Fig. 1 Liver necropsy specimen from zone 1. Intranuclear inclusions characteristic of herpes infection are seen (arrows) in comparison to normal nuclei (arrow head) $\times 627$

Fig. 2 Electron micrograph of herpes group viruses recovered from the necropsy material $\times 100\ 000$

virus. The patient deteriorated progressively and died nine days after admission from fulminant hepatitis.

At necropsy, there were no vesicular lesions present on skin, mouth, nasopharynx, oesophagus, external or internal genitalia. The liver was massively enlarged (2550g) and there were innumerable small yellowish necrotic foci surrounded by areas of haemorrhage and congestion. Histological examination showed massive focal necrosis in zones 2 and 3. In zone 1, most of the viable hepatocytes contained Cowdry type A intranuclear inclu-

sions, characteristic of herpes group virus infection (Fig. 1).

Electron microscopic examination of thin sections of liver, negatively stained, showed the presence of a virus of the herpes group (Fig. 2). Herpes simplex virus was recovered in tissue cultures inoculated with lung, kidney, brain, and liver tissue.

In this case, the only clinical sign which suggested a herpetic infection was the transient vesicular lesions on the lingula but the absence of antibodies to herpes simplex virus was taken, apparently reasonably, as strong evidence that this virus was not contributing to her clinical condition. For this reason, no antiviral treatment was given. We have since become aware of Flewett's report¹ of an adult with herpetic hepatitis in whom serology was unhelpful, the correct diagnosis being made on liver biopsy and electron microscopy.

The case of this unfortunate woman leads us to two conclusions. Firstly, a liver biopsy should be very helpful in reaching an early diagnosis in patients under immunosuppression who present with an otherwise undiagnosable deterioration in their clinical state and liver function tests. Secondly, in agreement with Walker and his colleagues², we consider that the administration of acyclovir, even in the absence of supporting conventional viral diagnostic evidence, may be a life-saving measure. The importance of attempting a histological diagnosis and the feasibility of administering acyclovir "blindly" are consequences of the efficacy and relative non-toxicity of this antiviral drug.

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Urine cyclic nucleotides in cancer and other conditions

I read with interest the paper by GA Turner *et al* in your issue of August 1982.¹ I would like to

give some additional remarks about the levels of cyclic nucleotides in urines of cancer patients, especially cytosine monophosphate (CMP).

We have studied²⁻⁴ the cyclic nucleotide contents of leucocytes and urines of healthy volunteers, of patients with solid tumours and with leukaemias. We found that the concentration of cyclic CMP is always lower than that of cyclic GMP or cyclic AMP and that, in urines, the concentrations of the three nucleotides are higher in patients than in normal controls. But the greatest difference is observed between the cyclic CMP concentrations of acute leukaemia patients and controls. The cyclic CMP concentration is higher in monoblastic cells and in leucocytes from patients with solid tumours.

High cyclic CMP concentrations are associated only with acute leukaemias. This suggests that cyclic CMP could be a biochemical marker of hematopoietic stem cell malignancy.

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Serum antibodies to hepatitis B virus in alcoholic liver disease

Conflicting data^{1,2} have been reported concerning the higher prevalence of serum antibody to hepatitis B virus antigens in patients with alcoholic cirrhosis. We have compared 60 hospital patients with biopsy-proven alcoholic cirrhosis (mean age 46 yr ± 10 SD; 45 men) with an age- and sex-matched hospital control population, a mixed group of HBsAg-negative chronic alcoholic cirrhosis (HBsAg-veCAC) (47

Hepatitis B antibodies in patients with alcoholic cirrhosis, hospital controls, HBsAg-negative chronic cirrhosis (HBsAg-veCAC) and renal unit patients

Group	No of patients				
	Total examined	anti-HBs alone	anti-HBc alone	anti-HBc and anti-HBs	Total with antibody
Alcoholic cirrhosis	60	13	9	21	43
HBsAg-veCAC	27	1	6	11	18
Renal unit	32	4	5	12	21
Hospital controls	60	3	1	18	22

± 11 yr; 15 subjects). A history of blood transfusion, previous jaundice, tattooing, or needle injections were excluded in the alcoholic cirrhosis group and hospital control group. In the HBsAg-veCAC group, six patients gave a previous history of jaundice, one a history of blood transfusion; in the other five patients a post-hepatitis B chronic liver disease could not be excluded.

Serum samples from each group were examined by RIA method (Abbott) for HBsAg, and antibody to HBsAg and HBcAg.

All sera were HBsAg-negative. Our antibody results are shown in the Table. These findings indicate that the prevalence of hepatitis B virus antibodies (χ^2 test with Yates' correction) was significantly increased in the alcoholic cirrhosis group when compared with the hospital control group ($p < 0.001$); in HBsAg-veCAC and renal unit patients there was no significant difference from alcoholic cirrhosis patients.

The high prevalence of serum antibodies to hepatitis B virus in alcoholic cirrhosis as well as in renal unit patients has been confirmed in this survey in the Milan area.

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Microbiological safety tests

In a recent paper "Guidelines for the evaluation of instruments used in haematology laboratories"¹ the authors recommend that "instruments should be tested for the production during normal operations of potentially infected droplets or aerosol". In describing how this should be done they state correctly that the most sensitive method requires the use of a biological tracer such as a bacterial spore and the services of an experienced microbiologist. They then go on to say that an estimate of the microbiological hazard can be obtained by using a fluorescent chemical marker and examining sheets of filter paper placed around the equipment under ultraviolet light for evidence of contamination. There is an implication that this procedure is an adequate substitute for the use of a biological tracer to assess any microbiological hazard that might arise from the equipment being tested. This is a dangerous assumption.

Work carried out in this laboratory to assess the sensitivity of various tracer materials added to human serum showed that microbiological challenge materials, normally used at a concentration of 1×10^{10} cells/ml could be detected when completely negative results were found using 1% (wt/vol) sodium fluorescein. In these tests a sensitive fluorimeter (Locarte Co, London) was used to measure fluorescence. The lower limit for detection of the biological tracers was 2500 times smaller than for the fluorescein solution. In a comparison of a spore tracer using settle plates, and sodium fluorescein and filter paper discs of a comparable area, up to 100 bacterial colonies were present on the settle plates: the filter papers were uniformly negative when examined under ultraviolet light. There are numerous examples of similar failure to detect contamination with a fluorescent marker when the use of a microbiological tracer showed heavy contamination.

When we consider the hazard from small airborne particles in the size range likely to

be inhaled and retained in the lungs, the situation is a good deal worse. The small particles have a low settling rate even in still air so relatively few are likely to be deposited on filter paper surrounding the equipment. Any that do settle will probably be too small to visualise by eye when the paper is examined under ultraviolet light. The collection of small airborne particles calls for the use of efficient air sampling equipment such as that used in this laboratory.²

As there is now considerable interest in drawing up international standards by bodies such as the European Committee for Clinical Laboratory Standards (ECCLS) and the International Standards Organisation (ISO) it is likely that papers such as that of Shipton, England and Kennedy¹ will be used in formulating new standards. For this reason it is important that it should be clearly stated that the use of fluorescent markers, while useful for rapidly detecting gross contamination on surfaces, should not be relied on for a proper assessment of microbiological hazards from equipment or laboratory techniques.

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