

TRANSMISSION OF HEPATITIS B TO PATIENTS FROM FOUR INFECTED SURGEONS WITHOUT HEPATITIS B e ANTIGEN

THE INCIDENT INVESTIGATION TEAMS AND OTHERS*

ABSTRACT

Background Transmission of hepatitis B virus (HBV) to patients by infected surgeons who carry hepatitis B e antigen (HBeAg) has been documented repeatedly. In the United Kingdom HBeAg-positive surgeons are not permitted to perform certain procedures that carry a risk that patients might be exposed to the blood of a health care worker. There are no practice restrictions for carriers of hepatitis B surface antigen without detectable HBeAg, unless transmission has been demonstrated.

Methods In four unconnected cases of acute hepatitis B, surgery was identified as a possible source, so we tested the surgical teams for serologic markers of HBV infection. In each case a surgeon was found to be infected with the virus. HBV DNA was amplified by a nested polymerase chain reaction from serum from the four infected surgeons and the four patients, and direct nucleotide sequencing of two regions of the HBV genome was performed. Alternative sources of infection were ruled out. Other patients on whom three of the surgeons had recently performed procedures were offered testing.

Results All four surgeons were carriers of HBV, but none had detectable serum HBeAg. The nucleotide sequences of HBV DNA from the surgeons were indistinguishable from those from the corresponding patients. The screening of other exposed patients identified at least two other patients who had probably acquired hepatitis B infection from one of these surgeons.

Conclusions Surgeons who are carriers of HBV without detectable serum HBeAg can transmit HBV to patients during procedures. (N Engl J Med 1997; 336:178-84.)

©1997, Massachusetts Medical Society.

TRANSMISSION of hepatitis B virus (HBV) from infected surgeons to patients during procedures associated with a risk of exposure to the virus (sometimes referred to as exposure-prone procedures¹) has been documented repeatedly. Between 1984 and early 1993, 10 clusters of patients whose infections were associated with contact with infected gynecologic, cardiothoracic, or general surgeons were identified in the United Kingdom,²⁻⁸ and transmission during colorectal,⁹ orthopedic,¹⁰ and cardiothoracic¹¹ surgery was reported in North America. All the reported clusters involved infected surgeons whose serum

contained hepatitis B e antigen (HBeAg), which is associated with higher levels of circulating virus and therefore greater infectivity. In both the United Kingdom and the United States recommendations on restricting the practice of health care workers who perform procedures involving a risk of exposure are based on the presence or absence of serum HBeAg.^{1,9,12} A procedure involving a risk of exposure is one in which injury to the health care worker would cause his or her blood to come into contact with the patient's open tissues. Most cardiothoracic, gynecologic, and abdominal surgery is considered to involve such a risk, as are most open orthopedic procedures.

In the United Kingdom all health care workers at risk for HBV infection must be vaccinated, and their immune response to the vaccination must be documented. Health care workers who perform procedures involving a risk of exposure, defined according to the 1993 guidelines,^{1,12} and who do not have an antibody titer against hepatitis B surface antigen (anti-HBs) of at least 10 mIU per milliliter after vaccination are further investigated; those in whom HBeAg is detected are not allowed to perform procedures involving a risk of exposure.^{1,12} Carriers in whom serum HBeAg is not detectable may perform such procedures unless their participation is shown to have been associated with the transmission of HBV.

We report four cases of transmission of HBV to patients by four infected surgeons whose serum did not contain HBeAg. Three were identified after the introduction of the current guidelines in the United Kingdom; the fourth was originally investigated in 1988.¹³

CASE REPORTS**Initial Investigation of the Index Patients**

All four index patients (Table 1) were female, presented with acute onset of jaundice, and had laboratory-confirmed infection. None had received transfusions. Surgery in the preceding six months was identified as an exposure risk during routine questioning by the clinicians responsible for the care of each patient

Address reprint requests to Dr. Julia Heptonstall at the Public Health Laboratory Service Communicable Disease Surveillance Centre, 61 Colindale Ave., Colindale, London NW9 5EQ, United Kingdom.

Dr. Heptonstall assumes responsibility for the overall content and integrity of the manuscript.

*The members of the Incident Investigation Teams and other investigators are listed in the Appendix.

TABLE 1. CHARACTERISTICS OF THE FOUR INDEX PATIENTS WHOSE HBV INFECTIONS WERE ASSOCIATED WITH CONTACT WITH HBV-INFECTED SURGEONS.

CHARACTERISTIC	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Sex	F	F	F	F
Age group (yr)	30–39	30–39	60–69	70–79
Date of onset of jaundice	June 1988	October 1993	August 1994	January 1995
HBV subtype	ayw	adw	ayw	ayw
Type of procedure	Elective cholecystectomy	Elective cesarean section	Elective hysterectomy and removal of ovarian cyst	Elective cholecystectomy and nephrectomy
Interval between procedure and onset of jaundice (wk)	12	11	12	12
Blood transfusion	No	No	No	No
Sexual partner tested for HBV markers	Not tested	Anti-HBc–negative*	Anti-HBc–negative*	Not applicable
Other identified risk factors for HBV	None known	No	No	No
Identified source†	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4
Role of infected surgeon in procedure	Main operator	Main operator	Assistant	Assistant

*Anti-HBc denotes antibodies against hepatitis B core antigen.

†All other members of the surgical teams were either immune to HBV or uninfected.

and reported to the local virologist or public health physician. This led to the initiation of the four investigations. Hepatitis B surface antigen (HBsAg) and IgM antibody against hepatitis B core antigen (anti-HBc IgM) were both detectable in specimens obtained during the acute infection in Patients 2, 3, and 4. Although HBsAg was not detected in the specimen obtained during the acute infection in Patient 1, the presence of anti-HBc IgM suggested recent infection, confirmed by the absence of anti-HBc in a sample archived on blood donation four months before surgery. Patients 1, 2, and 3 each had a sexual partner; the partners of Patients 2 and 3 had no serologic evidence of HBV infection, thus excluding sexual transmission. The sexual partner of Patient 1 was not tested. None of the patients had fulminant hepatitis; all recovered completely.

Initial Investigation of the Surgeons

Testing the members of the implicated surgical teams revealed the HBV carrier status (positive for HBsAg and negative for anti-HBc IgM) of three of the surgeons (1, 2, and 4). Surgeon 3 was known to be an HBeAg-negative carrier of HBV and had, in line with existing guidelines, continued to operate. All other members of the four implicated teams were either immune to HBV or uninfected.

METHODS

The HBsAg-positive serum samples obtained from the surgeons at the time the surgical teams were tested and specimens obtained earlier in their careers were tested for HBeAg and antibody against HBeAg (anti-HBe) by at least two reference virology laboratories using at least two different immunoassays (Amerlite Enhanced Luminescence HBe/anti-HBe assay, Kodak Amerlite; an in-house radioimmunoassay¹⁴; or Hepanostika HBeAg/anti-HBe Microelisa, Organon Teknika). HBV DNA levels in the surgeons' serum samples were determined by liquid hybridization with one or both of two assays (Abbott Genostics assay, Abbott Laboratories; and Digene Hybrid Capture HBV DNA assay, Digene Diagnostics) and estimated by an in-house HBV DNA enzyme-linked oligonucleotide assay (Watts P: unpublished data), based on methods described previously.^{15,16}

Amplification of HBV DNA by a nested polymerase chain reaction (PCR) and direct nucleotide sequencing of two regions of

the HBV genome (part of the surface gene and part of the X and core genes including the entire precore region) were performed on serum samples from surgeons and patients, according to methods described previously.^{16,17} The primers were complementary to the 3' end of the X region (codons 105 to 154), the 5' end of the core region (codons 1 to 10), and the surface gene (codons 112 to 166). Single-strand sequencing was carried out directly on the amplified complementary DNA.

Anti-HBe, but not HBeAg, was detectable in duplicate serum samples obtained from three of the surgeons (1, 2, and 4) at the time of testing of the surgical teams and in serum from Surgeon 2 obtained nine months before the investigation. Specimens antedating the investigations of Surgeons 1 and 4 were not available. Surgeon 3 had been tested intermittently between 1989 and 1993, and his serum consistently contained HBsAg without detectable HBeAg or anti-HBe. In late 1993 his HBV status was reviewed when he changed employers; an initial positive reaction in a test for HBeAg led to the retrospective examination of sequential stored blood specimens by five laboratories, which confirmed his HBsAg-positive, HBeAg-negative, anti-HBe-negative status.

HBV DNA was detectable by liquid hybridization in the sample from Surgeon 1, but was not detectable in any samples from Surgeons 2, 3, and 4. It was detectable by enzyme-linked oligonucleotide assay in samples from all four. The sample from Surgeon 1 was estimated to contain not less than 10 million detectable copies per milliliter, and those from Surgeons 2, 3, and 4 to contain not less than 4.4 million, 5.5 million, and 250,000 detectable copies per milliliter, respectively. The internal HBeAg-positive control sample contained not less than 2 billion detectable copies per milliliter.

RESULTS

HBV DNA Sequencing

HBV DNA was sequenced from all surgeons and patients. We were unable to detect any differences in the HBV DNA sequences from each surgeon-patient pair. Sequences of the HBV surface gene and precore region from Surgeon 1 and Patient 1 corresponded to subtype ayw of HBV. The sequence of

the surface gene did not differ from that of the reference strain.¹⁸ The sequence of the precore region differed from the reference strain by one nucleotide: A was substituted for G at codon 28, which resulted in a premature stop codon.

Surgeon 2 and Patient 2 were infected with subtype adw of the virus. As compared with the reference strain, the strain from Patient 2 and Surgeon 2 had four silent nucleotide substitutions in the surface-gene sequences: A to G, C to G, G to C, and C to T at codons 114, 115, 118, and 155, respectively. Subtype adw is the most prevalent in the United Kingdom, but these substitutions have not been detected in other carriers of this subtype (Tedder RS: unpublished data). The precore region differed from the reference strain by two nucleotide substitutions. The first, G to A at codon 25, coded for an amino acid change from glycine to arginine; the second, G to A at codon 28, coded for a premature stop codon. A further silent nucleotide substitution, C to G at codon 141 of the X gene, was also observed.

Surgeon 3 and Patient 3 were infected with subtype ayw. Four nucleotide substitutions were observed in the surface-gene sequences. Three, C to T at codon 127, A to T at codon 140, and T to A at codon 144, encoded the substitution of serine for proline, of serine for threonine, and of glutamine for aspartate, respectively. The fourth, C to A at codon 155, was silent. There was a substitution of A for G at codon 28 of the precore region.

Surgeon 4 and Patient 4 were infected with subtype ayw. No nucleotide substitutions were found in the surface-gene sequences. Precore-region sequences contained two nucleotide substitutions: G to A at codons 28 and 29. The mutation at codon 28 encoded a premature stop codon; that at codon 29 coded an amino acid change from glycine to aspartate.

Sequence data on the four patient–surgeon pairs are available elsewhere.*

Follow-up of the Surgeons

All four surgeons stopped performing procedures involving a risk of exposure once their possible association with the transmission of HBV was recognized. They were interviewed to determine details of vaccination and career histories, the frequency with which they wore two pairs of gloves during proce-

dures, and whether they recalled needle-stick exposures to blood at work. Surgeons 2 and 4 had been vaccinated against HBV but most likely acquired their infection before vaccination (Table 2). They and Surgeon 3 had been born in countries with a high prevalence of HBV and probably became infected there at birth or in childhood. Surgeon 1 probably became infected through occupational exposure, either in the United Kingdom or abroad. We could not determine when he became infected; he had no history of jaundice. Two of the surgeons were trainees in obstetrics and gynecology. The third was a clinical assistant who undertook one general and urologic surgical session each week but no others involving procedures associated with a risk of exposure; the fourth was a senior general surgeon. Only Surgeon 3 was aware of his HBV status when the surgical teams were tested. None of the surgeons had reported exposure to patients' blood or body fluids, recalled frequent unreported percutaneous exposures, or had routinely worn two pairs of gloves for all, or most, surgical procedures. All were regarded as technically competent.

All were referred for clinical assessment and given career counseling. On initial assessment, none had evidence of chronic severe liver disease; three had normal aminotransferase levels. All remain in medicine, three in work that includes contact with patients and the performance of invasive procedures, but not procedures involving a risk of exposure to the virus. One continues to work in the same department but in a different capacity. Three have changed specialties. One had considerable difficulty before the offer of alternative employment required by the current guidelines¹¹ was made.

Follow-up of Other Exposed Patients

Patients on whom the surgeons had operated, or at whose operation they had assisted, were identified from operating-theater records, and the following details were abstracted: surname, other names, date of birth, and date and nature of surgical procedure. These identifying characteristics were matched against local laboratory records and the national HBV-surveillance data base. The procedures performed by the surgeons were classified according to the risk of exposure of the patient to the surgeon's blood. The procedures involving a risk of exposure performed by Surgeons 2 and 3 were then subcategorized according to the likelihood of risk (possible or high) with a classification system developed during earlier follow-up exercises.^{3,19} The patients of Surgeon 4 who had undergone procedures involving a risk of exposure and the patients of Surgeons 2 and 3 who had undergone a procedure with a high risk of exposure (e.g., cesarean section or major gynecologic surgery) in the year preceding the date their surgeon ceased practicing were informed through

*See NAPS document no. 05357 for 2 pages of supplementary material. Order from NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) \$7.75 for photocopies or \$5 for microfiche. Outside the U.S. and Canada, add postage of \$4.50 for the first 20 pages and \$1.00 for each 10 pages of material thereafter or \$1.75 for the first microfiche and \$0.50 for each microfiche thereafter. There is a \$15 invoicing charge on all orders filled before payment.

TABLE 2. CHARACTERISTICS OF THE HBV-INFECTED SURGEONS ASSOCIATED WITH THE TRANSMISSION OF HBV TO PATIENTS.

CHARACTERISTIC	SURGEON 1	SURGEON 2	SURGEON 3	SURGEON 4
Sex	M	M	M	M
Specialty	General surgery	Obstetrics–gynecology	Obstetrics–gynecology	General surgery,* urology
Professional level	Senior surgeon	Trainee	Trainee	Clinical assistant
Region of birth	Europe	Southeast Asia	Sub-Saharan Africa	Indian subcontinent
HBV subtype	ayw	adw	ayw	ayw
Year HBV status first recognized	1988	1993	1989	1995
Reason for HBV testing	Investigation of infection in Patient 1	Investigation of infection in Patient 2	Routine medical check	Investigation of infection in Patient 4
Result of HBeAg test†	Negative	Negative	Negative	Negative
Result of anti-HBe test†	Positive	Positive	Negative	Positive
HBV DNA‡				
Abbott Genostics assay (pg/ml)	70	Not detectable	Not detectable	Not done
Digene assay (pg/ml)	145	Not detectable	Not detectable	Not detectable
In-house assay (detectable copies/ml)	1×10 ⁷	4.4×10 ⁶	5.5×10 ⁶	2.5×10 ⁵
HBsAg titer by reverse passive hemagglutination	>1:8000	1:200	1:800	1:32
Dane particles in serum on electron microscopy	No (HBsAg particles seen)	Not determined	Not determined	Not determined
Years of surgical experience at time transmission recognized	>20	<1	5	>15
Previous hepatitis B vaccine	No	Yes	No	Yes
Occupationally acquired infection	Probable	No	No	No
History of reported needle-stick injury	No	No	No	No
Double-gloving practice	Not known	Occasional	Occasional	Occasional
Surgeon aware of HBV status at time of transmission	No	No	Yes	No
Technical expertise as assessed by colleagues	Competent	Competent	Competent	Competent

*This surgeon conducted one surgical session each week.

†Tests were performed on at least two specimens by at least two reference centers.

‡HBV DNA levels were determined by liquid-hybridization (Abbott Genostics) assay, Digene Hybrid Capture HBV DNA assay, or an in-house enzyme-linked oligonucleotide assay.

their general practitioners and offered hepatitis B serologic testing.

No other patient operated on in the same hospital as Patient 1 was known to have had symptoms of acute HBV infection in the preceding two years. No serologic survey of patients exposed to Surgeon 1 was undertaken.

Additional cases of acute HBV infection were not revealed by the matching exercises undertaken for patients who came into contact with Surgeons 2, 3, and 4.

Surgeon 2 had been performing procedures with a high risk of exposure for only six months when Patient 2 was identified. An additional 104 patients had undergone such procedures, of whom 103 were contacted and 91 (88 percent) were tested for HBV markers more than six months after exposure (Table 3). Anti-HBc was detected in blood samples from nine patients who had undergone elective cesarean section. Tests on stored routine antenatal specimens

showed seven to have been anti-HBc–positive at the time of exposure; two (Patients 5 and 6) had seroconverted. HBsAg was not detectable in the samples obtained after exposure from either patient, nor could HBV DNA be detected by PCR. A review of the case notes and interviews revealed that one had had jaundice three months after exposure but had not been tested for HBV. The other had had jaundice and had been admitted to the hospital 14 weeks after exposure; anti-HBc IgM, but not HBsAg or HBV DNA, was detected in a serum specimen stored at admission. Neither patient had other identified risk factors; their sexual partners were tested and found to be negative for anti-HBc.

Of the 114 patients in addition to Patient 3 on whom Surgeon 3 had performed procedures with a high risk of exposure in the preceding year, 110 (96 percent) were tested. Anti-HBc, but not anti-HBc IgM, was detectable in samples from five. One was infected before surgery; the time and source of in-

TABLE 3. OUTCOME OF SEROLOGIC FOLLOW-UP OF PATIENTS EXPOSED TO SURGEONS 2, 3, AND 4, INCLUDING THE INDEX PATIENTS.*

VARIABLE	SURGEON 2			SURGEON 3			SURGEON 4
	SURGICAL SPECIALTY			SURGICAL SPECIALTY			
	Obstetrics	Gynecology	Total	Obstetrics	Gynecology	Total	General Surgery
Time covered by follow-up (mo)	6	6	6	12	12	12	12
No. of surgical procedures performed	70	322	392†	86	218	304‡	277
No. involving a risk of exposure§	70	143	213	82	119	201	22¶
No. involving procedures with a high risk of exposure	70	35	105	25	90	115	15
No. of patients tested ≥6 mo after exposure (%)**	64	28	92 (88)	25	86	111 (97)	21 (95)
No. of patients positive for anti-HBc IgG	10	0	10	2	4	6	1
No. of patients with previous HBV infection††	7	—	7	1	—	1	—
No. of patients with recent HBV infection‡‡	3	—	3	—	1	1	1
No. of patients for whom the time of HBV infection could not be determined§§	—	—	—	1	3	4	—
No. of susceptible patients infected/total susceptible patients (%; 95% CI)¶¶	3/57 (5)	—	3/85 (4; 0.7–10)	—	1/86 (1)	1/110 (0.9; 0.018–5)	1/21 (5; 0.11–24)

*Index Patients 2, 3, and 4 are included in appropriate numerators and denominators throughout.

†The procedures consisted of cesarean section in 70 patients, hysterectomy in 29, and other major gynecologic surgery in 6 (all procedures with a high risk of exposure); laparoscopy (a procedure involving a risk of exposure) in 108 patients; colposcopy in 7; hysteroscopy in 93; dilation and curettage in 70; and cystoscopy in 9. The number of patients undergoing episiotomy repair was not determined.

‡The procedures consisted of cesarean section in 25 patients and hysterectomy or other major gynecologic surgery in 90 (all procedures with a high risk of exposure); laparoscopy in 29 and episiotomy repair in 57 (both procedures involving a risk of exposure); nonlaparoscopic minor gynecologic procedures, including dilation and curettage, in 99 patients; and other procedures in 4 patients.

§The analysis covers procedures in which the surgeon was the main operator or an assistant, including those with a high risk of exposure.^{3,19}

¶The procedures consisted of appendectomy in 1 patient, inguinal-hernia repair in 4, laparotomy in 3, nephrectomy in 3, varicose-vein stripping in 3, and open ureterolithotomy in 1 (all procedures with a high risk of exposure); other procedures involving risk in 3; and transperineal needle biopsy of the prostate in 4.

||The analysis covers procedures in which the surgeon was the main operator or an assistant.

**For Surgeons 2 and 3, only patients who had undergone a procedure with a high probability of exposure were offered testing. For Surgeon 4, patients who had undergone any procedures involving a risk of exposure were offered testing.

††Evidence of HBV infection was detected in a specimen that antedated the procedure.

‡‡There was evidence of acute HBV infection (anti-HBc IgM with or without HBsAg in a postexposure specimen or seroconversion to anti-HBc-positive).

§§The postexposure specimen was positive for anti-HBc and negative for anti-HBc IgM and HBsAg; no preexposure serum sample was available.

¶¶The total number of susceptible patients was calculated as the number tested minus the number with evidence of previous HBV infection. CI denotes confidence interval.

fection in the remaining four could not be determined.

Twenty of the 21 patients in addition to Patient 4 who came into contact with Surgeon 4 were tested; none had serologic evidence of HBV infection.

DISCUSSION

These data provide evidence that surgeons who are carriers of HBV who do not have detectable HBeAg in their serum may transmit the virus to patients. Patients 2, 3, and 4 had no alternative sources for their infections; the regions of the viral genome studied by amplification of HBV DNA from serum samples obtained during acute infection contained sequences identical to those found in blood samples from Surgeons 2, 3, and 4, respectively. The only al-

ternative source for Patient 1's infection was her sexual partner, who had no history of jaundice or identified risks for HBV but who was not serologically tested. Sequences of virus from the specimen obtained from Patient 1 during acute infection matched those from Surgeon 1; we believe Surgeon 1 to have been the source of infection. Surgeon 2 probably infected two other patients (Patients 5 and 6) in addition to Patient 2.

These findings illustrate the value of obtaining an adequate clinical history from persons with acute hepatitis B. We suggest that a history of surgery in the six months before the onset of infection in the apparent absence of other risk factors should lead to a review of the HBV status of members of the implicated surgical team. If a member of the team is

found to be an HBsAg-positive carrier, neither a negative result of a test for serum HBeAg nor a negative result of an assay for HBV DNA based on liquid hybridization is sufficient to rule out the team member as the source of the patient's infection. Further virologic investigations, including HBV DNA detection by PCR and HBV DNA sequencing of samples from the surgeon and patient, may be indicated.

All four surgeons were carriers of HBV with a nucleotide substitution in the precore region of the viral genome. The single-base change (TGG to TAG) at codon 28 encodes a premature stop codon in place of a tryptophan residue. The mutation prevents transcription of the precore region and therefore the expression of HBeAg²⁰ but allows the continued assembly of infectious virus²¹ in the presence of serum anti-HBe. The importance of such mutations is uncertain. Early reports emphasized their relation to chronic severe liver disease in anti-HBe-positive carriers of HBV with high levels of circulating HBV DNA.²⁰ More recent reports indicate that the mutation may be found in anti-HBe-positive carriers who are asymptomatic, have essentially normal liver function, and do not have high levels of circulating serum HBV DNA.¹⁵ In three of the four surgeons serum HBV DNA was detectable by PCR, but not by a liquid-hybridization assay. In the case of two of the surgeons, tests of specimens stored before transmission yielded the same results as those of specimens obtained after transmission. This suggests that the absence of HBV DNA on liquid-hybridization assay was not an aberrant finding, although the possibility that HBV DNA may have been transiently detectable by this technique around the time of transmission cannot be excluded. It is interesting that the surgeons' HBV DNA levels estimated by enzyme-linked oligonucleotide assay ranged from no less than 250,000 detectable copies per milliliter (Surgeon 4) to 10 million detectable copies per milliliter (Surgeon 1, in whom HBV DNA was also detectable by liquid-hybridization assay), paralleling the HBsAg titers (Table 2), but that even the highest level was markedly below that of the internal control derived from an HBeAg-positive carrier.

The 1993 revision of the United Kingdom guidelines on hepatitis B^{1,12} had two main purposes. One was to minimize the risk of occupationally acquired infection by ensuring the vaccination of health care workers at risk, including students. The other was to reduce the risks to patients undergoing procedures involving a risk of exposure by identifying health care workers who, as carriers of HBeAg, would be most likely to transmit HBV and prospectively barring them from the performance of such procedures. The introduction of the guidelines may have contributed to the detection of the transmissions we re-

port, by raising professional awareness about the possibility of transmission of HBV from surgeons to patients and by instituting the prospective restriction of the practice of HBeAg-positive surgeons, which progressively reduces the likelihood that any identified transmission event will be associated with an infected surgeon whose serum contains detectable HBeAg.

At present, surgeons in the United Kingdom whose serum is found to contain HBsAg but not HBeAg may continue to perform procedures involving a risk of exposure unless they are shown to have been associated with transmission of the virus. They receive advice about preventing transmission and career counseling but are in the unenviable position of having to weigh the prospect of future restriction of practice against the desire to continue their chosen career. A better understanding of markers that predict transmission would benefit such surgeons, as well as those who provide counseling and those responsible for policy development. Serum HBsAg titers do not reliably predict transmission. One obvious strategy would be to measure serum HBV DNA levels. However, the absence of detectable HBV DNA by liquid-hybridization assay in three of the four surgeons suggests that these types of insensitive but robust assays, with detection limits of around 10 million to 100 million copies per milliliter, may be of limited value in predicting whether transmission will occur. The role, if any, of amplification-based assays remains to be seen. It is not known what proportion of HBeAg-negative carriers of HBV have the codon 28 mutation, nor whether it is found as commonly among surgeons who are HBeAg-negative carriers who have never been associated with transmission as among those who have. Further work, which relates the presence or absence of precore mutations to quantitative measurements of HBV DNA and evaluates these in relation to transmission risks in surgical and other settings, is needed. If a precore mutation is important in determining whether transmission will occur, then the development and evaluation of assays¹³ that would reliably detect such mutations could both further protect patients and help health care workers make better-informed decisions about the direction of their careers.

We are indebted to the many general practitioners who helped in the follow-up of patients; to our colleagues, including Pam Court, Pam Foulkes, Alastair Geddes, Sister Sheppey, Sister Szczepinska, Hugh Nicholas, Susan Turnbull, Ulrich Desselberger, Paddy Farrington, and especially Berangere Botto, Philip Mortimer, David Bell, and Mary Chamberland; and to Mark Zuckerman and Anna Hawkins for HBV DNA sequencing.

APPENDIX

Preparation of this report was coordinated by Dr. Heptonstall in collaboration with the following institutions and investigators in the United Kingdom: *Public Health Laboratory and Forest Healthcare Trust, Whipps Cross Hospital, Leytonstone, London* — J. Barnes, E. Burton, B. Chattopadhyay, L. McMillan, K. Sullivan, R. Tarling, and D. Viniker; *Public Health Laboratory, Birmingham Heartlands Hospital, Birmingham* — E. Boxall; *the Department of Public Health, Rochdale Health Authority, and Rochdale Trust, Rochdale* — I. Cartmill, M. Chatterjea, and R. Neill; *Public Health Laboratory Service Communicable Disease Surveillance Centre and Virus Reference Division, Central Public Health Laboratory, Colindale, London* — M. Collins, N. Gill, S.L. Ngui, C. Parker, M. Ryan, and C.G. Teo; *Regional Virus Laboratory, Royal Victoria Hospital, Belfast* — P. Coyle; *Public Health Laboratory, Withington Hospital, Manchester* — J. Craske and K. Paver; *the Departments of Virology and Sexually Transmitted Diseases, University College London Medical School, London* — R. Gilson, A. Hawkins, R. Tedder, P. Watts, and M. Zuckerman; *the Division of Virology, University of Manchester Medical School, Manchester* — D. Morris; and *the Department of Public Health, Redbridge and Waltham Forest Health Authority, Ilford, Essex* — B. Nazareth.

REFERENCES

1. UK Health Departments. Protecting health care workers and patients from hepatitis B: recommendations of the Advisory Group on Hepatitis. London: Her Majesty's Stationery Office, 1993.
2. Polakoff S. Acute hepatitis B in patients in Britain related to previous operations and dental treatment. *BMJ* 1986;293:33-6.
3. Welch J, Webster M, Tilzey AJ, Noah ND, Banatvala JE. Hepatitis B infections after gynaecological surgery. *Lancet* 1989;1:205-7.
4. Prentice MB, Flower AJE, Morgan GM, et al. Infection with hepatitis B virus after open heart surgery. *BMJ* 1992;304:761-4.
5. Polakoff S. Acute viral hepatitis B: laboratory reports 1980-4. *BMJ* 1986;293:37-8.
6. Surgeons who are hepatitis B carriers. *BMJ* 1991;303:184-5.
7. Heptonstall J. Outbreaks of hepatitis B virus infection associated with infected surgical staff. *Commun Dis Rep CDR Rev* 1991;1:R81-R85.
8. Heptonstall J, Collins M, Smith I, Crawshaw SC, Gill ON. Restricting practice of HBeAg positive surgeons: lessons from hepatitis B outbreaks in England, Wales, and Northern Ireland 1984-93. *Infect Control Hosp Epidemiol* 1994;15:344. abstract.
9. Recommendations for preventing transmission of human immunodeficiency virus and hepatitis B virus to patients during exposure-prone invasive procedures. *MMWR Morb Mortal Wkly Rep* 1991;40(RR-8):1-9.
10. Johnston BL, MacDonald S, Lee S, et al. Nosocomial hepatitis B associated with orthopedic surgery — Nova Scotia. *Can Commun Dis Rep* 1992;18:89-90.
11. Harpaz R, Von Seidlein L, Averhoff FM, et al. Transmission of hepatitis B virus to multiple patients from a surgeon without evidence of inadequate infection control. *N Engl J Med* 1996;334:549-54.
12. Health service guidelines: protecting health care workers and patients from hepatitis B. Leeds, England: National Health Service Management Executive, 1993. (Publication no. HSG(93)40.)
13. Hawkins AE, Gilson RJC, Beath SV, et al. Novel application of a point mutation assay: evidence for transmission of hepatitis B viruses with pre-core mutations and their detection in infants with fulminant hepatitis B. *J Med Virol* 1994;44:13-21.
14. Ferns RB, Tedder RS. Detection of both hepatitis B e antigen and antibody in a single assay using monoclonal reagents. *J Virol Methods* 1985;11:231-9.
15. Hawkins AE, Gilson RJC, Bickerton EA, Tedder RS, Weller IVD. Conservation of precore and core sequences of hepatitis B virus in chronic viral carriers. *J Med Virol* 1994;43:5-12.
16. Whitby K, Garson JA. Optimisation and evaluation of a quantitative chemiluminescent polymerase chain reaction assay for hepatitis C virus RNA. *J Virol Methods* 1995;51:75-88.
17. Zuckerman MA, Hawkins AE, Briggs M, et al. Investigation of hepatitis B virus transmission in a health care setting: application of direct sequence analysis. *J Infect Dis* 1995;172:1080-3.
18. Pugh JC, Weber C, Houston H, Murray K. Expression of the X gene of hepatitis B virus. *J Med Virol* 1986;20:229-46.
19. Crawshaw SC, Gill ON, Heptonstall J, et al. Outcome of an exercise to notify patients treated by an obstetrician/gynaecologist infected with HIV-1. *Commun Dis Rep CDR Rev* 1994;4:R125-R128.
20. Carman WF, Jacyna MR, Hadziyannis S, et al. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989;2:588-91.
21. Ulrich PP, Bhat RA, Kelly I, Brunetto MR, Bonino F, Vyas GN. A pre-core-defective mutant of hepatitis B virus associated with e antigen-negative chronic liver disease. *J Med Virol* 1990;32:109-18.