information be bounced around the media before critical analysis and evaluation by the medical or scientific communities.

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1 Marsh P. Porton International, a herpes vaccine, and the CAMR. *Br Med J* 1990;**300**:1291. (19 May.)
2 Skinner GRB. Nice work for everybody except the patient. *Vaccine* 1989;**7**:382-4.

SIR,—The news article on Porton International[1] was misleading and contained some important inaccuracies.

Mr Peter Marsh says that the herpes vaccine developed by Dr Skinner of Birmingham University took much longer than expected to progress through clinical trials in the United States and that the trials have now been abandoned. Both statements are inaccurate and misleading. As readers will be aware genital herpes is a complex condition and there are several aspects of the disease that can be addressed by the product developed by Dr Skinner. Initially Porton intended to concentrate on the use of the product as a vaccine to prevent or mitigate initial infection. But after an analysis of the scientific and commercial potential of the product and discussion with all the parties concerned in the development programme it was decided that it should be evaluated as a treatment to alleviate the condition in patients with herpes. Having taken this decision well structured double blind clinical trials for this indication were set up in the United States at three centres, and these have been carried out to the highest standards. While it can be argued that had we proceeded with trials for prevention of the infection they would have been completed earlier these trials were conducted in the fastest time possible consistent with trial design, patient recruitment, and the requirements of the Food and Drug Administration.

Mr Marsh says that Porton has taken a decision to abandon the trials. This is untrue. The trials have been completed on time, fully analysed, and a preliminary indication of the results made public in a letter to shareholders on 19 April.

The aim of clinical trials is to conduct objective experiments to establish whether a particular treatment is beneficial or not. Inevitably not every trial will produce a positive result in terms of showing clinical benefits. But well conducted trials can have immense value scientifically, and we believe that this is the case with our herpes trials. Though we are disappointed by the lack of clinical efficacy, we are proud to have carried out this work and supported an idea derived in a British university. Far from having abandoned this project we are still considering ways in which it can be brought to the market for the benefit of patients and their consorts.

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1 Marsh P. Porton International, a herpes vaccine, and the CAMR. *Br Med J* 1990;**300**:1291. (19 May.)

Meningococcal meningitis

SIR,—I was pleased to see that the editorial by Drs Philip D Welsby and Clayton L Golledge emphasised the variability of the rash in meningococcal meningitis because most short paediatric textbooks for junior hospital staff or general practitioners refer only to petechial or purpuric rashes.[1]

I recently reviewed the charts of 91 cases of acute meningococcal infection in children in the north east of Scotland. In all five cases of septicaemia without meningitis a purpuric rash developed eventually, but in four this was initially macular and evolved over one to eight hours. Of the 20 cases of meningitis with positive blood culture, six never developed a rash, six had macular rashes (one becoming purpuric), and in only eight was the rash purpuric from the onset.

Among the remaining 66 cases of meningitis blood cultures were negative (56 cases) or not taken (10 cases) and 26 never developed any rash, although 26 did have a petechial or purpuric rash at some stage in the illness. In 20 children the rash was initially recorded as macular or morbilliform and progressed to haemorrhagic skin lesions in only five.

This is important because a non-specific rash in a febrile child is often taken to indicate a viral illness, engendering a false sense of security. Two of the above cases were initially diagnosed as measles, one as chickenpox, and one as rubella—fortunately without ill effect. In one other case the rash was recorded as "macular—not a meningococcal rash" —and antibiotics were withheld until the child was found moribund the next morning.

In an ill child, particularly during an epidemic, fever and any rash may mean meningococcal infection and penicillin can be life saving.

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1 Welsby PD, Golledge CL. Meningococcal meningitis. *Br Med J* 1990;**300**:1150-1. (5 May.)

Illness preceding sudden infant death

SIR,—Dr Ruth E Gilbert and colleagues found that minor signs of illness, including snuffles and cough, preceded sudden infant death.[1]

We present data on the syndrome in the southern hemisphere. Because of the marked increase in the number of sudden infant deaths in winter a comparative study of the syndrome was conducted in Melbourne (latitude 38°S) and in Brisbane (latitude 28°S) where the winter is much less severe.[2] The study yielded an incidence of the sudden infant death syndrome of 1·6/1000 live births in Brisbane compared with an incidence of 2·2 in Melbourne and showed that infant deaths under 3 months showed no seasonal variation. One third of infants were aged above 3 months in Brisbane and half in Melbourne.

In Tasmania, Australia's most southerly state (latitude 41-43°S), the syndrome affects 4·4/1000 live births with nearly two thirds of affected infants aged more than 3 months.[3] Thus, in Australia as one travels southwards along the eastern coast, the incidence of the sudden infant death syndrome and the proportion of affected infants aged over 3 months both increase.

A recent study of the sudden infant death syndrome in New Zealand, which ranges from latitude 35°S to 47°S, used five broad geographical areas of increasing latitude.[4] The results show that there is a north-south gradient for the incidence of the syndrome—from 3·28/1000 live births in the north of the country to 6·46 in the most southern region. With the exception of the north of the South Island there is an increasing percentage of deaths over the age of 3 months with increasing latitude.

With the exception of the North Island of New Zealand, the populations of the areas mentioned above are of European origin, mainly Anglo-Saxon. In the North Island of New Zealand there is a large Maori population which has a high incidence of the sudden infant death syndrome (6·5/1000 live births) compared with that in the non-Maori population (3·8). Maternal and infant health care are good in Australia and New Zealand and of comparable standard. We also believe that in the studies reported above there has been consistency in the diagnosis of the sudden infant death syndrome.

The increased incidence of the syndrome with increased latitude in these countries suggests that one or more environmental factors are responsible for some infant deaths. The effect of this factor (or factors) appears to be most obvious in infants over 3 months. We believe that certain respiratory virus infections must be considered as the responsible factor. The seasonal and annual incidences of the sudden infant death syndrome correlate with the incidence of bronchiolitis in a community,[5] and tracheitis is commonly found in infants who die suddenly when aged over 3 months but not in younger affected infants or controls.[6] The incidence of the syndrome also correlates with isolations of respiratory syncytial virus in a population and, to a lesser extent, of influenza and para-influenza viruses.[7] These viruses can be isolated from the respiratory tracts of a significant number of infants aged over 3 months with sudden infant death syndrome, but not from infants under this age or from appropriate controls,[8] and they are known to produce apnoeic attacks in young infants.[9]

We agree that there are two types of infant deaths[10]—those occurring in infants under 12 weeks and those occurring in those over this age. We believe that most deaths in the older group are precipitated by certain respiratory viruses.

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Gall bladder function after endoscopic sphincterotomy

SIR,—The report by Mr L A Desa and colleagues of gall bladder dysfunction after endoscopic sphincterotomy is methodologically flawed and thus its conclusions are meaningless.[1]

Firstly, technetium-99m HIDA scanning is a technique designed to investigate patency, not function, of the biliary tree.[2] The true functional state of the gall bladder can be shown only by confirming its contractile response to cholecystokinin. Secondly, normal gall bladders may take up to four hours to accumulate isotope,[2] yet delayed images were taken at only two hours after injection. Thirdly, no conclusions can be drawn about individual patients because there are no control data. Each patient should have acted as his own control by having an isotope scan before sphincterotomy—without these data the report of any effect of sphincterotomy on the results of scintigraphic scanning is totally invalid. Finally, extrapolations

based on only six patients have doubtful statistical significance and clinical relevance.

Thus it is not surprising that the conclusions drawn by the authors are not supported in the existing literature. Indeed, there is a large body of data now available attesting to the long term safety of sphincterotomy in patients with intact gall bladders.[3] Furthermore, there is considerable evidence that sphincterotomy may enhance gall stone clearance from the gall bladder in animals and man. For example, dynamic scintigraphic studies using cholecystokinin in dogs have shown increased ejection fractions after sphincterotomy.[4] Safe and effective use of endoscopic sphincterotomy of the gall bladder in a wider population can be supported only by correctly designed controlled clinical trials.

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1 Desa LA, Grace PA, Vipond MN, Henderson B, Thompson JN. Gall bladder function after endoscopic sphincterotomy. *Br Med J* 1990;**300**:1111. (28 April.)
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SIR,—Mr L A Desa and colleagues report non-functioning of the gall bladder after sphincterotomy, but we wish to make the following comments with respect to their conclusions.[1]

Firstly, entry of contrast material into the gall bladder at endoscopic retrograde cholangiopancreatography demonstrates only patency of the cystic duct and does not represent intact gall bladder function. Secondly, failure of gall bladder filling in patients with previous sphincterotomy does not necessarily indicate gall bladder dysfunction. Indeed, this would be an expected finding, because the radiolabelled bile would freely flow through the dilated sphincter of Oddi.

In healthy subjects the mean peak pressure at the sphincter of Oddi during phasic contractions is 100 mm Hg greater than the intraduodenal pressure[2] and holds back bile so that it enters the gall bladder. This pressure is also similar in patients with common bile duct stones or gall stones. During the open relaxation phase the sphincter pressure decreases to about 15 mm Hg higher than the intraduodenal pressure.[3] In man the sphincter of Oddi functions as a variable resistor—variation in its tone routes hepatic bile into the duodenum or towards the gall bladder.[4]

In subjects with previous sphincterotomy, in whom this sphincter pressure is abolished, it would be natural for the bile to take the path of least resistance and drain freely into the duodenum without entering the gall bladder. This cannot be taken as evidence of a non-functioning gall bladder. The authors assume that the only stimulus to gall bladder contraction is distension by filling of bile. The implication that sphincterotomy would lead to failure of gall bladder contraction, with retention of stones and stasis of bile with consequent sepsis and carcinoma, is questionable.

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AUTHORS' REPLY,—We cannot agree with any of the criticisms of our study made by Drs Horton and Lauri.

Technetium-99m HIDA scanning is a functional test of hepatic uptake and excretion. It may be used to assess biliary system patency, but non-filling of the gall bladder or any other part of the biliary system does not necessarily imply mechanical obstruction. Indeed, non-filling of the gall bladder is seen in a number of conditions despite a patent cystic duct. The response of the gall bladder to exogenous cholecystokinin cannot be regarded as a true test of physiological function.

The reference quoted by Drs Horton and Lauri about delayed filling of normal gall bladders was thrice removed from any data (two textbooks and one letter leading to an abstract[1]). This refers to patients with suspected acute cholecystitis, not "normal" gall bladders, and shows that in 17 of 296 patients (6%) the gall bladder did not fill at one hour but did so later at one to four hours after injection of radioisotope. Three patients had acute and 14 chronic cholecystitis. As discussed in our report there is a low incidence (about 10%) of non-filling of the gall bladder on HIDA scanning in asymptomatic patients with stones, but the chances of this occurring in six consecutive patients are remote (approximately one in 10^6).

Presphincterotomy HIDA scans would have been difficult to interpret because most of our patients were jaundiced, and thus had impaired isotope excretion, and had common bile duct stones obstructing the biliary system. The absence of "controls" does not invalidate our observation.

We cannot agree that an observation based on "only six" patients is of doubtful clinical relevance. Indeed, an observation on a single patient may be of great clinical relevance. None the less, we have extended our series to 10 patients (four with scanning up to four hours) and none has shown gall bladder filling. Our finding is also supported by a recent necropsy study.[2] We have no doubt about the validity of our observation.

While we do not doubt the good short term results of sphincterotomy for ductal stones, the safety of sphincterotomy in the long term (more than 10 years) in such patients is not known. Our study suggests caution before extending such a policy to younger patients, who may be expected to live up to 30 or 40 years after operation. Controlled trials have little value in this respect.

Drs Horton and Lauri comment that considerable evidence exists in animals and man showing that sphincterotomy may enhance gall stone clearance from the gall bladder but support this only with a reference to cholecystokinin-induced gall bladder ejection fractions and the passage of glass beads after sphincterotomy in dogs.[3] The same study showed significantly lowered resting gall bladder volumes after sphincterotomy, which would be consistent with reduced gall bladder filling. The authors of this study were more cautious than Drs Horton and Lauri and concluded, "these preliminary results in an animal model should not be assumed to apply to humans and should not alter our clinical approach to gall stone disease."

Our study has clearly shown the absence of gall bladder filling on HIDA scanning in patients after endoscopic sphincterotomy. We believe that this observation may have important implications and that it certainly warrants further study.

We generally agree with the comments made by Dr Arnold and colleagues, although we find it difficult to understand how a gall bladder that does not fill with bile can be considered to function normally. While we agree that gall bladder filling is not the only stimulus to gall bladder contraction, a non-distended gall bladder will obviously have less scope for contraction than a distended one. The finding of our study may be expected, but it has not to our knowledge been documented before and it is certainly not widely appreciated.

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Screening for carcinoma of the prostate

SIR,—Dr Knud V Pedersen and colleagues are enthusiastic about digital rectal examination but doubt whether such screening for early curable cancer of the prostate will lead to prolonged survival.[1] This is yet another study on screening for cancer of the prostate that lacks a control group and is, therefore, vulnerable to two fundamental errors.[2,3]

Firstly, length time bias could occur by concluding that screening is beneficial because asymptomatic tumours diagnosed by screening may have been growing slowly for a long time. The second error, lead time bias, could occur when a tumour is detected early but the natural course of the disease and final outcome are not altered.

Digital rectal examination in non-randomly selected populations has been shown to be an insensitive device with poor predictive values of 26% and 22%.[4,5] In a similar study offering a free screening service that was publicised through local media and posters but no direct invitations digital rectal examination had a positive predictive value of only 29% and the important point was made that clinical staging understages the disease and pathological staging can upstage the tumour in a third of patients.[6]

Dr Pedersen and colleagues found 11 of 13 tumours to be "early"—of these patients, 10 underwent radical prostatectomy and one radiotherapy. The authors do not state how many of these patients underwent staging lymphadenectomy or whether on pathological staging there was evidence of lymph node disease or capsular invasion.

Although digital rectal examination may be sound medical practice and both cost effective and practical to set up in primary health centres, there is little evidence that it can achieve its target of reducing the morbidity and mortality from cancer of the prostate. The high prevalence of cancer of the prostate and its variable natural course require a prospective randomised controlled clinical trial to assess properly the value of mass screening.[5]

Transrectal ultrasound scanning studied in an uncontrolled trial was twice as sensitive as digital rectal examination.[7] It would be unethical to deny patients in the control group digital rectal examination, and therefore it would be reasonable to compare such examination alone and combined with transrectal ultrasound scanning. To prove that screening as proposed by Dr Pedersen and