especially if the degree and direction of inaccuracy is known. Many more uses would be possible if the input was brought up to at least 95% accuracy. For instance, if in our study we could have been sure that all or nearly all admissions with SGT were accurately recorded in the printout, we would effectively have had an extremely cheap follow-up of all cases remaining in Scotland over the seven-year period. We would also have been able to identify recurrences. Given adequate record-linkage facilities, a modest extension of the process might indicate all readmissions of cases in which SGT was not found, which would therefore be known negatives. Deaths could also be identified. The figures so obtained would be sufficient for many purposes. If we wished, for instance, to check the recurrences, the necessary correspondence would be limited to cases in which it was likely that there was something to report. The saving on current follow-up procedures, with their great expenditure of medical and clerical time and paper, would be immense, and costs could well be reduced a hundredfold. Such follow-up would be particularly valuable in cases such as these with SGT, which are few and need to be studied over a long period. Almost any kind of follow-up could be simplified, however—so much so that one can envisage a time when it would be exceptional if any member of staff was not engaged in some form of follow-up in his main field of interest. There are no doubt many other uses apart from follow-up for which the diagnosis files could be used.

All this is true to only a limited extent so long as errors in coded diagnoses are as common as they are now. The major factor is the lack of active participation of medical staff. A stir of interest is needed to break the present circular impasse, in which errors in the input lead to distrust of the output and distrust of the output condones carelessness in producing the input.

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Prevalence of hepatitis A and B infections in multiply transfused thalassaemic patients

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Summary and conclusions

Evidence of hepatitis B virus (HBV) and hepatitis A virus (HAV) infections was sought in 148 multiply transfused patients with thalassaemia and in healthy controls (2040 for HBV and 217 for HAV). The prevalence of the HBV surface antigen or antibody to it was significantly higher in patients than in controls and increased with the number of blood transfusions. In contrast, the prevalence of antibody to HAV was significantly lower in patients than in controls and decreased with the number of blood transfusions.

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These results support the view that blood transfusion does not play any appreciable part in transmitting HAV. Indeed, regular blood transfusion, where donors almost all have HAV antibody, seems to give protection against infection.

Introduction

Hepatitis A is transmitted parenterally in men and non-human primates.¹⁻³ Post-transfusion hepatitis with no evidence of infection by hepatitis B virus (HBV) has thus been assumed to be caused by hepatitis A virus (HAV). Very sensitive serological techniques, however, have failed to detect any response to the HAV,⁴⁻⁶ suggesting that it causes few if any cases of transfusion hepatitis. We have therefore studied Greek patients with thalassaemia, who have regular blood transfusions and live in an area in which hepatitis is highly endemic, to determine the prevalence of HAV and HBV infections in such patients and evaluate the role of blood transfusion.

Patients and methods

We studied a random sample of 148 patients (81 male, 67 female) with homozygous β -thalassaemia, aged from 1 to 29 years. They had received regular blood transfusions—ranging from 7 to 351 units—since early childhood at the Hellenic Red Cross Dracopoulion Transfusion Centre of Athens. Since 1971 all blood has been screened for HBV surface antigen (HBsAg) and all known HBsAg-positive donors

have been excluded. Agar gel immunodiffusion⁷ or counterimmuno-electrophoresis techniques⁸ were used up to 1975. Since then blood has been tested for HBsAg by passive haemagglutination (Hepanosticon).⁹ Thirty-two patients had a history of acute hepatitis.

There were 2040 controls for the HBV studies and 217 for the HAV (tables I and II), who had lived all their lives in the Greater Athens area. There were equal numbers of males and females in each age group. Controls under 5 were selected from child welfare centres, for the 5-19 age group from elementary and high schools in various districts of Athens, and for the 20-29 group from volunteer blood donors. Thus the sample is roughly representative of the population of Greater Athens and comparable in age, sex, social class, and domicile to the group of patients.

Venous blood specimens were taken under aseptic conditions. Sera were frozen at -20°C until tested.

We screened for HBsAg by counterimmuno-electrophoresis⁷ and passive haemagglutination⁹ and for antibody to it (anti-HBs) by passive haemagglutination using a microtitre system and HBsAg-coated red cells (obtained from Electronucleonics Inc, Bethesda, Maryland). A titre $\geq 1/8$ was considered positive. Antibody to HAV (anti-HAV) was tested by a solid-phase radioimmunoassay blocking test.¹⁰ Sera inhibiting binding by 50% or more at dilutions of 1/20 were considered positive for anti-HAV.

We estimated prevalence rates by number of blood transfusions after indirect standardisation for age.¹¹ Differences in prevalence rates between patients and controls were estimated by the method of Mantel and Haenszel.¹²

Results

The HBsAg carrier rate was 2.7% in both patients (four out of 148) and controls (56 out of 2040). Anti-HBs was detected in 130 of the 148 patients and in 297 of the 2040 controls. Evidence of HBV infections (detection of either HBsAg or anti-HBs) was more frequent in patients than in controls in each age group (table I). After adjustment for age the relative frequency of HBV infections was 56 times as great for multiply transfused thalassaemic patients than for comparable controls ($\chi^2_1 = 521.0$, $P < 0.001$).

TABLE I—Prevalence of hepatitis B virus infections (on evidence of either HBsAg or anti-HBs) by age in multiply transfused patients and controls

Age (years)	Patients		Controls	
	No examined	No (%) positive	No examined	No (%) positive
<5	9	6 (66.7)	37	4 (10.8)
5-9	46	39 (84.8)	408	17 (4.2)
10-14	57	54 (94.7)	643	81 (12.6)
15-19	23	22 (95.6)	421	98 (23.3)
20-29	13	13 (100.0)	531	153 (28.8)
Total	148	134 (90.5)	2040	353 (17.3)

Anti-HAV was detected in 19 out of 148 (12.8%) patients and in 130 out of 217 (59.9%) controls; it was less frequent in patients than in controls in each age group (table II). After adjustment for age its relative frequency was 3.7 times lower in the multiply transfused patients than in comparable controls ($\chi^2_1 = 34$, $P < 0.001$).

The age-standardised prevalence of HBsAg or anti-HBs increased from 82.5% for patients who had had less than 100 blood transfusions to 92.5% for those with 200 or more transfusions (table III).

TABLE II—Prevalence of antibody to hepatitis A virus by age in multiply transfused patients and controls

Age (years)	Patients		Controls	
	No examined	No (%) positive	No examined	No (%) positive
<10	55	2 (3.6)	42	10 (23.8)
10-14	57	2 (3.5)	42	17 (40.5)
15-19	23	5 (21.7)	41	26 (63.4)
20-29	13	10 (76.9)	92	77 (83.7)
Total	148	19 (12.8)	217	130 (59.9)

TABLE III—Prevalence of hepatitis B and hepatitis A virus infections by number of blood transfusions

No of blood transfusions	No examined	HBV	HAV
		No (%) positive	No (%) positive
<100	39	30 (82.5)	5 (21.0)
100-199	71	67 (93.5)	8 (15.2)
≥ 200	38	37 (92.5)	6 (8.4)

*Calculated after adjustment for age.

In contrast, the prevalence of anti-HAV infections decreased from 21% for patients with less than 100 transfusions to 8.4% for those with more than 200 transfusions.

In the controls an association was found between evidence of HAV and of HBV infections. Anti-HAV was significantly more prevalent ($\chi^2_1 = 4.88$, $P < 0.05$) among those positive than among those negative for HBsAg or anti-HBs (table IV). In the patients, however, anti-HAV was less frequent among those positive than among those negative for HBV infection, though this difference did not reach the 5% level of significance.

TABLE IV—Association between HAV and HBV infections in multiply transfused patients and controls

HBV infections		HAV infections	
		No examined	No (%) positive
Patients	No positive	134	17 (12.7*)
	No negative	14	2 (14.3*)
	Total	148	19 (12.8)
Controls	No positive	36	28 (77.8†)
	No negative	181	102 (56.4†)
	Total	217	130 (59.9)

* $\chi^2_1 = 0.06$, $P > 0.1$.

† $\chi^2_1 = 4.88$, $P < 0.05$.

Discussion

Analysis of the HBsAg status in the various groups of multiply transfused patients with thalassaemia is outside the scope of our study, and we have considered it only in relation to HAV infections. Our results confirm previous studies showing a high prevalence of serological evidence of HBV infections in multiply transfused patients with thalassaemia when sensitive techniques were used.¹³ Regular blood transfusions increase the opportunity for exposure to HBV because of the high HBsAg carrier rate in Greek blood donors.¹⁴

Hepatitis A can also be transmitted parenterally. Early experiments in volunteers showed that injection of serum or faeces obtained from patients during the late stage of the incubation period and the early acute phase of the disease could cause infection.^{2, 15} Anti-HAV would be expected to be more prevalent in multiply transfused patients if blood transfusion played any part in transmitting the disease. As anti-HAV infection was less prevalent in patients than controls, our results support the evidence from studies on post-transfusion hepatitis⁴⁻⁶ that HAV is rarely transmitted by blood transfusion.

The low titre of HAV in serum and the short viraemic stage of hepatitis A explain why the infection is rarely transmitted by blood transfusion. In contrast to hepatitis B, there is no epidemiological evidence that a prolonged carrier state can occur in hepatitis A.¹⁶ In faeces serially collected from infected human volunteers, chimpanzees, and marmosets HAV particles were found by immune electron microscopy during a short period at the acute stage of the disease.³ They were not found in stools collected before or after the acute stage or in the limited number of sera collected at various stages of the disease.¹⁷

The risk of exposure to HAV under usual conditions, however, must have been much the same in our patients as in the control group, since they were comparable in socioeconomic and

other epidemiological characteristics and both lived in an area where hepatitis A is highly endemic. The low prevalence of anti-HAV in patients with thalassaemia is unlikely to be due to a resistance to the infection endowed by the disease, since an increased prevalence of anti-HBs as well as of antibodies to cytomegalovirus and other viruses has been found in such children.¹⁸

Thus regular blood transfusion probably gives sufficient protection against HAV under usual conditions of exposure, postponing infection until later in life. The inverse relationship between the number of blood transfusions and the prevalence of HAV infections further supports this view. Transfusions may produce passive immunity—anti-HAV protects against re-infection by HAV both experimentally in man and animals^{2 3 15} and clinically when given immune globulin.¹⁵ The protection given to patients with thalassaemia should be highly efficient under the usual conditions of exposure, since they are transfused almost every month with blood from donors who are nearly all anti-HAV positive.¹⁹ The prevalence of HBV infections in contrast presumably increases with the number of blood transfusions because only about 20–25% of Greek blood donors have anti-HBs—but also because passively acquired anti-HBs cannot protect adequately against the enormous amount of HBV transmitted in a unit of blood positive for HBsAg.²⁰

The correlation between the prevalence of HAV and HBV infections in controls suggests that certain factors such as poor hygienic conditions increase the risk of exposure to both viruses.²¹ The inverse relationship observed in the patients with thalassaemia underlines the importance of blood transfusion in the transmission of HBV and its ability to protect against HAV infection.

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SIDE EFFECTS OF DRUGS

Unusual fetal malformations after antiemetics in early pregnancy

Debendox (dicyclomine hydrochloride 10 mg, doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg) is widely prescribed for nausea and vomiting in pregnancy and is generally regarded as non-teratogenic, though reduction deformities in infants whose mothers have taken the drug have occasionally been reported.¹ We describe three patients who took Debendox from an unusually early stage of pregnancy and subsequently gave birth to babies with a rare combination of abnormalities, including extrusion of abdominal contents and reduction deformity or total absence of a leg. The women lived in widely separated areas of the north-west of England and the babies were born between July 1975 and May 1977.

Case reports

Case 1—A 24-year-old primigravida with a regular menstrual history (4/28-32) took one Debendox tablet each morning and two at night for nausea, beginning six weeks from the first day of her last menstrual period. She took no other potential teratogens. In July 1975, when 18 weeks pregnant, she was admitted to hospital with lower abdominal pain and vaginal bleeding, and after four days spontaneously aborted. The fetus was macerated and at necropsy was found to have exomphalos and absence of the left leg. A subsequent pregnancy in 1976 was uneventful, no drugs being taken except an iron and folic-acid preparation, and a normal girl was delivered.

Case 2—A 29-year-old primigravida with a regular menstrual history (5/28-30) took one Debendox tablet twice daily and two at night for nausea and vomiting. The drug was begun five and a half weeks from the first day of the last menstrual period. She continued on this regimen until term and there was no history of infection or of exposure to other drugs, except for an iron and folic-acid preparation from 16 weeks' gestation. Spontaneous labour began at term in May 1977 and delivery was by forceps for delay in the second stage. The baby died 15 minutes after birth. It weighed 2600 g. The liver and most of the gastrointestinal tract were contained in a thin-walled sac protruding through a defect in the left lower abdominal wall. The right leg was thickened and bowed, while the left leg and foot were absent. At necropsy a solitary renal mass and a single gonad were found. The pelvis was hypoplastic and the thoracic spine showed gross kyphoscoliosis.

Case 3—A 22-year-old primigravida with a previously regular menstrual cycle (5/30) was prescribed Septrin (trimethoprim 80 mg, sulphamethoxazole 400 mg) twice daily for five days for a urinary tract infection, beginning three weeks from the onset of her last menstrual period. Debendox, one tablet daily and two at night, was prescribed at six weeks' gestation, and treatment continued for six weeks. She had no other infections and took no drugs apart from an iron and folic-acid preparation from 12 weeks' gestation. She was admitted in labour in March 1977 when 38 weeks pregnant, and had a breech delivery of a stillborn girl weighing 3885 g. Postmortem examination showed exomphalos containing small intestine, stomach, liver, and spleen. The left foot was attached to a grossly shortened leg and there was severe thoracic scoliosis giving rise to a reduced left hemithorax.

Comment

Protrusion of abdominal contents and reduction deformity or absence of a leg seems to be an extremely rare combination, though