shock syndrome and in three of 26 control strains; two of these latter strains were isolated from the vaginas of women with no history of toxic shock syndrome. This new enterotoxin has a molecular weight of 20 000 and an isoelectric point of 6.8 and induced vomiting when injected intragastrically into monkeys.

Further studies on staphylococcal toxins have been undertaken by Barbour,²¹ who detected an extracellular protein with a molecular weight of 22 000 and an isoelectric point of 7.0 in all of 15 strains causing toxic shock syndrome and half of 18 strains not causing the syndrome but isolated from the vagina. In Britain, de Saxe *et al*⁴ detected staphylococcal enterotoxin F in isolates from 10 of 12 patients with toxic shock syndrome and in 23% of 63 control strains, and they also found an extracellular protein band at 7.3 on isoelectric focusing in 10 of the 15 strains causing the syndrome. Whether or not all these toxins are the same is still not clear, nor has any been shown to be causative. Much remains to be elucidated.

Some other interesting theories have been propounded. Oskowitz²² has suggested that the pathogenesis of toxic shock syndrome may be related to prostaglandins, which seem to account for most of its clinical manifestations, while increased production of prostaglandins is known to occur in the endometrium at menstruation. He emphasises the need for circulating prostaglandins to be measured in patients with toxic shock syndrome.

Though toxic shock syndrome is clearly not only associated with tampons, the large number of cases that occurred in tampon users suggests some aetiological factor specific to tampon use and to Rely tampons in particular. Over the past few years synthetic "superabsorbent" materials have been incorporated into tampons, and microulcerations of the vagina have been shown to occur more often with the use of such tampons.²³ Rely tampons contained carboxymethylcellulose fibre in a unique "teabag" construction, thus rendering them particularly occlusive and absorbent (and thus very popular with American women). Furthermore, this synthetic fibre, thought to be inert and insoluble, has recently been shown to be liquefied *in vitro* by the cellulase activity of many Gram-negative bacilli,^{24 25} and microbial breakdown of carboxymethylcellulose might possibly occur *in vivo*. The relevance of this finding to the development of toxic shock syndrome is at present only speculative.

There is no justification at present for any suggestion that women should avoid using tampons, since the risk of developing toxic shock syndrome is extremely small. Equally unrealistic is the recent recommendation in a letter to the *Lancet*²⁶ (written by a man) suggesting that women should be instructed "at all times to exercise sparkling cleanliness handling or inserting tampons" and to avoid tampons when they have "infected pimples, paronychia, or a suspicion of a skin infection."

Predictably in view of the litigious atmosphere that prevails in the United States an 18-year-old American girl who developed toxic shock syndrome has begun a two-million-dollar damages suit against Proctor and Gamble; 200 further cases have been filed.²⁷

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¹ Schrock CG. Disease alert. *JAMA* 1980;**243**:1231.

² United States Department of Health and Human Services/Public Health Service. Toxic-shock syndrome—United States, 1970-1980. *Morbidity Mortality Weekly Report* 1981;**30**:25-9.

- ³ Holt P. Tampon-associated toxic shock syndrome. *Br Med J* 1981;**281**:1321-2.
- ⁴ de Saxe MJ, Wieneke AA, de Azvedo J, Arbuthnott JP. Staphylococci associated with toxic shock syndrome in the British Isles. *Ann Intern Med* (in press).
- ⁵ Neild G, Cameron JS. Tampon shock. *Lancet* 1980;ii:1196.
- ⁶ Anonymous. Toxic shock and tampons. *Br Med J* 1980;**281**:1426.
- ⁷ Williams ER, Macpherson J. Retrospective self-diagnosis of toxic-shock syndrome. *Lancet* 1981;ii:1042-3.
- ⁸ Whitfield JW, Valenti WM, Magnussen R. Toxic shock syndrome in the puerperium. *JAMA* 1981;**246**:1806-7.
- ⁹ Loomis L, Feder HM Jr. Toxic-shock syndrome associated with diaphragm use. *N Engl J Med* 1981;**305**:1585.
- ¹⁰ Jaffe R. Toxic-shock syndrome associated with diaphragm use. *N Engl J Med* 1981;**305**:1585-6.
- ¹¹ Lee RV, Dillon WP, Baehler E. Barrier contraceptives and toxic shock syndrome. *Lancet* 1982;i:221-2.
- ¹² Fisher CJ, Horowitz BZ, Nolan SM. The clinical spectrum of toxic shock syndrome. *West J Med* 1981;**135**:175-82.
- ¹³ Tack KJ. Possible tampon-associated toxic shock syndrome in a man. *Lancet* 1981;ii:1354.
- ¹⁴ Reingold AL, Dan BB, Shands KN, Broome CV. Toxic-shock syndrome not associated with menstruation. A review of 54 cases. *Lancet* 1982;i:1-4.
- ¹⁵ Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group I staphylococci. *Lancet* 1978;ii:1116-8.
- ¹⁶ Stevens FA. Occurrence of *Staphylococcus aureus* infection with a scarlatiniform rash. *JAMA* 1927;**88**:1957-8.
- ¹⁷ Aranow H Jr, Wood WB Jr. Staphylococcal infection simulating scarlet fever. *JAMA* 1942;**119**:1491-5.
- ^{17a} Dunnet WN, Schallibaum EM. Scarlet-fever like illness due to staphylococcal infection. *Lancet* 1960;ii:1227-9.
- ¹⁸ Schlievert PM, Schoettle DJ, Watson DW. Purification and physicochemical and biological characterization of a staphylococcal pyrogenic exotoxin. *Infect Immun* 1979;**23**:609-17.
- ¹⁹ Schlievert PM, Shands KN, Dan BB, Schmid GP, Nishimura RD. Identification and characterization of an exotoxin from *Staphylococcus aureus* associated with toxic-shock syndrome. *J Infect Dis* 1981;**143**:509-16.
- ²⁰ Bergdoll MS, Crass BA, Reiser RF, Robbins RN, Davis JP. A new staphylococcal enterotoxin, enterotoxin F, associated with toxic-shock syndrome *Staphylococcus aureus* isolates. *Lancet* 1981;ii:1017-21.
- ²¹ Barbour AG. Vaginal isolates of *Staphylococcus aureus* associated with toxic shock syndrome. *Infect Immun* 1981;**33**:442-9.
- ²² Oskowitz SP. Toxic-shock syndrome. *N Engl J Med* 1981;**304**:1040.
- ²³ Friedrich EG Jr, Siegesmund KA. Tampon-associated vaginal ulcerations. *Obstet Gynecol* 1980;**55**:149-56.
- ²⁴ Tierno PM Jr. Cellulase activity of microorganisms on carboxymethylcellulose from tampons. *Lancet* 1981;ii:746-7.
- ²⁵ Hanna BA. Microbial degradation of carboxymethylcellulose from tampons. *Lancet* 1982;i:279.
- ²⁶ Snelley WB. Preventing tampon-associated toxic shock. *Lancet* 1982;i:221.
- ²⁷ Thomas C. Doctor tells woman to avoid the coil. *The Times* 1982;Mar 5: 8 (col 7).

Of woodchucks and men: the continuing story of hepatitis B and hepatocellular carcinoma

"The greatest intellectual prize . . . a virologist can hope for is that some day he will be the first to explain . . . the natural history of serum hepatitis." So wrote F M Burnet in 1962.¹ Twenty years later many puzzles still remain, though there have been some notable advances, including most recently the discovery of the link between hepatitis B virus infection and the development of hepatocellular carcinoma. After the discovery of the Australia antigen,² later shown to be a marker of the surface coat of the hepatitis B virus (hepatitis B surface antigen; HBsAg), it soon became apparent that infection with hepatitis B virus is an antecedent rather than a complication of the development of a tumour³ and that areas of the world where the prevalence of HBsAg is high (up to 15% in some

populations) are the same areas in which hepatocellular carcinoma is most common. In studies from such areas—Africa,⁴ south Asia,⁵ and Japan⁶—HBsAg was found in the serum of up to 80% of those with hepatocellular carcinoma. The most convincing evidence, however, has come from a prospective study from Taiwan, in which over 22 000 Chinese men, 15% of whom were HBsAg-positive, have been studied for up to five years. To date, 41 cases of hepatocellular carcinoma have developed, and, of these, 40 were in patients who were HBsAg-seropositive.³

A causal relation between viral infection and eventual malignant change has been established in both naturally occurring and experimental animal tumours. For example, polyomavirus (a small DNA virus) infects mice and may cause a wide variety of tumours in other rodents.^{7 8} An early step in viral oncogenesis seems to be the integration of viral DNA into the host genome (that is, viral DNA is inserted and linked by covalent bonds into the host cell's DNA). This may also occur in some human tumours; examples include nasopharyngeal carcinoma and Burkitt's lymphoma with Epstein-Barr virus,⁹ and Kaposi's sarcoma with cytomegalovirus.¹⁰ Our ability to detect such molecular events has come from advances in recombinant DNA technology (for a very readable non-specialist review of this technique, see Emery¹¹). Such analysis requires tumour tissue. At first, specimens of hepatocellular carcinoma were difficult to obtain in the West, but development of a tissue-culture cell line from a Mozambican patient with HBsAg-positive hepatocellular carcinoma which produced HBsAg into the culture fluid¹² provided the starting material for several groups to employ recombinant DNA technology to test for integration of hepatitis B virus. In 1980 three groups reported that integration did occur, and one of these also reported similar findings in three further patients with hepatocellular carcinoma.¹³⁻¹⁵ A second source of material is the woodchuck (or groundhog, *Marmota monax*), a small American rodent. The woodchuck carries a hepatitis virus which is serologically related to human hepatitis B virus and which is also integrated into the DNA of woodchuck hepatocellular carcinoma tissue.^{16 17}

Two groups have now reported that tumour tissue from all the HBsAg-seropositive patients examined (22 in total) had integrated virus, the series including some patients in whom the only serological evidence of infection was the presence of antibody to the surface antigen (anti-HBs).^{18 19} Nevertheless, five patients with hepatocellular carcinoma and with anti-HBs alone in the serum did not have integration of the virus into the tumour, suggesting that this is not the sine qua non of tumour development—though, as the authors point out, analysis of tumour tissue when it is largely necrotic could give false results.¹⁸ The next step will be the result of studies in patients with hepatocellular carcinoma but with no serological evidence of infection with hepatitis B virus; in one such patient integration of hepatitis B virus has been found.¹⁹ Hepatitis B virus may therefore be an aetiological factor even in liver cancers thought up to now (on the basis of a negative serum HBsAg test result) not to be associated with the virus.

Somewhere within the undoubted association of hepatitis B virus infection, hepatocellular carcinoma, and the integration of hepatitis B virus into the host genome lies another association—namely, that of hepatocellular carcinoma and hepatitis B virus with chronic liver disease and cirrhosis. In areas of low incidence, such as Britain, about 80% of patients with hepatocellular carcinoma have preceding cirrhosis.²⁰ In areas of high incidence the data are less certain. The proportion of cases in which a necropsy is performed is low and even in these it may

be difficult to establish whether there has been pre-existing liver disease since the tumour tends to be rapidly growing and extensive.

Brechot *et al*¹⁹ found integration of hepatitis B virus into the liver cells in 14 HBsAg-positive patients, most of whom had inactive cirrhosis, and Shafritz *et al*¹⁸ detected integrated hepatitis B virus in two of five of their HBsAg-positive patients with non-malignant liver disease, both of whom were long-term carriers. Thus integration is probably a late event in the clinical course of infection with hepatitis B virus, and this leads to the attractive hypothesis that in susceptible people the hepatitis B virus causes either a healthy carrier state or chronic liver disease depending on the host's immunological reaction to the virus. After many years the virus becomes part of the host genetic material, and in some cases this may lead to malignant change.

An alternative hypothesis is that cirrhosis caused by any viral or hepatotoxic agent is associated with an increased risk of development of hepatocellular carcinoma, and that hepatitis B virus is but one of several such possible agents. With the prospect of effective vaccination against hepatitis B virus^{21 22} the distinction between the two hypotheses becomes largely academic, at least in the areas of high incidence. Purification and manufacturing costs of the current vaccines which have been developed with inactivated HBsAg derived from healthy human carriers are high, and Third World countries with large numbers of susceptible people seem unlikely to be able to afford the vaccine. Nevertheless, potentially cheaper approaches to vaccine development are now being actively pursued, including the use of polypeptide vaccines, genetic engineering techniques, and direct synthesis of certain amino-acid sequences of the hepatitis B virus responsible for eliciting the host immune response.²² Control by vaccination of what is probably the most common human cancer now seems on the horizon, but, with an estimated 200 million HBsAg carriers alive today, the problems associated with hepatitis B virus will still be with us for the next 50 years. This emphasises the importance of continuing research into other possible approaches such as antiviral chemotherapy in carriers.

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- 1 Burnet FM. *Natural history of infectious disease*. 3rd ed. Cheshire: Willmer Brothers, 1962:183.
- 2 Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukaemia sera. *JAMA* 1965;**191**:541-6.
- 3 Beasley RP, Hwang L-Y, Lin CC, Chien C-S. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981;iii:1129-33.
- 4 Vogel CL, Anthony PP, Mody N, Barker LF. Hepatitis-associated antigen in Ugandan patients with hepatocellular carcinoma. *Lancet* 1970;iii:621-4.
- 5 Tong MJ, Sun SC, Schaeffer BT, *et al*. Hepatitis-associated antigen and hepatocellular carcinoma in Taiwan. *Ann Intern Med* 1971;**75**:687-91.
- 6 Kubo Y, Okuda K, Hashimoto M, *et al*. Antibody to hepatitis B core antigen in patients with hepatocellular carcinoma. *Gastroenterology* 1977;**72**:1217-20.
- 7 Eddy BE, Stewart SE, Stanton MF, Marcotte A. Induction of tumors in rats by tissue-culture preparations of SE polyoma virus. *JNCI* 1959;**22**:161-71.
- 8 Eddy BE, Stewart SE, Kirchstein RL, Young RD. Induction of subcutaneous nodules in rabbits with the SE polyoma virus. *Nature* 1959;**183**:766-7.
- 9 Kaschka-Dierich C, Falk L, Bjursell G, Adams A, Lindahl T. Human lymphoblastoid cell lines derived from individuals without lymphoproliferative disease contain the same latent forms of Epstein-Barr virus DNA as those found in tumour cells. *Int J Cancer* 1977;**20**:173-80.
- 10 Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G. Kaposi's

sarcoma. 4. Detection of CMV DNA, CMV RNA and CMNA in tumor biopsies. *Int J Cancer* 1981;**28**:469-74.

- ¹¹ Emery AEH. Recombinant DNA technology. *Lancet* 1981;iii:1406-9.
- ¹² Macnab GM, Alexander JJ, Lacatsas G, Bey EM, Urbanowicz JM. Hepatitis-B surface antigen produced by a human hepatoma cell line. *Br J Cancer* 1976;**34**:507-15.
- ¹³ Edman JC, Gray P, Valenzuela P, Rall LB, Rutter WJ. Integration of hepatitis B virus sequences and their expression in a human hepatoma cell. *Nature* 1980;**286**:535-8.
- ¹⁴ Chakraborty PR, Ruiz-Opazo N, Shouval D, Shafritz DA. Identification of integrated hepatitis B virus DNA and expression of viral RNA in an HBsAg-producing human hepatocellular carcinoma cell line. *Nature* 1980;**286**:531-3.
- ¹⁵ Brechot C, Pourcel C, Louise A, Rain B, Tiollais P. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* 1980;**286**:533-5.
- ¹⁶ Werner BG, Smolec JM, Snyder R, Summers J. Serological relationship of woodchuck hepatitis virus to human hepatitis B virus. *J Virol* 1979;**32**:314-22.
- ¹⁷ Summers J, Smolec JM, Werner BG. Viruses in naturally occurring cancers. In: Essex M, Todaro G, zur Hausen H, eds. *Viruses in naturally occurring cancers*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1980:459-70.
- ¹⁸ Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC. Integration of hepatitis B virus DNA into the genome of liver cells in chronic liver disease and hepatocellular carcinoma. *N Engl J Med* 1981;**305**:1067-73.
- ¹⁹ Brechot C, Hadchouel M, Scotto J, et al. State of hepatitis-B virus DNA in hepatocytes of patients with hepatitis-B surface antigen-positive and antigen-negative liver diseases. *Proc Natl Acad Sci USA* 1981;**78**:3906-10.
- ²⁰ Edmondson HA, Steiner PE. Primary carcinoma of liver; study of 100 cases among 48 900 necropsies. *Cancer* 1954;**7**:462-503.
- ²¹ Szumness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med* 1980;**303**:833-41.
- ²² Zuckerman AJ. Developing synthetic vaccines. *Nature* 1982;**295**:98-9.

Dexamethasone deleterious in cerebral malaria

Quinine (given by intravenous infusion) is effective treatment for most patients with falciparum malaria even when this is complicated by coma, jaundice, or renal failure. About 20% of patients with falciparum malaria develop cerebral symptoms such as coma, convulsions, or confusion.¹ Mild coma may improve after a small dose of intravenous quinine or chloroquine, but deep coma may proceed to death despite treatment—and, indeed, the death rate in cerebral malaria remains at 20%. Coma of intermediate severity may persist for up to about 10 days and be cured only by painstaking titration of the dose of quinine, fluid balance, and other factors.²

Many additional forms of treatment have been tried in the hope of improving the prognosis of falciparum coma. In November 1967 Daroff *et al* described 19 patients with cerebral malaria, not all of whom were in coma.¹ Besides antimalarials, those more severely affected (number not specified) were given dexamethasone, dextran, and diphenylhydantoin. The report implied that this polypharmacy was effective. In July 1968 Woodruff and Dickinson described one patient with falciparum coma in this journal.³ He had acquired the malaria in India and had a parasitaemia of 5% on admission, which was reduced to 0.1% after intravenous chloroquine. The coma persisted, however, and 24 hours after its onset 10 mg of dexamethasone was given intravenously. Four hours later the patient woke. The authors concluded that "dexamethasone had a dramatic and life-saving effect" and recommended that dexamethasone should be given routinely in cases of cerebral malaria. Quickly, however, Harding commented that observations on a single

case were not conclusive and called for a controlled study.⁴ Another single case was reported in which a corticosteroid had not been helpful⁵; yet another writer considered that a controlled trial was not indicated,⁶ and Woodruff considered that such a trial would be unethical.⁷ The bandwagon rolled, and since 1968 all but a few books and review articles have recommended treatment with corticosteroids for cerebral malaria.

As long ago as 1972, however, a controlled study by Reid and Nkrumah found no benefit from dexamethasone in four patients.⁸ A review in the *BMJ* in 1976⁹ concluded that a controlled trial of corticosteroids in falciparum coma was long overdue because their value had not been established. Warrell *et al* have now compared dexamethasone with placebo in a double-blind trial in 100 patients (aged 6 to 70) in Thailand.¹⁰ In adults the initial dose of dexamethasone was 0.5 mg per kg followed by seven doses of 10 mg each. The total duration of treatment was 48 hours. Dexamethasone increased the duration of coma (63 versus 47 hours) and the incidence of complications including pneumonia and gastrointestinal bleeding. The authors concluded that dexamethasone is deleterious in cerebral malaria and should no longer be used. Those writing textbooks and review articles please note.

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¹ Daroff RB, Deller JJ Jr, Kastl AJ Jr, Blocker WW. Cerebral malaria. *JAMA* 1967;**202**:679-82.

² Hall AP. The treatment of severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1977;**71**:367-79.

³ Woodruff AW, Dickinson CJ. Use of dexamethasone in cerebral malaria. *Br Med J* 1968;iii:31-2.

⁴ Harding T. Cerebral malaria. *Br Med J* 1968;iii:250.

⁵ Smith DH, Harper PS. Cerebral malaria. *Br Med J* 1968;iii:618.

⁶ De Swiet J. Cerebral malaria. *Br Med J* 1968;iii:377.

⁷ Woodruff AW. Current practice in tropical medicine. *Trans Med Soc Lond* 1969;**85**:111-25.

⁸ Reid HA, Nkrumah FK. Fibrin-degradation products in cerebral malaria. *Lancet* 1972;i:218-21.

⁹ Hall AP. The treatment of malaria. *Br Med J* 1976;ii:323-8.

¹⁰ Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *N Engl J Med* 1982;**306**:313-9.

Lumbar spinal stenosis

The first recognisable example of lumbar spinal stenosis is provided by the achondroplastic Greek god Hephaestus, who limped as the result of trauma to an already narrowed spinal canal.¹ Spinal stenosis has become familiar only recently as an important cause of chronic debility—and one that responds to treatment. The term is used to describe any type of narrowing of the lumbosacral canal, nerve tunnels, or intervertebral foramina.² The L5 and S1 roots are especially vulnerable, since they run a long, oblique course within the spinal canal before changing direction to emerge through the exit foramina.³ Compression may occur at any level through central prolapse of a disc, as in the original case reports of intermittent claudication of the cauda equina (the Blau-Logue syndrome)⁴; from hypertrophic changes within a narrowed spinal canal; angulation through loss of disc height; with degenerative disc disease, Paget's disease, spondylolisthesis, and spondylolysis