injected host. *Journal of Experimental Medicine*, **101**, 437.
- KILBOURNE, E. D. (1955b) The influence of cortisone on experimental viral infection II. *Proceedings of the Society for Experimental Biology and Medicine*, **90**, 685.
- KILBOURNE, E. D. (1957) The influence of cortisone on experimental viral infection V. *Journal of Experimental Medicine*, **106**, 863.
- KILBOURNE, E. D., SMART, K. M. & POKORNY, B. A. (1961) Inhibition by cortisone of the synthesis and action of interferon. *Nature*, **190**, 650.
- KOFMAN, S., GAVIN, J. S., NAGAMANI, D. & TAYLOR, S. G. (1957) Treatment of cerebral metastases from breast carcinoma with prednisolone. *Journal of the American Medical Association*, **163**, 1473.
- KOZAKI, T. (1969) Clinical studies of interferon. II. Recovery of interferon from cerebrospinal fluid of patients with aseptic meningitis. *Nagoya Journal of Medical Sciences*, **32**, 121.
- KRUEGER, R. F. & MAYER, G. D. (1970) Tilorone hydrochloride: an orally active antiviral agent. *Science*, **169**, 1213.
- LANCINI, G., CRICCHIO, R. & THIRY, L. (1971) Antiviral activity of rifamycins and N-amino-piperazines. *Journal of Antibiotics*, **24**, 64.
- LATERRE, E. (1972) Personal communication.
- LEIDER, W., MAGOFFIN, R. L., LENNETTE, E. H. & LEONARDS, L. N. R. (1965) Herpes-simplex virus encephalitis: its possible association with reactivated latent infection. *New England Journal of Medicine*, **273**, 341.
- LERMAN, S., DOYLE, J. & DOYLE, R. F. (1962) Effect of fluorinated pyrimidines on herpes simplex virus. *Nature*, **194**, 986.
- LEVY, H. B. (1970) Interferon and interferon inducers in the treatment of malignancies. *Archives of Internal Medicine*, **126**, 78.
- LEVY, H. B., AXELROD, D. & BARON, S. (1965) Effect of FUDR on interferon production. *Proceedings of the Society for Experimental Biology and Medicine*, **118**, 1013.
- LEVY H. B., LAW, L. W. & RABSON, A. S. (1969) Inhibition of tumor growth by polyinosinic-polycytidylic acid. *Proceedings of the National Academy of Sciences*, **62**, 357.
- LEWIN, M., PAPPIUS, H. M. & HANSEBOUT R. R. (1972) Effects of steroids on edema associated with injury of spinal cord. In: *Workshop on the Effects of Steroids on Brain Edema* (Ed. by K. Schürmann and H. J. Reulen), p. 24. Mainz University Press.
- LINDH, H. F., LINDSAY, H. L., MAYBERRY, B. R. & FORBES, M. (1969) Polyinosinic-cytidylic acid complex (Poly I : C) and viral infections in mice. *Proceedings of the Society for Experimental Biology and Medicine*, **132**, 53.
- LIU, C., MUANGMANEE, L., CHO, C. T., WENGLIN, B. D. & VOTH, D. W. (1971) Rapid diagnosis of *Herpes virus hominis* encephalitis by immunofluorescent staining (abstract). *Proceedings of the 11th Interscience Conference on Antimicrobial Agents and Chemotherapy*, p. 1. American Society of Microbiology.
- LONG, D. M., CHOI, K. S., MAXWELL, R. E., O'COLE, H. & FRENCH, L. A. (1972a) Multiple therapeutic approaches in the treatment of brain edema. In: *Workshop on the Effect of Steroids on Brain Edema* (Ed. by K. Schürmann and H. J. Reulen), p. 20. Mainz University Press.
- LONG, D. M., MAXWELL, R. E. & FRENCH, L. A. (1972b) The effects of glucocorticoids upon experimental brain edema. In: *Workshop on the Effects of Steroids on Brain Edema* (Ed. by K. Schürman and H. J. Reulen), p. 14. Mainz University Press.
- LONGSON, M. (1970) Treatment of severe cutaneous herpes. *Lancet*, **i**, 81.
- LONGSON, M. (1973) Immunofluorescence and the urgent diagnosis of herpes encephalitis. *Postgraduate Medical Journal*, **49**, 403.
- LONGSON, M. & BESWICK, T. S. L. (1971) Dexamethasone treatment in herpes-simplex encephalitis. *Lancet*, **i**, 749.
- MALONEY, E. D. & KAUFMAN, H. E. (1965) Dissemination of corneal herpes simplex. *Investigative Ophthalmology*, **4**, 872.
- MANN, J. R. (1971) Cytosine arabinoside and herpes zoster. *Lancet*, **ii**, 166.
- MARAL, R. & WERNER, G. H. (1971) Antiviral activity of L-aparaginase. *Nature New Biology*, **232**, 187.
- MARSHALL, W. J. S. (1967) Herpes simplex encephalitis treated with idoxuridine and external decompression. *Lancet*, **ii**, 579.
- MASQUIN, L. (1970) *Troubles mentaux au cours des encéphalites aiguës nécrisantes herpétiques*. Thesis, Marseille.

- MAXWELL, E. (1963) Treatment of herpes keratitis with 5-iodo-2'-deoxyuridine (IDU). A clinical evaluation of 1500 cases. *American Journal of Ophthalmology*, **56**, 571.
- MAYER, G. D. & KRUGER, R. F. (1970) Tilorone hydrochloride mode of action. *Science*, **169**, 1214.
- MCCOY, G. A. & LEOPOLD, I. H. (1960) Steroid treatment of herpes simplex infections of the cornea. *American Journal of Ophthalmology*, **49**, 1355.
- MCKELVEY, E. M. & KWAAN, H. C. (1969) Cytosine arabinoside therapy for disseminated herpes zoster in a patient with IgG pyroglobulinaemia. *Blood*, **34**, 706.
- MCQUEEN, J. D. & JEANES, L. D. (1964) Dehydration and rehydration of the brain with hypertonic urea and mannitol. *Journal of Neurosurgery*, **21**, 118.
- MERIGAN, T. C. (1970) Interferon stimulated by double stranded RNA. *Nature*, **228**, 219.
- MERIGAN, T. C. & FINKELSTEIN, M. S. (1968) Interferon-stimulating and *in vivo* antiviral effects of various synthetic anionic polymers. *Virology*, **35**, 363.
- MEYER, H. M., JOHNSON, R. T., CRAWFORD, I. P., DASCOMB, H. E. & ROGERS, N. G. (1960) Central nervous system syndromes of 'viral' etiology. A study of 713 cases. *American Journal of Medicine*, **2**, 334.
- MILLER, F. A., SLOAN, B. J. & SILVERMAN, C. A. (1969) Antiviral activity of 9- β -D-arabinofuranosyladenine. VI. Effect of delayed treatment on herpes simplex virus in mice. *Antimicrobial Agents and Chemotherapy*, **192**.
- MILLER, J. K., HESSER, F. & TOMPKINS, V. N. (1966) Herpes simplex encephalitis. Report of twenty cases. *Annals of Internal Medicine*, **64**, 92.
- MITCHELL, M. J., WADE, M. E., DECONTI, R. C., BERTINO, J. R. & CALABRESI, P. (1969) Immunosuppressive effects of cytosine arabinoside and methotrexate in man. *Annals of Internal Medicine*, **70**, 535.
- NEUBERGER, H. & SCHNEWEIS, K. E. (1963) Le comportement des anticorps dans la keratite expérimentale par la cortisone. *Annales Oculistiques*, **196**, 189.
- NOLAN, D. C., CARRUTHERS, H. M. & LERNER, A. M. (1970) Herpes virus hominis encephalitis in Michigan—report of thirteen cases, including six treated with idoxuridine. *New England Journal of Medicine*, **282**, 10.
- OLSON, L. C., BUESCHER, E. L., ARENSTEIN, M. S. & PARKMAN, P. D. (1967) Herpes virus infections of the human central nervous system. *New England Journal of Medicine*, **277**, 1271.
- OSBURY, J. M. & MACCALLUM, F. O. (1973) Herpes simplex virus encephalitis: clinical features and residual damage. *Postgraduate Medical Journal*, **49**, 387.
- PAGE, L. K., TYLER, H. R. & SHILLITO, J. Jr (1967) Neurosurgical experiences with herpes simplex encephalitis. *Journal of Neurosurgery*, **27**, 346.
- PAPPIUS, H. M. (1972) Effect of steroids on cold injury edema. In: *Workshop on the Effect of Steroids on Brain Edema* (Ed. by K. Schürmann and H. J. Reulen), p. 13. Mainz University Press.
- PARK, J. H. & BARON, S. (1968) Herpetic kerato conjunctivitis: therapy with synthetic double stranded RNA. *Science*, **162**, 811.
- PATTERSON, A. & JONES, B. R. (1967) The management of ocular herpes. *Transactions of the Ophthalmologic Society (U.K.)*, **87**, 59.
- PERKINS, E. S., WOOD, R. M., SEARS, M. L., PRUSSOFF, W. H. & WELCH, A. D. (1962) Anti-viral activities of several iodinated pyrimidine deoxyribonucleosides. *Nature*, **194**, 985.
- PIERCE, N. F., PORTNOY, B., LEEDS, N. E., MORRISON, R. L. & WEHRLE, P. F. (1964) Encephalitis associated with herpes simplex infection presenting as a temporal-lobe mass. Report of two cases with survival. *Neurology*, **14**, 709.
- POTTER, J. M. (1969) Clinical aspects of herpes simplex encephalitis. In: *Virus Diseases and the Nervous System* (Ed. by C. M. W. Whitty, J. T. Hughes and F. O. McCallum), p. 17. Blackwell Scientific Publications, Oxford.
- RABSON, A. S., TYRRELL, S. A. & LEVY, H. B. (1969) Inhibition of human cytomegalovirus *in vitro* by double stranded polyribocytidylic-inosinic acid (Poly Ir-Cr) (33909). *Proceedings of the Society for Experimental Biology and Medicine*, **131**, 495.
- RAPP, F. (1964) Inhibition by metabolic analogue of plaque formation by herpes zoster and herpes simplex viruses. *Journal of Immunology*, **93**, 643.
- RAPPEL, M. & BRIHAYE, J. (1969) Traitement de l'encéphalite nécrasante herpétique par l'idoxuridine. *Revue Neurologique*, **121**, 93.
- RAPPEL, M., DUBOIS-DALCO, M., SPRECHER, S., THIRY, L., LOWENTHAL, A., PELC, S. & THYS, J. P. (1971) Diagnosis and treatment of herpes encephalitis—a multidisciplinary approach. *Journal of Neurological Sciences*, **12**, 443.
- RAPPEL, M. & VIOLON, A. (1973) Benign herpes encephalitis. To be published.
- ROOK, A. J., WILKINSON, D. S. & EBLING, F. J. G. (1968) In: *Textbook of Dermatology* (Ed. by A. J. Rook, D. S. Wilkinson and F. J. G. Ebling), Vol. 1, p. 770. Blackwell Scientific Publications, Oxford.
- ROY, S. & WOLMAN, L. (1969) Electron microscopic observation on the virus particles in herpes simplex encephalitis. *Journal of Clinical Pathology*, **22**, 51.
- SCHIED, W. & JOCHHEIM, K. A. (1956) Akute Encephalomyelitis und Virus der Lymphocytären Choriomeningitis. *Nervenarzt*, **27**, 385.
- SCHNEWEIS, K. E., NEUBERGER, H. & MEYER, H. (1963) Zur Cortison-Wirkung bei experimenteller Keratitis herpetica. *Albrecht v. Graefes Archiv für Ophthalmologie*, **166**, 277.
- SCIENTIFIC COMMITTEE ON INTERFERONS (1962) Effect of interferon on vaccination in volunteers (A report to the Medical Research Council from the Scientific Committee on Interferon). *Lancet*, **i**, 872.
- SELIGMAN, B. R. & ROSNER, F. (1970) Varicella and cytosine arabinoside. *Lancet*, **i**, 307.
- SEROTA, F. T. & BASERGA, R. (1970) Polyinosinic acid-poly-cytidylic acid: inhibition of DNA synthesis stimulated by isoproterenol. *Science*, **167**, 1379.
- SILK, B. R. & ROOME, A. P. C. H. (1970) Herpes encephalitis treated with intravenous idoxuridine. *Lancet*, **ii**, 411.
- SUBAK-SHARPE, J. H., TIMBURY, M. C. & WILLIAMS, J. F. (1969) Rifampicin inhibits the growth of some mammalian viruses. *Nature*, **222**, 341.
- TALLEY, R. W. & VAITKEVICIUS, V. K. (1963) Megaloblastosis produced by a cytosine antagonist, 1- β -D-arabinofuranosylcytosine. *Blood*, **21**, 352.
- THOMAS, C. H. I., PURNELL, E. W., & ROSENTHAL, M. S. (1965) Treatment of herpetic keratitis with IDU and corticosteroids. Report of 105 cases. *American Journal of Ophthalmology*, **60**, 204.
- TOKUMARU, T. (1967) The protective effect of different immunoglobulins against herpetic encephalitis and skin infection in guinea-pigs. *Archiv für die gesamte Virus forschung*, **22**, 332.
- TOMLINSON, A. H. & MCCALLUM, F. O. (1969) Herpes simplex encephalitis—virological diagnosis. In: *Virus Diseases and the Nervous System* (Ed. by C. W. Whitty, J. T. Hughes and F. O. McCallum), p. 21. Blackwell Scientific Publications, Oxford.
- TOOLE, J. F. & MCCALL, C. E. (1969) Brain inflammation and steroids: two double edged swords. *Annals of Internal Medicine*, **70**, 221.

- UNDERWOOD, G. E. (1962) Activity of 1-β-D-arabinofuranosylcytosine hydrochloride against herpes simplex keratitis. *Proceedings of the Society for Experimental Biology and Medicine*, **111**, 660.
- UNDERWOOD, G. E., WISNER, C. A. & WEED, S. D. (1964) Cytosine arabinoside (CA) and other nucleosides in herpes virus infections. *Archives of Ophthalmology*, **72**, 505.
- UPTON, A. R. M., BARWICK, D. D. & FOSTER, J. B. (1971) Dexamethasone treatment in herpes simplex encephalitis. *Lancet*, **i**, 290.
- VAN BOGAERT, L., RADERMECKER, J. & DEVOS, J. (1955) Sur une observation mortelle d'encéphalite aigüe nécrosante. *Revue Neurologique*, **92**, 329.
- VITAL, C. (1972) Personal communication.
- WALKER, W. E., WAISBREN, B. A., MARTINS, R. R. & BATAYIAS, G. E. (1972) *In vitro* determinations of viral susceptibility to drugs for possible clinical use. *Antimicrobial Agents and Chemotherapy*, 380.
- WEINSTEIN, L. (1962) Corticotropin and corticosteroids in human viral infections. *Medical Clinics of North America*, **46**, 1141.
- WHEELLOCK, E. F. & SIBLEY, W. A. (1964) Interferon in human serum during clinical viral infections. *Lancet*, **ii**, 382.