marrow recovery refer, therefore, solely to the regression of leukaemic blast cells. By three weeks only 65.6% of the patients in the Concord trial and 67.5% in the UKALL I trial but 80.4% in the UKALL II trial had less than 5% of blast cells in the marrow. A higher proportion of UKALL II marrow specimens, however, showed severely decreased cellularity at three weeks, though this finding was not sufficiently quantitative to be analysed further. At six and 13 weeks there was no significant difference between the bone marrow regression rates in the three trials.

Discussion

The validity of comparing trials not carried out simultaneously is often called into question but it seems unlikely that this caused any serious bias in this instance. In particular there was no reason to suppose that the methods of measurement and management had significantly altered within the four years under study.

Our evidence shows that the addition of colaspase during the first week of the remission induction regimen of vincristine and prednisolone causes a significantly increased suppression of both normal and leukaemic cells in the bone marrow, as shown by the increased blast-cell regression and lower blood neutrophil and platelet counts. The induced neutropenia resulted in an increased liability to serious and fatal infections to which the immunosuppressive effect of colaspase (Maral *et al.*, 1970), the alteration of neutrophil function by asparagine depletion (Strauss *et al.*, 1970; Skeel *et al.*, 1971), or an effect of colaspase on the gut mucosa might also have contributed. The clinical importance of the added period of thrombocytopenia is difficult to assess, since bleeding was largely prevented by platelet transfusion.

Colaspase could cause marrow depression either directly or by potentiating the myelotoxicity of vincristine. A potentiating effect might be mediated by the liver, since the hepatotoxicity of colaspase (Land *et al.*, 1970; Pratt and Johnson, 1971) could interfere with drug catabolism, or might directly affect the

susceptibility of bone marrow cells to vincristine. Alternatively deprivation of asparagine may simply retard the proliferation rate of the regenerating haemopoietic cells. The absence of significant neurotoxicity and alopecia from vincristine in the UKALL II trial is rather against a hepatic mechanism of vincristine potentiation and favours the bone marrow as the site of action.

Notwithstanding its observed toxicity, colaspase significantly increased the rate of blast-cell regression in the UKALL II trial. It is possible that this initial reduction of leukaemic cells might lead to an increased duration of remission (Jones and Holland, 1973), but this could not be tested in these trials because of the differences in subsequent therapy. An increased death rate during remission induction, however, is not an acceptable price to pay for this theoretical advantage. It is probable that a similar long-term effect could be obtained by giving colaspase at a later phase in treatment. It is therefore recommended that colaspase should not be given during the induction phase of treatment in A.L.L. until there is evidence of marrow regeneration or until it becomes clear that other agents are failing to induce remission.

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Hepatitis B Antigen in Viral Hepatitis in West London

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Summary

During the first 12 months of a total population survey 249 patients were seen with viral hepatitis. A total of 215

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of these were tested for hepatitis B antigen (HB Ag) by radioimmunoassay and 32 (15%) were positive.

More than five times as many men (27) as women (5) were HB Ag positive and 19 of the men were between the ages of 20 and 39 years. There were only four drug addicts among those tested, two of whom were positive, as were two of the four patients who were tattooed.

Sixty out of 86 children (under 15 years) were tested for HB Ag and none was positive.

Introduction

Australia antigen, now referred to as hepatitis B antigen (HB Ag) in view of its association with hepatitis B infection provides a reliable serological marker of an agent which causes this type of infection (World Health Organization, 1973).

In Great Britain the reported prevalence of HB Ag in patients admitted to hospital with hepatitis has varied between 4% (Ross

and McMichael, 1970) and 40% (Cossart *et al.*, 1969). Ross and McMichael examined samples of serum from patients admitted consecutively to a Glasgow hospital, over half of whom were under the age of 15. Cossart *et al.*, tested patients admitted consecutively from a predominantly urban community in West London, but only one of the 27 patients tested was under 15 years of age. Results were not classified epidemiologically in either of these reports. In another group studied in West London Farrow *et al.* (1970) found 13 (33%) out of 39 patients positive for HBsAg; none of these patients were under 15 years old.

Since 15 June 1968 infective jaundice has been notifiable throughout England and Wales under the Public Health (Infective Jaundice) Regulations. Notification, however, reflects an initial diagnostic impression, which in some cases may not be confirmed by subsequent investigation. Such reports are not always revised. Notifications to the Registrar General form the basis of national statistics on hepatitis, and it is these that are most often quoted.

We decided to determine the incidence of HBsAg among all patients accepted as having viral hepatitis* within a defined area, whether or not they were admitted to hospital. At the same time we examined the epidemiology of viral hepatitis with special reference to its distribution in the community, possible modes of spread, and factors affecting severity in relation to the presence of HBsAg.

A 12-month pilot study was undertaken to assess the value of such an investigation. The most interesting feature of this study was a low incidence (14%) of HBsAg in sporadic hepatitis in an urban area, which contrasted with previous reports from London (Cossart *et al.*, 1969; Farrow *et al.*, 1970). The results might not have been representative, however, because the study lasted only one year and was confined to the London Borough of Hounslow with a population of only 206,000.

It therefore seemed appropriate to conduct a three-year prospective survey of all suspected cases of hepatitis in a larger urban population, namely that of the three London Boroughs of Hounslow, Ealing, and Richmond—a total of 706,000 people. We report here the results of the first 12 months of the survey.

Plan of Three-year Survey

To achieve a more comprehensive survey with early detection of cases and collection of serum samples a field team was appointed consisting of a full-time doctor and a health visitor supported by a part-time secretary. From the start the survey was planned as a collaborative community study between the general practitioners, the local health authorities, and the South Middlesex and West Middlesex Hospitals. Other hospitals also helped by reporting cases and by providing information and samples of serum from their patients admitted from the area under study. The field team received information about patients from the local health authorities and often directly from the general practitioners. Some patients were able to trace contacts, and schools also co-operated.

Patients

During the first 12 months of the survey there were 310 patients who had an illness notified as infective jaundice. After referral 61 patients were excluded from the survey. These comprised 18 with either biliary tract or pancreatic disease, three with drug jaundice, four with chronic liver disease, and one with Gilbert's disease. Eight patients had infectious mononucleosis. Twenty-seven patients who presented with febrile or alimentary symptoms were found not to have evidence of hepatitis.

A diagnosis of viral hepatitis was accepted on clinical and biochemical grounds in 249 patients, an incidence of 36 per 100,000 population. The vast majority of these patients gave a

history of a febrile or gastrointestinal illness and dark urine followed by jaundice. In 15 (6%) cases, however, jaundice was not confirmed. Seven of these patients were detected as contacts of patients who were jaundiced because of viral hepatitis.

The patients were allocated to the following arbitrary epidemiological groups based on the history of the possible mode of exposure to infection: (a) Ingestion—definite close contact with another case of jaundice thought to be due to viral hepatitis between 15 and 60 days before the onset of symptoms; (b) parenteral—known history of skin puncture between 15 days and six months before the onset of symptoms; (c) unknown—no known history of exposure to either ingestion or parenteral infection; (d) equivocal—history of exposure to both ingestion and parenteral infection within the relevant periods. This grouping seemed to be a reasonable device to gain more insight into the aetiological agents.

Methods

All patients on whom the field team received information were interviewed by the health visitor using a questionnaire developed during the pilot study. The visiting doctor made a clinical assessment and obtained blood for biochemical tests to support the diagnosis and for serological tests. Epidemiological data were collected at the time of the initial interview and were transferred to punch cards. The patients were seen initially about once a week for clinical assessment and collection of further blood samples and then less often until they had recovered both clinically and biochemically and until any antigenaemia had cleared.

Serum bilirubin (Malloy and Evelyn, 1937), alkaline phosphatase (Marsh *et al.*, 1959), and alanine aminotransferase (Mohun and Cook, 1957) were measured by standard methods. The HBsAg was detected by a sandwich-type radioimmunoassay technique (Ausria¹²³) as previously used by Reed *et al.* (1973), which combines the specificity of antigen-antibody reaction with the sensitivity of radioisotope detection and is now accepted as the most sensitive technique available (World Health Organization, 1973).

Results

HBsAg was found in 32 (15%) of the 215 patients tested who were accepted as having viral hepatitis. There were 60 patients below the age of 15 years, none of whom showed the antigen. Thus 21% of those over the age of 15 were antigen positive. The prevalence of HBsAg did not depend on the interval between the testing of the first blood sample and the onset of the illness. There was no significant difference between patients tested during the first week (five (12%) positive out of 43) and those tested in the first four weeks (25 (15%) positive out of 168). The mean number of tests carried out during the first four weeks (1.5) was identical for the antigen-positive and antigen-negative groups. Six patients remained positive after the 12th week and at the time of writing one had been positive for six months. The median period of antigenaemia was seven weeks (mean 8.5 weeks) in the 25 adequately followed antigen-positive patients who subsequently became negative. Blood was obtained for HBsAg testing in 82% of the patients tested within four weeks of the onset of the illness and in 94% of those tested within seven weeks.

Of the 81 patients tested for HBsAg and thought to have acquired their infection parenterally 18 (22%) were positive. The findings in the equivocal group were similar, four (17%) out of 23 tested being HBsAg positive, while a smaller proportion was found in the unknown group, 10 (14%) out of 70 tested. None of the ingestion group was positive (table I).

In the parenteral group four of the 10 patients who had a non-therapeutic skin puncture were HBsAg positive whereas 14 (21%) of the 67 whose parenteral exposure was therapeutic

*Viral hepatitis includes both type A and type B hepatitis.

showed the antigen. Four HBAG-negative patients had both therapeutic and non-therapeutic exposures. In the non-therapeutic group there were four drug addicts, two of whom were HBAG positive. Four had been tattooed, of whom two were positive.

There were more than five times as many men (27) as women (five) with the HBAG though the overall ratio of male (129) to female (86) patients tested was 1.5:1 (table II). Nearly half the males were in the parenteral group. The unknown group contained about equal numbers of males and females but the HBAG was found only in the males.

In the 20-39 age group there were nearly twice as many men as women (table III), and 19 of the 62 men (31%) were HBAG positive compared with only four of the 35 women (11%). This age group contributed two thirds (23 out of 32) of all the HBAG-positive patients. All but two of these antigen-positive patients fell into the parenteral or unknown groups (table I).

Half the patients in the ingestion and equivocal groups were under the age of 15 whereas only one in 7 of the parenteral and unknown groups were of this age (see table I). No patient under the age of 15 was found to have circulating HBAG.

Of the 69 patients admitted to hospital 14 (20%) were HBAG positive, compared with 18 (12%) of the 146 patients seen at home. Adult men (39 out of 95; 41%) were more likely than women (18 out of 60; 30%) to be admitted to hospital. Neither of these differences has reached statistical significance after one year of the survey.

There was a clear seasonal fluctuation in incidence of hepatitis. This was confined to the HBAG negative patients and showed peaks in the early spring and autumn. Apart from one outbreak in a housing estate there was no appreciable clustering of patients. None of the patients in this outbreak was HBAG positive, and 19 of the 32 affected were under the age of 15.

In the HBAG-positive patients the mean ($\pm$ S.D.) duration of clinical jaundice was significantly greater, 41.6 ± 24.8 days, than in those not showing the antigen, where it lasted for a mean ($\pm$ S.D.) of 24.3 ± 21.5 days ($P < 0.01$, using a χ^2 test).

TABLE I—Relation of HBAG to Age and Epidemiological Group in 215 Patients Tested. Figures in parentheses are Numbers of Antigen-positive Patients

Age	Ingestion	Parenteral	Unknown	Equivocal	Total
0-4	2	1	2	1	6
5-9	21	8	5	6	40
10-14	3	1	5	5	14
15-19	1	12 (1)	7	3 (2)	23 (3)
20-29	8	25 (6)	23 (5)	3 (1)	59 (12)
30-39	3	21 (9)	10 (1)	4 (1)	38 (11)
40-49	3	6 (2)	9 (3)	1	19 (5)
50-59	0	5	6 (1)	0	11 (1)
60-69	0	2	3	0	5
Total	41	81 (18)	70 (10)	23 (4)	215 (32)

TABLE II—Relation of HBAG to Sex and Epidemiological Group in 215 Patients Tested. Figures in Parentheses are Numbers of Antigen-positive Patients

	Ingestion	Parenteral	Unknown	Equivocal	Total
Male	21	56 (15)	38 (10)	14 (2)	129 (27)
Female	20	25 (3)	32	9 (2)	86 (5)
Total	41	81 (18)	70 (10)	23 (4)	215 (32)

TABLE III—Relation of HBAG to Sex and Age in 215 Patients Tested. Figures in Parentheses are Numbers of Antigen-positive Patients

Age	Male	Female	Total
0-4	1	5	6
5-9	24	16	40
10-14	9	5	14
15-19	13 (2)	10 (1)	23 (3)
20-29	36 (10)	23 (2)	59 (12)
30-39	26 (9)	12 (2)	38 (11)
40-49	12 (5)	7	19 (5)
50-59	6 (1)	5	11 (1)
60-69	2	3	5
Total	129 (27)	86 (5)	215 (32)

Discussion

The results of the first 12 months of the three-year survey showed two salient features. Firstly, the prevalence of HBAG in patients with viral hepatitis was only 15% though a highly sensitive technique was used to test serial samples of serum. Secondly, there was a concentration of positive cases among men aged between 20 and 39 years (19 out of 62; 31%).

Previous reports from West London (Cossart *et al.*, 1969, Farrow *et al.*, 1970) suggested that the prevalence of HBAG in sporadic hepatitis in the United Kingdom was in the region of 30-40%. Both studies were of patients admitted to hospital, however, whereas we attempted to investigate all patients developing this illness irrespective of their place of care. Our data suggested that the higher prevalence of HBAG in hospital patients might be due to the larger number of adult males admitted.

The pilot study had shown the vital importance of full collaboration with the general practitioners and they were therefore involved in the three-year survey through discussions at meetings held for this purpose both before and during the survey. A domiciliary diagnostic service was provided on all patients referred by family doctors, who reciprocated by informing the survey team of possible preicteric cases and with early notifications. As a result of this collaboration most sera were taken early in the illness.

The proportion of positive results showed no significant difference throughout the first four weeks, nor was there a significant difference between the mean number of tests in the HBAG positive and negative patients. The proportion of patients tested in the two groups was the same. Though we cannot exclude the possibility of clearance of the antigen before the onset of jaundice other studies suggest that this is unusual (Krugman and Giles, 1970).

The 20-39 age groups accounted for 19 of the 27 positive men and all but one of the five positive women (table III). The predominance of young adults was not explained by drug addiction, because only four patients in the whole survey admitted to this practice. The possibility of venereal transfer has been raised by Mirick and Shank (1959), Hersh *et al.* (1971), and Fulford *et al.* (1973).

The preponderance of males has been noted previously (reviewed by Zuckerman, 1972) and may be due to a sex difference in susceptibility to infection. It is of interest that nearly half the HBAG positive patients in this survey were men with a history of parenteral exposure though most of these exposures involved the use of disposable equipment—for instance, in vaccinations, inoculations, and dental local anaesthetics. One third of the children (under 15 years) had had a skin puncture under similar conditions and none of them was HBAG positive.

Fewer children than adults were tested for HBAG—60 out of 86 (70%) as compared with 155 out of 163 (95%). This could lead to an underestimate of the proportion of children in this survey. Whereas only 60 of the 215 patients tested (28%) were under the age of 15 86 (35%) of the 249 patients seen with hepatitis were children. Furthermore, we cannot exclude the possibility that the HBAG might have been present in some of the 26 children not tested.

During this initial period of the survey there was a brief localized outbreak of hepatitis mainly affecting children who, in our experience, are HBAG negative. Such outbreaks could have a considerable effect on the prevalence of HBAG during a relatively short period of observation. Analysis of the three-year figures should clarify the effect of such outbreaks on the prevalence of HBAG viral hepatitis in urban communities in this country.

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Requests for reprints should be sent to Dr. J. S. Stewart.

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DDAVP in Treatment of Vasopressin-sensitive Diabetes Insipidus

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Summary

In 11 patients with vasopressin-sensitive diabetes insipidus the effectiveness of the vasopressin analogue 1-desamino-8-D-arginine vasopressin (DDAVP) for controlling diabetes insipidus has been compared with that of lysine vasopressin. DDAVP in equivalent intravenous dosage has been found to be at least as potent and to have a more prolonged action, lasting 13-22 hours instead of 1-2 hours. Twice-daily intranasal DDAVP effected satisfactory control in all these patients, without side effects, and all the patients preferred this to their previous treatment. Single daily intramuscular injections of DDAVP were found to offer excellent control for any subject unable to manage intranasal administration.

Introduction

Improvements in the treatment of diabetes insipidus (D.I.) have obviated the need for injections in mild vasopressin-sensitive cases by the use of either chlorpropamide (Wales and Fraser, 1971) and related drugs (Arduino *et al.*, 1966) or lysine vasopressin (LVP) nasal sprays (Dashe *et al.*, 1964). Neither of these treatments, however, can control the more serious cases satisfactorily. The recent synthesis of an analogue of arginine vasopressin (AVP), 1-desamino-8-D-arginine vasopressin (DDAVP) (Vara *et al.*, 1968), has produced an agent administrable intranasally which has the full antidiuretic effects of AVP with minimal vasopressor activity and scarcely any side effects in the dose range required (Anderson and Arner, 1972; Edwards *et al.*, 1973). DDAVP has been found to have a greater antidiuretic effect and a longer duration of action than the natural hormone AVP (in man) or LVP (in some other species) and has been shown to be effective in controlling vasopressin-sensitive diabetes insipidus

(Anderson and Arner, 1972). We report here a comparison with LVP showing the more prolonged action of DDAVP, its effective control of a wide range of cases of vasopressin sensitive diabetes insipidus on a twice-daily intranasal regimen, and its potential usefulness in controlling such cases by single daily injections when necessary.

Patients

Altogether 11 patients were studied (table I). All had previously been investigated and diagnosed as having vasopressin-sensitive diabetes insipidus either alone or with associated pituitary lesions. None of the patients were satisfied with their immediate previous therapy (table I). On their current regimens all had some persisting symptoms of mild thirst, polyuria, and nocturia. Six patients had had trials with either clofibrate or chlorothiazide or carbamazepine carried out by us or at other hospitals. Five patients previously treated with chlorpropamide 250-500 mg daily had had to have the drug withdrawn or the dosage reduced because of hypoglycaemia, and one patient had had an "Antabuse" effect with alcohol. Five patients were maintained on vasopressin tannate in oil (5 IU intramuscularly on alternate days) with or without LVP nasal spray supplementation. One patient (case 2) who had been maintained on posterior pituitary nasal snuff for 10 years had not had an undisturbed night's sleep or been free of rhinitis throughout that time.

Method

Previous therapy was discontinued (five days for those on chlorpropamide and one to three days for those receiving vasopressin preparations). Thereafter all the patients' 24-hour urine volumes were measured, initially when off all previous treatment and later while on maintenance intranasal DDAVP.

Before establishing the patients on maintenance therapy a series of acute studies were performed of their diuretic response both uncontrolled and after LVP or DDAVP, either as inpatients or as outpatients. Firstly, a full diuresis was ensured by an oral water load of 20 ml/kg given over 30 minutes, after which they were urged to drink an amount at

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