PAPERS AND ORIGINALS

Unexplained hepatitis following halothane

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Summary

Full clinical and laboratory details of 203 patients with postoperative jaundice were submitted to a panel of hepatologists. All patients whose jaundice may have had an identifiable cause were excluded, which left 76 patients with unexplained hepatitis following halothane anaesthesia (UHFH). Hepatitis in 95% of these cases followed multiple exposure to halothane, with repeated exposure within four weeks in 55% of cases. Twenty-nine patients were obese, 52 were aged 41-70, and 53 were women. Thirteen patients died in acute hepatic failure. Rapid onset of jaundice after anaesthesia, male sex, and obesity in either sex were poor prognostic signs. Of the clinical stigmata of hypersensitivity, only eosinophilia was impressive. The UHFH group had a much greater incidence of liver kidney microsomal (LKM) and thyroid antibodies and autoimmune complement fixation than those patients whose jaundice related to identifiable factors. Thirteen of the 19 patients with LKM antibodies also had thyroid antibodies. In six patients retested two to three years later LKM antibodies had disappeared, although thyroid antibodies persisted.

Rapidly repeated exposure to halothane may cause hepatitis, but such a complication is probably rare. Possibly obese women with a tendency to organ-specific autoimmunity may be more at risk. Nevertheless, the comparative risks of rapidly repeated halothane or non-halothane anaesthesia cannot be determined from the present data. If alternative satisfactory agents are available halothane should be avoided in patients with unexplained hepatitis after previous exposure, although in three of five patients with UHFH who were re-exposed to halothane jaundice did not recur.

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Introduction

In view of the continuing controversy about a direct relation between halothane and postoperative liver damage, we decided to attempt a nationwide survey of postoperative jaundice as it occurred.

The survey was designed to provide answers to the following questions: (1) Is unexplained hepatitis following halothane (UHFH) synonymous with "halothane hepatitis"? (2) What is the population at risk? (3) Is hypersensitivity implicated? (4) Can commonly held concepts about the syndrome of halothane hepatitis be substantiated?

Methods

In November 1970 all consultant anaesthetists in the British Isles were asked to inform us of any patients with postoperative jaundice in their practice. During the next three years 203 patients were notified to us and visited by BW to ensure that all available information was obtained. Blood samples were taken during their acute illness, usually within one or two days of the onset of jaundice. The patients' case histories were subsequently submitted to a panel of hepatologists, who, without knowledge of the anaesthetic agents concerned, classified the patients' conditions (table I) as follows: (*a*) unexplained hepatitis—biochemical results indicated hepatocellular damage without identifiable aetiological factors; (*b*) unexplained hepatitis (? contact)—as in *a* results indicated hepatocellular damage but there had been contact with viral hepatitis or transfusion with blood or blood products within the previous 21-160 days; (*c*) unexplained equivocal hepatitis—minor increases in aminotransferases suggested mild hepatocellular damage, but the damage was too mild to classify as *a* (this group may represent the lower end of the unexplained hepatitis spectrum); (*d*) unexplained non-hepatitis—biochemical results did not suggest hepatocellular damage; (*e*) jaundice with identifiable cause—liver damage was related to aetiological factors such as biliary tract disease, cirrhosis, preoperative illness, septicaemia, or cardiovascular insufficiency.

Coded blood samples were analysed (in two independent laboratories) by indirect immunofluorescence for the following autoantibodies: liver kidney microsomal (LKM), mitochondrial

TABLE I—*Classification of 203 patients with postoperative jaundice and division according to anaesthetic used.*

Anaesthetic	Unexplained				Jaundice with identifiable cause	Total
	Hepatitis	Hepatitis (? contact)	Equivocal hepatitis	No hepatitis		
Halothane	76	13	14	8	66	177
Non-halothane	2	1		6	17	26

TABLE II—*Intervals between halothane exposures in patients with postoperative jaundice and complete histories. Results are numbers (percentages) of patients*

Interval:	Weeks		Months				Years			No previous halothane
	<2	2–4	1–3	–6	–9	–12	1–5	–10	>10	
Unexplained hepatitis (n = 75)	25 (33)	16 (21)	9 (12)	4 (5)	1 (1)	1 (1)	7 (9)	6 (8)	2 (3)	4 (5)
Jaundice with identifiable cause (n = 64)	14 (22)	5 (8)	2 (3)	1 (2)	1 (2)	2 (3)	13 (20)	5 (8)		21 (33)

(AMA), thyroid microsomal, gastric parietal (GPC), smooth muscle (SMA), and antinuclear (ANA). Thyroid microsomal autoantibodies were also measured by haemagglutination[1] and complement fixation. Thyroglobulin autoantibodies were measured by haemagglutination.[2] In the autoimmune complement fixation test (AICF) a crude rat liver homogenate was used as the antigen. IgG, IgM, and IgA were assayed on sera by the Mancini immunodiffusion method,[3] and results were expressed as a percentage of a mean normal standard pool of adult sera. Hepatitis B surface antigen (HBsAg) and antibody (HBsAb) were detected by radioimmunoassay. Liver biopsies were performed when possible, and the results of both light and electron microscopy will be published elsewhere.[4]

Results

CLINICAL AND EPIDEMIOLOGICAL FINDINGS

Of the 203 patients with postoperative jaundice investigated 177 (87%) received halothane (table I). Of the 75 patients with UHFH and complete anaesthetic histories 71 (95%) had already been exposed to halothane, with the previous exposure within four weeks in 55% of cases (table II). Similar analysis of the patients with an identifiable cause for their jaundice after halothane showed that only 43 (67%) had had previous exposure, although in 30% of cases exposure had been repeated within four weeks.

Of the 76 patients with UHFH nine had had unexplained jaundice after previous halothane exposure and in seven of these the latent period before onset of jaundice was shorter during the current episode. One of these patients had had unexplained jaundice after three successive exposures to halothane, with progressively shorter latent periods. A further two of these seven patients had had an uneventful postoperative course after exposure to halothane during the intervening period. All these nine patients survived. Four of the 76 patients had had rapidly repeated exposures to halothane some years previously without overt hepatic dysfunction.

Twenty patients in the UHFH group were exposed to inhalational anaesthesia subsequently without overt hepatic problems. Although halothane was ostensibly avoided in all these cases, a "halothane-free" machine was used in only one case. Four of the remaining 19 patients were exposed to other halogenated hydrocarbons (three trichloroethylene, one methoxyflurane) without problems.

Among the 76 patients the mean latent period between anaesthesia and the onset of jaundice was 6·6 days (range 1-23 days) with the jaundice appearing within the first week after operation in 51 cases (67%). The influence of previous exposure to halothane on the day of onset of postoperative jaundice is shown in table III. The latent period was longer after a single exposure than after multiple exposures, although the small number in the single-exposure group (with a lower mean age) rendered this difference statistically insignificant. Similar analysis of the patients in the identifiable group showed neither the longer latent period nor the lower mean age in patients with single exposure.

In the UHFH group bilirubin levels remained less than 85 μmol/l (5 mg/100 ml) in 17% of patients, although in a further 17% of patients levels greater than 425 μmol/l (25 mg/100 ml) were seen. Jaundice in the 61 surviving patients lasted from under one week (five patients) to over 12 weeks (one patient). In 39 patients (64%) jaundice lasted two to six weeks. There was a wide variation in the degree of increase in aspartate aminotransferase, although alkaline phosphatase levels were generally less than twice the upper limit of normal. Sixteen patients

TABLE III—*Influence of number of exposures to halothane on the day of onset of jaundice*

	No of patients	Latent period	Mean age (years)
Unexplained hepatitis:			
After 1 exposure	4	9·3	27·0
After 2 exposures	25	6·4	46·3
After 3 exposures	24	6·7	55·8
After ≥4 exposures	19	6·0	61·4
Jaundice with identifiable cause:			
After 1 exposure	21	6·7	55·9
After 2 exposures	15	9·6	58·6
After 3 exposures	7	8·0	45·7
After ≥4 exposures	15	3·8	52·4

(21%) had no fever after operation. In most of the remainder the greatest fever was seen during the four days before the onset of jaundice, and it subsided with the onset of jaundice.

Analysis of the temperature patterns after previous exposure to halothane (table IV) shows that 31% of patients with UHFH had been apyrexial after their previous exposure. Pyrexia of undetermined origin (PUO) occurred with similar frequency in those with unexplained hepatitis and those with jaundice with an identifiable cause. Exclusion of the common minor postoperative temperature increases by concentrating only on a PUO occurring during the second week after operation showed little difference between the two groups.

TABLE IV—*Temperature patterns after penultimate exposure to halothane in patients with jaundice*

	No fever	Fever				
		Cause for fever	Pyrexia of unknown origin			
			1st Week	1st-2nd Week	2nd Week	Total
Unexplained hepatitis (n = 68)						
No	21	16	25	4	2	31
%	31		37	9		46
Jaundice with identifiable cause (n = 44):						
No	16	6	17	5	0	22
%	36		39	11		50

The means and ranges of ages and sex distribution of the 203 patients are shown in table V. In the UHFH group the female:male ratio was 2·3:1 and obesity was twice as common as in the identifiable group after halothane. The incidence of malignant disease and histories of allergy, excess alcohol intake, and jaundice (table V) was not increased in the UHFH group. There was no correlation between UHFH and the degree of surgical stress. Of the 76 patients, five had been subjected to radiotherapy and no fewer than 12 were being treated for ocular disease.

Eosinophilia was found in 24 (32%) of the 76 patients with UHFH (fig 1), although low-order eosinophilia was often found in the other groups. White cell counts of 4-10 × 10^9/l (4000-10 000/mm^3) were found in 49 (65%) of the patients with UHFH. Nine (12%) of the 76 had counts over 15 × 10^9/l (15 000/mm^3), but in seven there were relevant clinical causes present, such as infection. Of the 76 patients

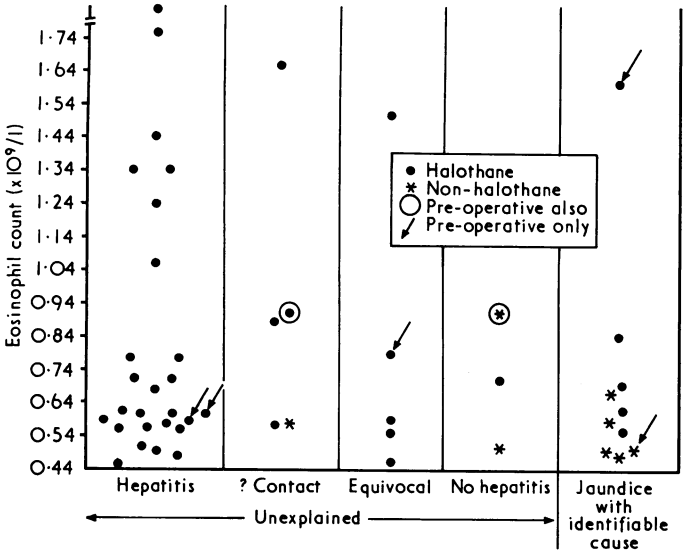

FIG 1—Incidence of eosinophilia in patients with postoperative jaundice.

with UHFH only three had unexplained rashes—for example, those not related to antibiotic treatment—and only one patient had arthralgia (table V).

The death rate among the 203 patients was 23% (table V), with a crude death rate of 20% in the UHFH group. The death rate due to hepatic failure among these latter patients was 17%, with the rate higher among men (22%) than women (15%). Obesity in either sex and a short latent period between exposure to anaesthesia and onset of jaundice were poor prognostic signs.

IMMUNOLOGICAL FINDINGS

HBsAg was detected in only one patient with UHFH (table VI). In the UHFH group the incidences of LKM ($P<0.001$) and thyroid ($P<0.05$) autoantibodies and autoimmune complement fixation ($P<0.01$) were significantly higher than in patients in the identifiable group after halothane. Owing to small numbers statistical analysis by sex and age were not valid, nor was a comparison possible with patients with postoperative hepatitis who had not been exposed to halothane.

LKM antibody was found in 19 (25%) of the patients with UHFH. Some titres reached 1/160, although levels of 1/40 to 1/80 were more common. No tests for this antibody were done before operation, but in seven patients retested two to three years later the antibody had disappeared in six and in the seventh the titre was significantly reduced.

The presence of thyroid antibodies in 13 of the 19 patients with LKM antibody in the UHFH group was highly significant ($P<0.001$). Furthermore, the incidence of thyroid antibodies in women in this category was significantly higher ($P<0.05$) than that in women in the identifiable group.

AMA was found in only two patients, neither of them classified as having UHFH. SMA was detected with similar frequency among patients in the UHFH (25%) and identifiable (21%) groups after halothane, and there was no obvious difference in the range of titres, which varied from 1/10 to 1/80, between the two groups.

IgM and IgA levels were raised in many cases (fig 2), with no obvious differences between patients with UHFH and the other categories. The various patterns of immunoglobulin variations in the UHFH group are shown in table VII.

Discussion

The categories within the independent classification cannot be considered watertight, but the UHFH group included patients whose hepatic dysfunction was thought most likely to relate

TABLE V—*Clinical features of patients with postoperative jaundice. Results are numbers (percentages) of patients. Results are numbers (percentages) of patients*

	No of patients	Age (years)		Sex		Incidence of:								Death rate	
		Mean	Range	Male	Female	Obesity	Malignant disease	Allergic history	Previous jaundice	Excess alcohol intake	Rash: All rashes	Rash: Unexplained	Arthralgia	Overall	In hepatic failure
Patients exposed to halothane															
Unexplained Hepatitis	76	52·1	4–83	23 (30)	53 (70)	29 (38)	23 (30)	16 (21)	19 (25)	13 (17)	11 (15)	3 (4)	1	15 (20)	13 (17)
Hepatitis (? contact)	13	48·3	5–77	6 (46)	7 (54)	4	1	1	1	4	3			4 (31)	4 (31)
Equivocal hepatitis	14	49·2	16–77	8 (57)	6 (43)	2	5	2	2	2	2	1			
No hepatitis	8	32·6	13–68	7 (88)	1 (12)	1		1	2	1					
Jaundice with identifiable cause	66	53·8	14–87	40 (61)	26 (39)	11 (17)	26 (39)	13 (20)	18 (27)	22 (33)	5 (8)			19 (29)	6 (9)
Patients exposed to other anaesthetics															
Unexplained Hepatitis	2	62·5	58–67		2	1	2		1					1	1
Hepatitis (? contact)	1		59	1						1					
Equivocal hepatitis															
No hepatitis	6	39·5	12–67	4	2					2					
Jaundice with identifiable cause	17	57·0	22–78	8 (47)	9 (53)	2 (12)	9 (53)	2 (12)	4 (24)	2 (12)	2 (12)			7 (41)	2 (12)

TABLE VI—*Immunological findings in patients with postoperative jaundice*

	Numbers of patients tested in each group		HBsAg		HBsAb		LKM		Thyroid		GPC		Autoimmune complement		SMA		ANA		AMA	
Type of anaesthesia*:	H	N	H	N	H	N	H	N	H	N	H	N	H	N	H	N	H	N	H	N
Unexplained Hepatitis	75	2	1		2		19		26		9		28	1	19	1	11	1		
Hepatitis (? contact)	13	1	2†						1		1		3		4		2			
Equivocal hepatitis	14								2		1		5		2				1	
No hepatitis	8	6			1		1			2		1		3	2	2				
Jaundice with identifiable causes	66	16		1	9		1		8		6		9	4	14	2	5		1	

*H = Halothane anaesthesia. N = Non-halothane anaes
†Only 12 patients tested.

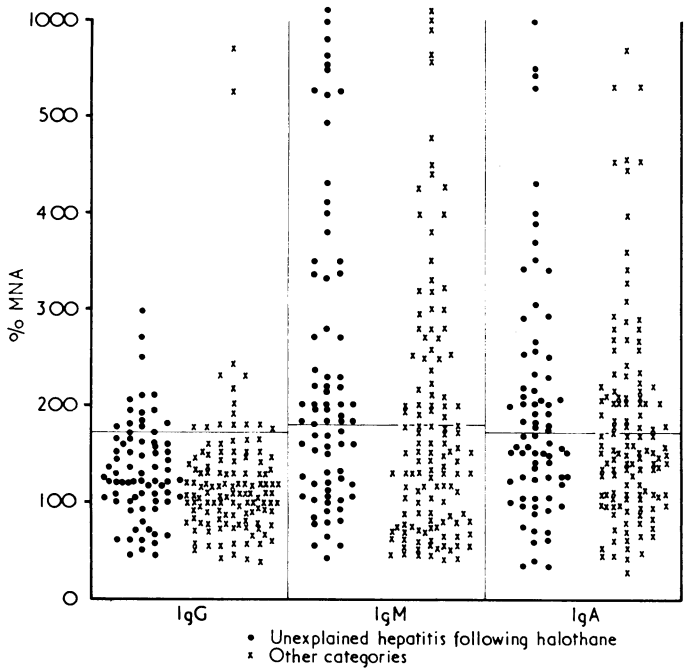

FIG 2—Immunoglobulin levels in patients with postoperative jaundice. Results expressed as percentage of mean normal adult values (% MNA). Horizontal lines show normal ranges.

TABLE VII—*Immunoglobulin patterns in patients with unexplained hepatitis following halothane*

IgG	IgM	IgA	No (%) of patients
Normal	Raised	Raised	16 (21)
Normal	Normal	Normal	15 (20)
Normal	Raised	Normal	15 (20)
Normal	Normal	Raised	12 (16)
Raised	Raised	Normal	5 (7)
Raised	Raised	Raised	4 (5)
Raised	Normal	Raised	4 (5)
	Other patterns		4 (4)

directly to halothane. That UHFH may often by synonymous with "halothane hepatitis" is supported by the fact that 95% of our cases followed multiple exposure to the agent (55% within four weeks), compared with 66% in the identifiable group (30% within four weeks). The clinical and biochemical features of UHFH were indistinguishable from those of viral hepatitis. Although HBsAg was found in only one patient with UHFH, virus A hepatitis (for which serological tests are only now becoming available) may be more common than virus B, and virus A hepatitis is not confined to the young.[5] Altogether 66% of the patients with acute viral hepatitis are unaware of contact[6] and the ratio of subclinical to overt cases may be as high as 12:1.[7] Immunological competence is altered by exposure to anaesthesia and surgery[8] and the mortality among mice infected with murine hepatitis virus is increased by exposure to halothane.[9] Thus, although it has been argued[10] that the high death rate among patients with postoperative jaundice reported to the Committee on Safety of Medicines rendered a viral aetiology unlikely, patients with viral hepatitis in the general population have not been subjected to anaesthesia and surgery and therefore valid comparisons cannot be drawn. On the other hand, unexplained hepatitis after non-halothane anaesthesia did not occur often enough to reflect the 10-30% usage of non-halothane anaesthesia in Britain.[11] Both patients who had unexplained hepatitis after non-halothane anaesthesia had received halothane as part of their very recent penultimate anaesthetic. Their hepatitis may therefore have been related to halothane, and if so then we did not see unexplained hepatitis after non-halothane anaesthesia. Nevertheless, Hart and Fitzgerald have recently reported such a case.[12]

Halothane was probably responsible for at least some of the cases of UHFH. The syndrome seems to be clearly associated with multiple exposures to halothane, particularly within one month, but the incidence of UHFH cannot be estimated from this survey. It is of interest, however, that the hepatologists classified two patients with syndromes indistinguishable from UHFH as having hepatitis with an identifiable cause (probably viral hepatitis) merely on the basis of latent periods between exposure to anaesthesia and onset of jaundice of 38 and 39 days.

Of the stigmata of hypersensitivity reactions reported in association with halothane hepatitis[13] eosinophilia was more common in the UHFH group; the incidences of rashes, arthralgia, and leucocytosis were unimpressive, however, and bronchospasm was not reported. In one of the seven patients with UHFH and a high eosinophil count HBsAg was found transiently. Eosinophilia is rare in viral hepatitis but exposure to anaesthesia and surgery may change the immunological response to viral infection.[9]

TIME RELATIONSHIP

Inman and Mushin[10] suggested that the shorter latent period between halothane anaesthesia and onset of jaundice after multiple exposures than after a single exposure indicated a hypersensitivity response. Their unclassified data, however, may have included some cases in which the anaesthetic agent was not primarily involved. A study by McPeek and Gilbert[14] and initial analysis of our unclassified data[15] failed to confirm their findings. Analysis of our classified cases of UHFH, however, now supports the findings of Inman and Mushin, although the small number in our single exposure group renders the results statistically insignificant. Moult and Sherlock[16] showed a sequence in five of their 26 patients that suggested a decreasing latent period with increasing numbers of multiple exposures. Neither our own or other reported data follow this pattern.

Wright and Eade have suggested[17] that the patients most at risk may be those who have had relatively few exposures to halothane over a short period. Although our results provide some support for this hypothesis, 19 of our 76 patients had had four or more exposures to halothane and a further four had only a single exposure.

Inman and Mushin[10] suggested that a decreasing latent period in nine of their patients with more than one episode of jaundice after halothane implied an accelerated immunological response. This pattern was seen in seven of the nine patients of our 76 who had multiple episodes of UHFH, and the one patient with three such episodes showed progressively shorter latent periods. Two of the seven patients, however, had had uneventful halothane anaesthesia in the period between the exposures related to the episodes of postoperative jaundice. Furthermore, the absence of hypersensitivity reactions to rapidly repeated exposures to halothane some years earlier in four of our 76 patients is difficult to explain. It is also surprising that three of the 76 patients were subsequently re-exposed to the drug without overt problems. The suggestion that cross-sensitisation may occur[18] was not supported by the fact that four patients with UHFH were subsequently exposed to either trichloroethylene or methoxyflurane without problems.

PROGNOSTIC FACTORS

Our evidence confirms the view that patients with UHFH are often obese and that obesity is a poor prognostic sign.[16] There is a female preponderance among these patients, although the mortality is slightly higher among men. About 35% of a general surgical population are estimated to be aged between 40 and 70,[19] and, as 68% of our patients with UHFH fell within this age range, our findings confirm the relation between late middle age and this condition, notwithstanding the preponderance of patients in this age group within other categories. Only two of

our patients were under 20 years, which confirmed the rarity of UHFH in the young. The hepatologists were not unanimous in classifying the disease in the two children (aged four and five) as UHFH, and exclusion of these doubtful cases shows an age range for UHFH (halothane hepatitis) of 20 to 83 years.

Avoidance of halothane in patients with unexplained fever and jaundice after previous exposure has been suggested.[20] This recommendation has often been misinterpreted to include patients with unexplained fever *or* jaundice. This would largely preclude the use of halothane, since at least 60% of postoperative surgical patients develop fever[21] and in half of these this is unexplained.[22] Our analysis of the temperature patterns after previous exposure to halothane casts further doubt on the prognostic value of this index. Although halothane should be avoided in patients with unexplained hepatitis after previous exposure if alternative agents are available, it is interesting in that three patients with UHFH subsequently re-exposed to halothane jaundice did not recur.

The reported death rate among patients with halothane hepatitis varies from 20%[23] to 96%.[24] The view that this syndrome carries a high mortality rate may be attributable to the referral of most severe cases to special units, and in this survey of the whole spectrum of UHFH, the mortality from hepatic failure was 17%. The low death rate among patients aged 40 and under (6%), compared with the 20% mortality rate among the older patients, is in contrast to the recent conclusion[16] that age does not adversely affect the prognosis.

Moult and Sherlock[16] reported that a short latent period between anaesthesia and the onset of jaundice was a poor prognostic sign and death did not occur after a latent period longer than seven days. Our data lend some support to this view, although three of our 76 patients died after latent periods of nine, 13, and 23 days.

IMMUNOLOGICAL ASPECTS

The lack of sufficient controls, particularly patients exposed to little-used alternative anaesthetics, and insufficient numbers to enable valid statistical comparisons by age and sex are two weaknesses of the immunological analysis. Nevertheless, LKM antibody[25] is found in only 0·1% of a general hospital population,[26] and the 25% incidence among patients with UHFH was unexpected. This antibody is often associated with liver diseases,[25] although in active chronic hepatitis, for example, titres reach much higher levels than those we found. In our patients the episode of UHFH apparently resulted in the transient appearance of LKM antibody, in definite contrast with its persistence in some types of chronic liver disease. The antibody has been reported only rarely in acute viral hepatitis[26] and, notwithstanding the alterations of immune response engendered by exposure to anaesthesia and surgery, its incidence in this study further suggests that UHFH and viral hepatitis are usually different conditions.

The increased incidence of thyroid antibodies (in the absence of overt thyroid disease) in addition to LKM antibodies among patients with UHFH is further evidence that these two autoimmune responses are often associated[25] and possibly subjects prone to develop organ-specific autoimmunity are more liable to develop halothane hepatitis.

The AICF test using a crude rat liver homogenate as antigen identifies several autoantibodies directed against various cellular antigens. Their identities still require definition but may include mitochondrial antigens, ANA—protein complexes, soluble cytoplasmic proteins, and possibly microsomes.[27 28] This test gives positive results in a wide range of diseases, including cirrhosis of the liver and acute hepatocellular damage.[29] The increased incidence of positive results among patients with UHFH may reflect an increased autoimmune response to liberated liver cytoplasmic antigens, possibly including LKM antigen, from the microsomal membrane.

The incidence of AMA accords with that found in the general population and does not support suggestions that this antibody is associated with halothane hepatitis.[30–32] Although the incidence of SMA in both the unexplained hepatitis and identifiable groups was higher than the 12% incidence found in the normal population,[33] it does not compare with an incidence of 87% in acute viral hepatitis[34] or of 81% in infectious mononucleosis.[35] This further suggests that UHFH is not due to viral infection.

The immunoglobulin results were not obviously different in the UHFH group compared with the other groups. The significance of the increase in IgA and IgM in so many cases is obscure. No preoperative serum specimens were obtained and the pattern of immunoglobulins must often have been determined by the disease for which surgery was undertaken. The immunoglobulin most commonly abnormal in a hospital population is IgA, owing to the common occurrence of alimentary, renal, and respiratory tract disease, and levels are also increase in certain types of toxic cirrhosis of the liver.[36] A raised IgM concentration is characteristic of acute virus infections, including hepatitis,[36] although, as we have indicated, there was little evidence for a viral aetiology in most patients. Little is known of the effects of exposure to anaesthesia and surgery on immunoglobulin levels in the absence of postoperative complications. A study of eight patients before and after anaesthesia with either nitrous oxide and halothane or nitrous oxide and a narcotic agent failed to show significant changes in IgG, IgM, or IgA concentrations.[37]

Conclusions

Clearly, in most cases postoperative jaundice is likely to relate to non-anaesthetic factors and, therefore, in each patient all possible alternative causes must be excluded. Epidemiologically it is reasonable to suggest that halothane caused the liver damage in at least some of the patients with UHFH. Our data lend some support to the hypothesis that hypersensitivity may be relevant aetiologically, and that patients prone to develop organ-specific autoimmunity seem to be more at risk. Nevertheless, the many anomalies in the data suggest that viral hepatitis, metabolic phenomena, or other factors cannot be ruled out. All anaesthetic agents and techniques carry some risk. From our data we could not estimate the true incidence of UHFH, although it is probably rare. The dangers of rapidly repeated exposure to halothane for short surgical procedures may be outweighed by the morbidity and mortality associated with the inappropriate use of other anaesthetic drugs and muscle relaxants, particularly in inexperienced hands.

Members of the panel of hepatologists were: Dr N McIntyre, Royal Free Hospital; Dr R Williams, King's College Hospital; and Professor R Wright, University of Southampton.

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Folate-responsive neuropathy: report of 10 cases

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Summary

Ten patients with severe neurological disease that was clinically indistinguishable from subacute combined degeneration of the spinal cord were found to have normal serum vitamin B_{12} levels. All were folate deficient. Specific folate treatment led to significant reversal of the neuropathy. These findings indicate the need to review orthodox concepts of the role of folic acid in maintaining the integrity of the nervous system.

Introduction

Neuropathic effects of folate deficiency have been widely reported.[1-4] In some studies improvement in the neuropathy has coincided with folate administration and relapse has followed cessation of treatment indicating probable cause and effect. Despite this, folate deficiency is not universally accepted as a cause of neuropathy.[5 6] Our purpose is to illustrate the neuropathic consequences of folate deficiency by describing a group of 10 patients with a characteristic neuropathy, clinically manifesting as loss of tendon reflexes (knee and ankle), impaired or absent vibration sense, and bilateral extensor plantar responses indicating posterolateral involvement of the spinal cord. The patients were severely deficient in folate.

Patients and methods

Neuropathic findings (absent knee and ankle jerks, loss of vibration sense, and extensor plantar responses) were first noted in an 83-year-old man (case 1) referred from local authority care with a diagnosis of senile dementia because of increasing confusion and difficulty in walking. He had become doubly incontinent. In addition to the neurological findings he had extensive involvement of the left tibia with Paget's disease. Haemoglobin was 10·6 g/dl and mean cell volume 117 fl (117 μm^3). Serum B_{12} levels were normal (340 ng/l), but serum folate concentrations were low (1 $\mu g/l$). Specific treatment with folic acid resulted in unexpected and dramatic resolution of the psychosis and incontinence, and progressive, and ultimately complete, ambulation was achieved. Further neurological examination showed that there was loss of vibration sense in the legs, but pain and temperature appreciation was retained. The clinical disorder was therefore indistinguishable from subacute combined degeneration of the spinal cord but was folate-dependent.

The demonstration of a specific neurological lesion in folate-depleted subjects that was reversed by folate treatment would provide conclusive evidence for the neuropathic consequences of folate deficiency. To this end, nine other patients (seven men, two women) with similar neurological abnormalities were identified; they were either already in continuing care or had been referred to a geriatric assessment unit. The clinical details, referral diagnosis, mental state, mobility, and the nature of intercurrent disease in these patients are shown in table I. Blood was withdrawn for standard haematological and biochemical measurements. On the second aliquot the serum folate and vitamin B_{12} levels were measured microbiologically by the *Lactobacillus casei* and *Lactobacillus leishmanii* assays respectively. Serum samples were assayed in duplicate. Equivocal values were repeated. The coefficient of variation of replicate measurements for these assays was similar ($\pm$ 7%).

Treatment—Since the patients' serum B_{12} levels were normal, a trial of oral folic acid (10 mg three times a day) could be carried out. Drug treatment was otherwise rigidly controlled. Two patients (cases 2 and 3) initially received several doses of chlorpromazine. Except in one patient (case 2) formal rehabilitation was not attempted, nor was it required subsequently. Psychiatric intervention was not required. Since all patients were severely disabled and spontaneous improvement was improbable, any response to folic acid would be apparent clinically and could be confidently ascribed to it. Acceptable objective criteria of response would be the restoration of tendon reflexes, the recovery of posterior column sensation, and regression of the extensor plantar responses.

Vitamin B_{12} metabolism—Since the patients' clinical disorder was indistinguishable from subacute combined degeneration of the spinal cord, vitamin B_{12} metabolism had to be demonstrably normal in these patients before the pathogenetic role of folate-deficiency in their neuropathy could be accepted. We therefore looked not only for normal serum vitamin B_{12} levels but also for the presence of gastric parietal cell antibodies (six cases), and we measured the gastric acid response to pentagastrin stimulation (six cases). The absorption of labelled vitamin B_{12} (Dicopac test) was measured in six patients, but since the

TABLE I—*Referral diagnosis, intercurrent disease, mental state, and mobility in 10 neuropathic patients*

Case No	Age (years)	Sex	Referral diagnosis	Intercurrent disease	Mental state	Mobility
1	71	F	Multiple sclerosis	Idiopathic steatorrhoea	Normal	Chairfast
2	52	F	Spastic paraparesis	Thyrotoxicosis	Psychotic	Bedfast
3	88	M	Senile dementia	Paget's disease of bone	Psychotic	Bedfast
4	80	M	Senile dementia	Chronic bronchitis	Confused	Bedfast
5	83	M	Exposure	Alcoholism	Confused	Bedfast
6	93	M	Anaemia	Diverticulitis	Normal	Bedfast
7	72	M	Senile dementia	Chronic bronchitis	Psychotic	Bedfast
8	74	M	Chronic depression	Uraemia (prerenal)	Confused	Bedfast
9	80	M	Senile dementia	Epilepsy	Confused	Bedfast
10	73	M	Senile dementia	Peripheral vascular disease	Confused	Bedfast

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