*Letters to the editor***Betel-nut chewing and diabetes in Papua New Guinea and elsewhere**

Dear Sir,

Boucher et al. [1] recently speculated that betel-nut (*Areca catechu*) chewing might have a role in the aetiology of non-insulin-dependent diabetes mellitus (NIDDM), and might at least partially explain the high prevalence of the disease in people of Asian origin living in Britain and elsewhere. Their hypothesis that nitrosamines present in betel-nut might induce either insulin-dependent diabetes (IDDM) or NIDDM or both was supported by experimental data which demonstrated an increased incidence of impaired glucose tolerance (IGT) in mice fed betel-nut (as well as in their offspring), compared to controls [1].

However, a consideration of epidemiologic data suggests that betel-nut chewing is unlikely to contribute much, if anything, to geographic patterns of occurrence of either IDDM or NIDDM. Firstly, IDDM appears to be generally uncommon throughout the parts of Asia, South-East Asia and the Western Pacific (as far south and east as the Solomon Islands) where betel-nut chewing occurs [2–4].

Secondly, while reliable information on the relative frequency of NIDDM and betel-nut chewing in different populations is not available, for populations of which we are aware there does not appear to be an obvious ecological relationship between the two. People of the Indian sub-continent are highly susceptible to NIDDM and IGT, the expression of which seems to be associated with modernization of lifestyle, and particularly with obesity and physical inactivity [5–7]. This is observed in both migrants to other countries [5, 6], and in those who remain in the Indian region [7]. We have documented a high prevalence of NIDDM in people of Indian origin in Fiji [5, 8] and Mauritius [6, 8], yet betel-nut consumption is rare to non-existent in those communities.

Similarly, the prevalence of NIDDM is high in many Pacific island Micronesian and Polynesian communities (e.g. Nauru, Kiribati, Western Samoa, Cook Islands) [8, 9] where betel-nut chewing is not practised. By contrast, betel-nut consumption is common in Melanesians of Papua New Guinea, but most studies there have found NIDDM to be rare [4, 8, 9].

As a more specific example, we cite data from Papua New Guinea, where we have recently performed a prevalence study of glucose intolerance in adults aged 25 years and above in three coastal and three highland villages [10]. At the same time we collected information on individual consumption of betel-nut. Table 1 displays the age-standardized prevalence of IGT and NIDDM (no cases of IDDM were identified), and

the frequency of betel-nut chewing by village. The coastal Wanigela people of Koki and Wanigela villages had by far the highest prevalence of glucose intolerance (over 50 % of adults in Koki), but negligible betel-nut chewing. Conversely, in the nearby coastal village of Kalo 91 % of subjects chewed betel-nut 6–7 days per week, yet the prevalence of NIDDM was only 1.6 %, and of IGT 3.0 %. Similarly, in the highland villages the frequency of current betel-nut chewing ranged between 43.6 % and 58.4 %, but glucose intolerance was uncommon.

The prevalence of glucose intolerance, and mean levels of fasting and 2-h (post 75-g glucose load) plasma glucose were also examined across betel-nut consumption categories (never, ex-chewer, 1–2 days/week, 3–5 days/week, and 6–7 days/week) in Kalo and the highland villages. There was no evidence of a trend for increases in any of these parameters with increasing betel-nut consumption.

In conclusion, although consideration of the ecological relationship between diabetes occurrence and betel-nut chewing throughout South Asia and South-East Asia is hampered by lack of data, there is little indication of an association for either IDDM or NIDDM. More directly, studies in Papua New Guinea show no association of the frequency of betel-nut chewing with fasting or post-load glucose concentrations, or the prevalence of glucose intolerance, either within or be-

Table 1. Age standardized prevalence of impaired glucose tolerance and non-insulin-dependent diabetes and frequency of betel-nut chewing by village

Village	Number	Age-standardized prevalence (%)			
		IGT	Diabetes	Betel-nut chewing	
				Overall	≥ 6 days/week
<i>Coast</i>					
Koki	750	21.0	30.3	5.1	2.5
Wanigela	541	17.0	11.7	1.1	0.6
Kalo	198	3.0	1.6	92.2	90.8
<i>Highlands</i>					
Masila	198	4.3	0.5	43.6	13.1
Gamusi	110	7.3	0.3	58.1	30.6
Gimisave	78	1.3	0.6	58.4	16.7

tween communities. These epidemiologic observations call into question the relevance of the finding that mice fed betel-nut have an increased incidence of glucose intolerance [1].

Yours sincerely,
G. K. Dowse

References

1. Boucher BJ, Ewen SWB, Stowers JM (1994) Betel nut (*Areca catechu*) consumption and the induction of glucose intolerance in adult CD1 mice and in their F1 and F2 offspring. *Diabetologia* 37: 49–55
2. Ramachandran A, Snehalatha C, Khader OMSA, Joseph TA, Viswanathan M (1992) Prevalence of childhood diabetes in an urban population in south India. *Diabetes Res Clin Practice* 17: 227–231
3. Karvonen M, Tuomilehto J, Libman I, LaPorte R (1993) A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 36: 883–892
4. Dowse GK (1990) Prevention and control of diabetes mellitus in Papua New Guinea. Assignment report (WP)NCD/ICP/NCD/001-E. World Health Organization, Manila
5. Zimmet P, Taylor R, Ram P, King H, Sloman G, Raper LR, Hunt D (1983) The prevalence of diabetes and impaired glucose tolerance in the biracial (Melanesian and Indian) population of Fiji – a rural-urban comparison. *Am J Epidemiol* 118: 673–688
6. Dowse GK, Zimmet PZ, Gareeboo H et al. (1991) Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. *Diabetes Care* 14: 271–282
7. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M (1992) Prevalence of glucose intolerance in Asian Indians: urban-rural difference and significance of upper body adiposity. *Diabetes Care* 15: 1348–1355
8. King H, Rewers M, WHO Ad Hoc Diabetes Reporting Group (1993) Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16: 157–177
9. Zimmet PZ, Dowse G, Finch C, Serjeantson S, King H (1990) The epidemiology and natural history of NIDDM – lessons from the South Pacific. *Diabetes Metab Rev* 6: 91–124
10. Dowse GK, Spark RA, Mavo B et al. (1994) Extraordinary prevalence of non-insulin-dependent diabetes mellitus and bimodal plasma glucose distribution in the Wanigela people of Papua New Guinea. *Med J Aust* 160: 767–774

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Response from the authors

Dear Sir,

We are grateful to Dr. Dowse for the additional epidemiological data that he has provided [1], in relation to our demonstration of the ability of betel-nut (*Areca catechu*) to induce glucose intolerance in mice [2], including data on betel-chewing and diabetes in man in areas where these prevalences both vary greatly. Were our hypothesis simply that betel-nut was a direct inducer of diabetes in individuals this data would throw doubt on the hypothesis that betel consumption could be relevant to the development of human diabetes [2]. However, since we reported that betel feeding produced comparatively little glucose intolerance in fed adults but produced a striking prevalence of glucose intolerance in the descendants of betel-fed animals, both in the F1 and F3 generations and also now in 22 % of the F4 generation [J.M.Stowers, personal communication], the hypothesis must be that betel consumption can induce an inheritable increase in susceptibility to glucose intolerance as well as glucose intolerance in some fed animals [2]. Betel-nut has been used by mankind since before 500 BC [3], and if it has had a similar effect in man to that seen in the mouse, it has had over two thousand years (and many generations) in which mutations may have been disseminated by population movements away from the areas in which the relevant exposure took place: this could apply to Indians now living in Fiji or Mauritius [1]. Studies of existing communities may not therefore be as useful in assessing a hypothesis of this sort as they have been in the investigation of habits which cause disease directly in the habitue, such as cigarette smoking in relation to lung and other cancers. The investigation of the betel-diabetogenicity hypothesis in man can be confounded by importation of the nuts to sites remote from the natural habitat of the *Areca* palms. It may well be further complicated by genetically determined susceptibility to betel-nut. It is

known for example that betel-induced submucous fibrosis, a pre-cancerous condition, occurs in the mouth of those with the HLA A10/DR3 genes [4] which are also associated with increased susceptibility to insulin-dependent diabetes mellitus. Susceptibility to low-dose streptozotocin as a diabetogenic compound is determined by HLA type in mice and can be inhibited by the concomitant administration of antisera to the susceptibility genes, HLA Ia, Ij, and Ie [5, 6]. Streptozotocin is a nitrosamide [7], and consumption of cured dried betel-nut is associated with the appearance of specific carcinogenic arecal nitrosamines in the blood and urine [8, 9], as well as in the saliva.

Consumption of fresh green betel-nut (without tobacco or cigarette smoking) is not associated with increased risk of oral cancer or with the production of arecal nitrosamines apart from N-nitrosoguvacoline (NG) [10]. Though populations eating fresh nuts do get oral cancer, this has been blamed on concomitant cigarette smoking [11]. The literature suggests that betel-nut is eaten green, i.e. fresh, in many areas including areas of Papua New Guinea [12]. If this is correct, the diabetogenicity of current betel use might relate only to the use of the cured/dried nuts. We would like to test this hypothesis if fresh green (uncured) nuts could be made available to us. Consideration of the intake of agents protective against arecal carcinogenicity, including use of green leaves to make quids, and specifically beta carotene and vitamin A [13], is also relevant in such studies since the leaves used in pan quids contain carotenoids [C.Mitchell, personal communication], and feeding beta carotene reduced rather than abnormally increased the size of pancreatic islets in betel fed animals [2]. It is of interest that fresh green nuts are said to be eaten with many parts of the *Piper* betel vine; seeds and stems as well as leaves, in Papua New Guinea [12], and that the leaves also contain the anti-

oxidant chavicol, as may other parts of the plant [14]. Various phenols, including those in tea in particular, inhibit damage from nitroso-compounds [15], whilst vitamin D deficiency, common in Asians in the northern hemisphere relates directly to reductions in insulin secretion [16], further complicating the dietary history needed for adequate assessment of individual glycaemia in relation to the diet, including betel-consumption.

Preliminary examination of dietary information covering these points in a British Asian community originating from Bangladesh, suggests a significant increase in body weight and in waist size in betel-chewers, but a reduction in spot blood glucose (after correction for age, sex and time after eating) [Boucher et al. unpublished data], which could be due to the hypoglycaemic action of arecoline [17], one of the psychoactive betel-nut alkaloids. Epidemiological data may not therefore be able to determine whether betel-nut has increased genetic susceptibility to diabetes, unless it includes the examination of appropriate susceptibility genes and their distribution in communities with varying prevalence of diabetes. Environmental triggers, such as affluence and physical inactivity provoke the appearance of diabetes in those who are susceptible, and such factors are usually taken into account in any investigation of factors relating to susceptibility or to precipitation of diabetes. Further studies in this field are hampered by uncertainty as to the genes associated with susceptibility to non-insulin dependent diabetes [18]. It is possible however that the search for genetic changes associated with the diabetes precipitated by betel consumption in susceptible animals may reveal genetic defects which have homologies with diabetic mutations in man. If these were amenable to study, they might help to explain the basis of susceptibility to the commonest but most in-explicable type of human diabetes.

Yours sincerely,

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References

1. Dowse GK (1994) Betel-nut chewing and diabetes in Papua New Guinea and elsewhere. *Diabetologia* 37: 1062–1063 (Letter)
2. Boucher BJ, Ewen SWB, Stowers JM (1994) Betel nut (*Areca catechu*) consumption and the induction of glucose intolerance in adult CD1 mice and their F1 and F2 offspring. *Diabetologia* 37: 49–55
3. Krenger W (1942) History and culture of betel chewing. Synthesis and preparation of betel (Ger.). *Ciba Z* 84: 2922–2941
4. Canniff JP, Batchelor JR, Dodi IA et al. (1985) HLA typing in oral submucous fibrosis. *Tissue Antigens* 26(2): 138–142
5. Tanaka SI, Nakajima AS, Inoue S et al. (1990) Genetic control by Ia subregions on H-2 complex of incidence of streptozotocin induced autoimmune diabetes in mice. *Diabetes* 39: 1298–1304
6. Kiesel U, Iscilewski M, Taniguchi M, Kolb H (1989) Modulation of low-dose streptozotocin-induced diabetes in mice by administration of antibodies to IA, IE and IL determinants. *Diabetologia* 32: 173–176
7. Herr RR, Jahnke HK, Arogoudelis AD (1967) The structure of streptozotocin. *J Amer Chem Soc* 89: 4808–4809
8. International Agency for Research on Cancer (1985) IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans; tobacco habits other than smoking; Betel-quid and Areca nut chewing; and some related nitrosamines (review) Betel-quid and Areca-nut chewing. 37: 141–200
9. Prokopyk BP, Rivenson A, Bertinato P et al. (1987) 3-(methylnitrosamino) propionitrile: occurrence in saliva of betel-chewers, carcinogenicity and DNA methylation in F344 rats. *Cancer Res* 47: 467–471
10. Stich HF, Rosin MP, Brunneman KD (1986) Oral lesions, genotoxicity and nitrosamines in betel quid chewers with no obvious increase in oral cancer risk. *Cancer Lett.* 31(1): 15–25
11. Atkinson L, Purohit R, Reay-Young P et al. (1982) Cancer reporting in Papua New Guinea. 1958–70 and 1971–78. *Monog Nat Cancer Inst* 62: 65–71
12. Pindborg JJ, Barmes D, Roed-Petersen B (1968) Epidemiology and histology of oral leukoplakia and leukoedema among Papuans and New Guineans. *Cancer* 22 (2): 379–384
13. Stich HF, Mathew B, Sankaranarayan R et al. (1991) Remission of oral precancerous lesions of tobacco/areca nut chewers following administration of beta-carotene or vitamin A, and maintenance of the protective effect. *Cancer Detect Prev* 15(2): 93–98
14. Sethi SC, Aggarwal JS (1956) Stabilization of edible fats by spices. Part 11. A new antioxidant from betel leaf. *J Sci Ind Res* 15B: 34–36
15. Stich HF (1992) Teas and tea components as inhibitors of carcinogen formation in model systems and man. *Preventative Med* 21(3): 377–384
16. Boucher BJ, Mannan N, Noonan K et al. (1994) Reduction in insulin secretion with vitamin D deficiency in Asians living in East London and improvement after treatment with vitamin D. *Diabetic Med* (1994) 11 [Suppl 1]: S 38
17. Chempakam B (1993) Hypoglycaemic activity of arecoline in betel nut *Areca catechu* L. *Ind J Exp Biol* 31(5): 474–475
18. Leahy JL, Boyd AE (1993) Diabetes genes in non-insulin dependent diabetes mellitus *New Eng J Med* 328(1): 56–58

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