third 24-hour periods of treatment, but comparison of the mean values obtained during the control periods and those obtained during treatment showed that the increase in excretion of calcium was highly significant only during the first 24-hour period ($P<0.001$). On day 4, when doses of frusemide were still being administered, the excretion of calcium was not significantly higher in any of the patients than it had been during the period of control.

The average excretions of sodium and calcium in the urine were closely correlated ($r=0.94$; $P<0.001$). No significant changes in levels of calcium in serum were observed during treatment with frusemide.

Discussion

Excretion of calcium in the urine depends on the ratio of volumes filtered in the glomeruli to degree of absorption in tubules. Under normal conditions 98% of the filtered load of calcium will be reabsorbed. Walser (1961) showed in experiments on dogs that there was a positive correlation between clearances of calcium and sodium. Later, this fact was found to apply also to man (Kleeman *et al.*, 1964). Our findings support the observation by Tambyah and Lim (1969) of an increased excretion of calcium in the urine after administration of a single dose of frusemide. According to those authors the excretion of calcium was more than redoubled throughout an eight-hour interval after oral administration of 80 mg of frusemide. The daily excretion observed in our series was only slightly increased, and only for a short period; the excretion became normal within a few days despite continued daily administrations of frusemide. The action of frusemide on the renal excretion of calcium is apparently tied up with its natriuretic property, and since the excretion of sodium is increased only during the initial stages of frusemide therapy, the rise in the excretion of calcium in the urine will be only of transient nature.

Our findings suggest that frusemide can hardly be considered suitable as a permanent treatment of hypercalcaemia, whereas it may be of value as an adjunct to sodium infusions in the treatment of hypercalcaemic crises, in which cases the effects are intensified and the hazards of acute cardiac arrest reduced.

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PRELIMINARY COMMUNICATIONS

Association between Psychopathic Disorder and Serum Antibody to Herpes Simplex Virus (Type 1)

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Summary

The sera of a small series of patients has been examined for herpes simplex virus antibody. Three clinically-defined groups of patients were compared: (*a*) aggressive psychopaths, (*b*) psychiatric controls, and (*c*) general hospital patients. The first group had an unusually high average kinetic neutralization constant against type 1 herpes simplex virus.

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Introduction

We wish to report some preliminary results which indicate an association between antibody to herpes simplex virus (type 1) and psychopathic disorder. As a working hypothesis we postulate a virus infection during childhood (either inapparent or at least unrecognized) which damages those areas of the brain related to personality. This concept is in accordance with the ideas put forward by Knobloch and Pasamanick (1958).

Several papers have suggested that herpes simplex virus infection may be associated with psychiatric disorder—for example, Drachman and Adams (1962) and Shearer and Finch (1964). Rimon and Halonen (1969) reported that 28 psychotic depressives (mean age 47 years) showed higher complement fixation titres against herpes simplex virus than did other psychiatric patients and non-psychiatric persons. It is well known that herpes infections can persist through life, giving recurrent lesions in some individuals and in others no apparent illness at any time. Indeed, Scott (1957) estimated that clinical illness was observed in only 10 to 15% of primary infections. Herpes simplex virus may therefore cause minimal brain damage.

Subjects and Methods

We have examined the sera of 13 aggressive psychopaths, 14 non-aggressive psychiatric cases, and 13 non-psychiatric controls for neutralizing antibody to herpes simplex virus type 1 and type 2. All subjects gave consent after the purpose of the investigation had been explained to them. The aggressive psychopaths were selected on the following criteria: (1) a history of severe and/or persistent violence against the person—that is, self-injury or bodily harm to others; and

(2) an overall clinical picture which would be generally accepted by most psychiatrists as being incontrovertibly psychopathic. The psychiatric controls were mixed, comprising persons with neurotic reactions, inadequate personalities, and three schizophrenics. The non-psychiatric controls came from a general hospital. All cases were males between the ages of 16 and 26. A single specimen from each case was examined.

The sera were inactivated at 56°C for 30 minutes and were tested by a kinetic neutralization test at room temperature. An equal volume of serum diluted 1/10 with saline was mixed with a virus suspension containing 4×10^4 plaque-forming units/ml of an established type 1 strain of herpes simplex virus (HFEM) and 2×10^4 plaque-forming units/ml of an established type 2 strain (Lovelace) kindly provided by Dr. A. Nahmias. The reaction was stopped at 10, 20, and 30 minutes by dilution 1/100 in ice-cold medium and titrated in BHK 21 cells by the method of Russell (1962). Since the plaques of the two strains could easily be distinguished, the rate of neutralization of each virus was readily measured. The k-value was calculated as follows:

$$k = \log \frac{V_o}{V_t} \times \frac{2{\cdot}303 \times D}{t}$$

(V_o = inital virus concentration; V_t = virus concentration at time t in minutes; D = overall dilution of serum.)

Results and Discussion

The results are given in the Table. Analysis of variance of k-values against type 1 virus shows that the differences between all groups of patients are significant ($P<0{\cdot}01$). There are two striking features of the results. Firstly, there is an association between high type 1 k-values and a well-defined psychiatric syndrome—aggressive psychopathy. Secondly, the k-values against type 1 virus were very high; indeed, four of them lay between five and six. There was, however, one patient with a k-value of five in group B. We have not yet encountered such high k-values in sera from 89 female patients of a comparable age group.

Table of Results

Group	No. of People	k-Values	
		Type 1 Herpes Virus Mean (standard error)	Type 2 Herpes Virus Mean (standard error)
A. Aggressive psychopaths	13	3·02 (±0·54)	0·48 (±0·39)
B. Psychiatric controls	14	1·27 (±0·46)	0·18 (±0·07)
C. Non-psychiatric controls	13	0·68 (±0·25)	0·24 (±0·09)

We were led to consider whether these high k-values reflect specific antibody responses or abnormal responses of a general nature. The first alternative was supported by the k-values found against herpes virus type 2 which are not unusual, and though they mirror those against the type 1 virus, this was expected since the two viruses share some common antigens. Further evidence in favour of specific antibody response was provided by titrating the sera for antibody to two viruses unrelated to herpes virus and by determining serum immunoglobulin levels. Antibodies against the influenza virus strains A_2/Singapore/58 and A_2/Hong Kong/67 (kindly supplied by Dr. T. H. Flewett) were titrated by the haemagglutination inhibition test. The distribution of titres fell within normal limits and no differences were found between groups A and B. The levels of IgG, IgM, IgA, and IgD were kindly determined for us by Dr. G. Blandford, using immunological assays. Again, the determination fell within normal limits. There was no significant difference between the mean values of the groups for IgG, IgA, and IgD. Sera in group A had significantly higher levels of IgM than the other groups, but these were found to correlate negatively with the type 1 herpes k-values ($r = -0{\cdot}27$). Thus, though their origin is unexplained, the high k-values against herpes virus type 1 appear to indicate a specific immunological response.

Though we have examined only a few sera, the results are arresting. They suggest that the syndrome we define is associated with infection with type 1 herpes virus. We are now extending the investigation, using more rigorously-defined control groups.

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