

shigatoxin release by STEC organisms and so potentially worsen clinical outcomes. The most compelling evidence to date on the effects of antibiotic therapy on course of the disease comes from the report by Craig Wong and colleagues¹⁷ of a multicentre prospective review of 71 cases of confirmed *E coli* O157:H7 infection in children. It showed a strong statistical association between the development of HUS and early antibiotic therapy. Although a definitive prospective randomised trial of antibiotic therapy in acute STEC disease has not been conducted, the evidence to date is against the administration of antibiotics when STEC infection is a possibility. This has to include all cases of bloody diarrhoea until STEC (including non-O157 strains) have been excluded. Clinical judgment must prevail especially in the adult with multiple differential diagnoses.

What are the prospects for the reduction of HUS? As Wong and colleagues point out, society must review again the origins of STEC infections and its approach to food hygiene. The ability to rapidly identify STEC infection in appropriate clinical situations must be refined, and inconsiderate use of antimicrobials in cases of gastroenteritis should be limited. There remains the exciting possibility that with early recognition of infection there is an opportunity for intervention to block the pathogenetic process of toxin-mediated damage. The excellent clinical/scientific liaison in this emerging infection must continue.

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The new pan-asian paan problem

When Magellan's ship reached the Philippines in 1521, the ship's doctor recorded the practice of chewing pieces of areca nut with lime folded into a betel leaf (a preparation known in South Asia as "paan").¹ By then this habit had prevailed for at least 2000 years throughout south Asia, Southeast Asia, and the South Pacific. Although other ingredients, such as tobacco and various spices, are commonly added, paan almost always includes calcium hydroxide, areca nut (from the *Areca catechu* tree) and betel leaf (from the *Piper betle* vine). This basic recipe, which produces a pharmacologically addicting stimulant, may have been intentionally distributed, even millenia ago, just as opium, tobacco, and other popular narcotics have been or are more recently. The hindi word paan is preferable to the more conventional term betel quid, because the latter suggests a single ingredient, and tends to belittle an important issue by conjuring up the distracting image of a wad of red spittle in the mouth or on the sidewalk.

The link between use of paan and oral cancer has been recognised for more than a century,² and heavy users have a significantly increased mortality rate.³ Unfortunately, efforts to control the habit have been less ambitious, and generally less successful, than those to control cigarette smoking.⁴ A report from southern Taiwan by J-F Tsai and colleagues⁵ is likely to refocus attempts at control. It makes a convincing case for a link (OR 3.49, 95% CI 1.74–6.96) between use of paan and the development of hepatocellular carcinoma (HCC), a substantially more lethal neoplasm than oral cancer.

The chewing of paan is more widespread than is commonly realised. The habit is generally associated with south Asia, and although many people know that it is common in Southeast Asia and the South Pacific, the widespread use in Taiwan may come as a surprise. Moreover, even in countries where it is widely used, health authorities do not know the prevalence of use.⁶ Paan chewing is a traditional activity, closely tied to local cultural practices and ceremonies and often associated with aesthetically pleasing paraphernalia.¹ It is a cheap pleasure, indulged in to excess primarily by the least advantaged members of each society.

The conclusions of this case-control study are well supported by a modest but independent and dose-dependent association between the habit and liver cancer. As expected, liver cancer was more strongly associated with hepatitis B (OR 16.69, 9.92–28.07) or hepatitis C (38.57, 18.15–81.96), both prevalent in Taiwan, than with the chewing of paan. The most important finding, which should be confirmed as soon as possible, is that paan chewers infected with hepatitis B (synergy index 5.37) or C (1.66) were at greater risk of liver cancer than those with infection of either virus alone.

Paan chewing is a habit difficult to discourage. The threat of a superficial oral tumour does not seem to induce the same fear that cancer in a major organ does. Precancerous oral lesions can be successfully treated, but early detection requires the availability of regular dental services. Paan permanently discolours the teeth and anything it comes in contact with, and those willing to accept such stigmata do not quickly recognise the value of screening. Higher priority should therefore be given to strategies designed to prevent first use, now commonly in childhood.

Because tobacco is commonly included in the quid in most areas, control of paan usage is generally subsumed under programmes aimed at other forms of smokeless tobacco. Only recently have links been established between paan and oral cancer that cannot be explained by the inclusion of tobacco,⁷ which is not normally put into the mixture as used in Taiwan. Although paan is recognised to be hepatotoxic,⁸ the specific carcinogen is not known. Candidates in the mixture include nitrosamines and aracholine, a pharmacologically active alkaloid constituent of the nut, and contaminants, such as aflatoxin. Safrole, a known rodent hepatocarcinogen,⁹ is present in the betel buds and leaves, and safrole-DNA adducts have been found in the oral tissues of users¹⁰ and in the hepatoma cells of at least one user.¹¹ Although all the cancer cases among users with viral hepatitis had been cirrhotic, the results of Tsai and colleagues' study do not suggest a multiplicative synergism, as might be produced by a failure of detoxification. However, whether the additional risk of HCC conferred by paan in patients with viral hepatitis is due to failure of detoxification or whether it is independent of the general carcinogenic susceptibility of virus-induced regenerating liver cells remains to be determined.

Whatever the mechanism, if the results of the study in Taiwan are confirmed, much higher priority should go to paan-control programmes, not just in Taiwan. In south Asia, where the habit is most common, the prevalence of hepatitis virus is not high but is probably rising, and although the prevalence of HCC is even lower, that may also change quickly.

Paan usage in Taiwan is especially common among the least educated, such as agricultural workers and members of the aboriginal community, and also in the south of the country,¹² groups also at high risk of hepatitis.¹³ Despite government efforts at control, the prevalence is rising, unlike that of hepatitis, which is on the decline because of an effective vaccination programme. Entrepreneurs are buying land for the propagation of the areca palm and the betel vine.¹³ Their efforts include the setting up of urban outlets manned by girls in short skirts, reminiscent of early cigarette promotions.

Taiwanese entrepreneurial appetites may not stop there. Paan is now used in some areas of the People's Republic of China, traditionally by the minority population on Hainan¹⁴ and possibly by those near the Vietnamese border in Yunnan and Guangxi. However, except for localised areas of Hunan that are especially suited for growing the constituent crops,¹⁵ usage is modest among the Han majority. Direct commercial ties between Taiwan across the strait to the province of Fujian have increased greatly in recent months. HCC is one of the commonest cancers in China, in accord with the prevalence of hepatitis B virus and of food contaminated by aflatoxin. If those who market paan in Taiwan were to succeed in exploiting the large mainland market, the risk of HCC for many people in China would rise sharply. This commercial link with China is one that

should be strongly discouraged, both by Taiwanese and mainland authorities.

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Leprosy and the genome—not yet a burnt-out case

Important advances in optimisation of antimicrobial therapy in the 1980s led the World Health Organisation to declare elimination of leprosy as a public-health problem as one of its goals for the year 2000. Elimination was defined as a reduction in the prevalence of the disease below 1 in 10 000 of the population. In a formidable concerted effort, charities and governmental agencies have made major strides towards this goal. The current global estimate of the prevalence of leprosy stands at 1.25 cases per 10 000; 98 of 122 countries considered endemic in 1985 have reached the elimination goal; and more than 10 million patients have been cured.¹

Viewing disease in terms of the rate of detection of new cases rather than the total number of patients presents a less encouraging perspective. Although longstanding disease has been cured, there has been no sign of any reduction in the number of new cases. Case-detection has in fact shown a progressive increase over the past decade, reaching a current annual total of around three-quarters of a million. Most notably in India, saddled with more than