CORRESPONDENCE

Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

Invasive cervical cancer and combined oral contraceptives

SIR,—The report of the WHO Collaborative Study on Neoplasia and Steroid Contraceptives (30 March, p 961) is the latest in what is now a fairly long series of reports providing evidence that the risk of developing cervical cancer (or its premalignant predecessors) is somewhat greater in women who have taken oral contraceptives for several years or have been regular cigarette smokers or both.

The idea that oral contraceptives and cigarette smoking might both contribute to the cause of this disease is supported by some laboratory evidence, but even so most of those who have had much experience of epidemiological research are likely to agree with the authors of the WHO report that the results could also have been due to confounding between the use of oral contraceptives, cigarette smoking, and sexual behaviour of either the affected women or their partners. Several of the reported studies (including the WHO collaborative study) have attempted to allow for such confounding, and all, or nearly all, have found that by so doing the risk is materially diminished, and in these circumstances it is difficult to be sure that if the allowance made had been perfect a small increase in relative risk might not have been eliminated altogether. The causal nature of the observed associations must therefore remain in doubt.

What is not in doubt, however, is that some change took place in about 1960 in Britain which has led to a progressive increase in the incidence of cervical cancer in women born after about 1935. This is shown very clearly in the national vital statistics published by the Office of Population Censuses and Surveys, which are summarised in the table. These show (*a*) a progressive decrease in mortality in women aged over 50 years since the early 1950s, when precise figures for cervical cancer began to be published separately from those for cancers of the body; (*b*) an initial increase in younger age groups reaching a maximum in women born between about 1915 and 1924 followed by a fall; and (*c*) a substantial increase in the past few years in women born since 1935.

Annual death rates due to cervical cancer per million women according to age group and period. Minimum values in each age group are italicised

	Period						
Age (years)	1951-5	1956-60	1961-5	1966-70	1971-5	1976-80	1982-3
20-	*1*	*1*	*1*	2	3	3	3
25-	10	9	*5*	7	10	15	20
30-	30	37	18	*15*	22	23	45
35-	58	74	67	44	*38*	53	52
40-	93	119	134	106	67	*59*	77
45-	136	154	180	176	130	*92*	93
50-	203	181	187	204	190	157	103
55-	254	197	178	201	199	192	133
60-	285	246	222	193	199	214	183
65-	304	284	232	217	193	203	187
70-	315	313	274	247	206	201	198
75-79	361	336	301	271	247	217	193

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Hepatitis B virus DNA and e antigen in serum from blood donors positive for HBsAg

SIR,—We read with interest the article by Dr T J Harrison and colleagues (2 March, p 663). Four out of 161 carriers of hepatitis B surface antigen (HBsAg) who were anti-HBe positive gave such a weak hepatitis B DNA signal on autoradiography that it was not detected at three days but only after a two week exposure. The authors conclude that DNA hybridisation should be the method of choice for determining whether carriers of HBsAg are infectious. This would have a profound effect on the work patterns of clinical virology laboratories which are concerned in

advising clinicians on relative risks and patient management after hepatitis B contacts.

We are reluctant to carry out DNA hybridisation (with a two week autoradiography exposure) routinely on patients who are known to be anti-e carriers in clinical settings such as institutions for the mentally subnormal and acute dentistry, where needlestick injuries, scratches, or bites have occurred before action is taken. Clearly all such events involving contact with HBsAg positive blood of unknown e status should result in the administration of immune globulin and a course of vaccine to the injured member of staff.

We accept that certain staff at high risk should be vaccinated but we are aware that this is not always done. We wonder what the risk of HBsAg transmission is from such DNA positive patients in the situations outlined above, where minute volumes of blood are involved? We know that under experimental conditions transmission can occur from anti-e positive carriers if very large volumes of blood are involved.[1]

We conclude that further information on the infectiousness of hepatitis B anti-e carriers at the clinical as opposed to the academic level is necessary before the introduction of a technique which clearly requires some weeks for a definitive answer.

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1 Shikata T, Karasawa K, Abe Y, *et al.* Hepatitis B e antigen and infectivity of hepatitis B virus. *J Infect Dis* 1977;**136**:571-6.

**Dr Harrison and Professor Zuckerman reply below.—Ed, *BMJ*

Sir,—We agree with Drs Roome and Caul that in most circumstances all carriers of hepatitis B surface antigen (HBsAg) should be treated as potentially infectious and appropriate action undertaken without delay. We do not at present wish to burden clinical virology laboratories with the task of testing large numbers of specimens by DNA:DNA hybridisation. We are only able to assess the need for highly sensitive and specific methods for establishing relative risks of transmission or potential infectivity by the numerous requests which we receive from clinicians for diverse reasons. Some of these requests include the possible risk of transmission to patients by surface antigen carriers working in the health services, carrier pregnant women in whom e antigen and anti-e are not detectable, unravelling the problem of people found with hepatitis B anti-core only, adoption of orphans and children who are from areas highly endemic for hepatitis B and found to be carriers, the evaluation and monitoring of antiviral therapy of carriers with liver disease, and cases of litigation. After all, the carrier state has enormous social, economic, and health implications which virologists and clinicians encounter only too often, including the fact that many carriers of HBsAg are finding it difficult to obtain medical, surgical, and dental treatment. Yet only a relatively small proportion of carriers are infectious. The ability to reassure carriers of hepatitis B markers, using sensitive and specific assays, that they present no risk or only low risk of transmission, or, alternatively in the more uncommon instances, that there is a risk of transmission, is the duty of the clinical virologist.

Among the functions of academic and reference laboratories is the development of new diagnostic methods and the transfer of technology to clinical laboratories. This is being done. Current research in this laboratory includes further development of DNA:DNA hybridisation to make it available as a simple diagnostic test. Radiolabelled DNA probes have several disadvantages: they are hazardous to handle, the nuclide ^{32}P has a relatively short half life, and times for autoradiographic exposure may be long (though there is the alternative of cutting up the filter and measuring the signal by liquid scintillation counting). We are therefore investigating various methods of labelling DNA chemically so that hybridisation can be detected by a simple chemical or enzymatic reaction.

It will be tiresome to quote again the few selected references listed in our paper of 2 March on the value of detecting hepatitis B virus DNA in the serum and, where appropriate, in liver biopsy specimens obtained from carriers. However, the following statements and recommendations[1] from one of several reports of the World Health Organisation emphasise the value of the type of technique we are using and developing further:

> An important application of recombinant DNA techniques has been in studies of the epidemiology and diagnosis of HBV using cloned HBV-specific DNA as a probe. . . . Techniques based on molecular hybridisation are highly discriminating for closely related viruses and may enable the analysis of a large number of isolates. They have been shown to be of value for the epidemiological study and characterisation of influenza, papilloma and hepatitis B viruses, rotaviruses and retroviruses. . . . The wider use of the new biotechnological techniques to study viruses or reagents, based on their use for the epidemiology and control of viral disease, is strongly encouraged.

This is one of the aims of the WHO programme for prevention and control of viral, chlamydial, and rickettsial diseases.[2]

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1 World Health Organisation. *Molecular biological and monoclonal antibody techniques. Their application to the diagnosis, epidemiological study and control of viral infections of man.* Geneva: WHO, 1983. (EURO Reports and Studies 88.)
2 Assaad FA, Schild GC. The WHO programme for prevention and control of viral, chlamydial and rickettsial diseases. Brief review. *Arch Virol* 1983;**76**: 275-88.

Sir,—In the report (2 March, p 663) of a comparison between two tests of the infectivity of serum containing hepatitis B surface antigen (HBsAg) Dr T J Harrison and colleagues show that among 161 sera in which antibody to hepatitis e antigen (anti-HBe) was detected DNA hybridisation tests indicated the presence of hepatitis B virus particles in four (2%). Although the DNA test responses in these four sera were weak, suggesting few virus particles and low infectivity, the authors consider that the presence of hepatitis DNA in serum has important consequences in the assessment of the risk in pregnant women who are HBsAg carriers.

Since the newborn of women who are carriers of anti-HBe are not offered immunisation in the national surveillance programme[1] this opinion may cause concern about the frequency and severity of hepatitis B infection of the newborn of anti-HBe positive carrier women and therefore it seems opportune to re-examine evidence on this point and present some recent information.

Longitudinal serological and clinical studies, made in several countries, of the newborn of HBsAg carrier women show the outcome of exposure to the mother's blood at birth (table).[2-7] Persistent HBsAg carriage in early infancy, which carries a high risk of cirrhosis and primary liver carcinoma in later life, developed in 60 of the 69 infants born to mothers with hepatitis e antigen (HBeAg) in their serum but in none of the infants born to the 71 anti-HBe positive mothers. The presence of some virus particles in the serum of some of the anti-HBe positive mothers was shown by evidence of hepatitis B virus infection in 10% of their infants in the early months of life but these infections resulted in no more than symptomless transient antigenaemia, leading to active immunity. The neonate's immune system appears to be able to mount an adequate response to the small dose of hepatitis B virus presented by the serum of some anti-HBe positive mothers but not to the large dose of virus presented by HBeAg positive mothers. The observations of the studies cannot be expected to be absolute and therefore it is not surprising that a few infants of both HBeAg positive and anti-HBe positive mothers in the USA and Japan are reported to have developed acute hepatitis B in the early months of life.[8,9] Although these cases were few, their frequency in Britain was important in deciding whether to design a national programme which concentrated efforts on infants with about a 90% risk of infection or to include infants of anti-HBe carrier mothers and thereby cause a threefold to fourfold increase in the number to be offered immunisation.

All indices of acute clinical hepatitis in infancy—statutory notifications, death certificates, and, in particular, PHLS communicable disease reports—supported the view that the illness is rare among infants and suggested that less than one infant of an anti-HBe positive carrier woman would develop clinical hepatitis B in any year in Britain. Information collected in the course of the national surveillance of infants at risk of hepatitis B virus infection at birth confirms these assessments. Although immunisation is not offered to infants of anti-HBe carrier women it can be estimated reliably, on the basis of regular reports from some collaborating microbiologists of both HBeAg positive and anti-HBe positive identifications, that more than 600 infants have been born to women identified as anti-HBe positive carriers since the

Outcome of exposure at birth to HBsAg positive mothers. Results are numbers of cases (and numbers of infants, of anti-HBe mothers, with transient antigenaemia)

Study	Country	HBeAg positive mothers: No	HBeAg positive mothers: Infants with persistent HBsAg carriage	Anti-HBe positive mothers: No	Anti-HBe positive mothers: Infants with persistent HBsAg carriage
Okada *et al*[2]	Japan	10	10	7	0
Stevens *et al*[3]	Taiwan	47	40	14	0 (3)
Reesink *et al*[4]	Holland	6	4	11	0 (1)
Tong *et al*[5]	USA	3	3	11	0 (1)
Papaevangelou and Hoofnagle[6]	Greece	0	0	5	0
Chin *et al*[7]	Scotland	3	3	23	0 (2)