Oral submucous fibrosis, areca nut and pan masala use: A case–control study

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Oral submucous fibrosis (OSF) is a chronic debilitating disease in which fibrous bands develop in the mouth. There is a marked intolerance for spicy food and opening the mouth becomes progressively more difficult. This disease does not regress and has no known cure. The most serious aspect of the disease is its precancerous nature. In a cohort study, the relative risk for development of oral cancer among OSF cases was 397.3 compared to individuals without any oral precancerous lesions after controlling for tobacco use. Several aetiological factors have been proposed, and the current consensus seems to be the habit of chewing areca nut. There is great concern about the increasing incidence of this disease in India, especially among adolescents and young adults.

A case–control study was undertaken in the Government Dental College and Hospital, Nagpur, Maharashtra where 200 consecutively diagnosed outpatients with OSF over a period of one year (June 1996–May 1997) were selected as cases. Every fifth outpatient was designated as a potential control, roughly matched for age. Almost all patients and controls were in the age range of 15–54 years and 16% of cases and 38% of controls were women. Details of areca nut and tobacco use were obtained by an interviewer-administered, structured questionnaire in a face-to-face interview.

A wide variety of areca nut and tobacco chewing habits were reported; the most common (50%) being the use of pan masala. Pan masala, which literally means betel quid mixture, is a commercially manufactured product almost always containing tobacco and areca nut. This is widely advertised, aggressively marketed and the industry has grown from scratch to almost a billion rupees within a few decades. The next most popular habit among patients was the use of kharra, a local preparation containing pieces of areca nut (7–8 g), a small amount of tobacco flakes, and drops of slaked lime, mixed, homogenized and wrapped in a cellophane paper ball. Other chewing habits were tobacco–lime and betel quid in different combinations. Table 1 shows the number of cases and controls according to the daily frequency of use of areca nut-containing products and the relative risk.

The relative risk and the trend for dose–response were highly significant (p<0.01). The relative risks were of the same order of magnitude as reported in earlier case–control studies.

The likelihood of an emerging epidemic of OSF seems to be justified by the present data. Over 70% of the cases were less than 35 years of age. Since almost all OSF cases use tobacco as well—and OSF is a high-risk pre-cancerous condition—an increase in the incidence of oral cancer can be predicted. In this study, 5.5% cases had associated oral cancer and 3.5% had associated leukoplakia. Urgent regulatory actions are, therefore, warranted to control the manufacture, marketing and consumption of products containing areca nut and/or tobacco, especially pan masala.

2 October 1998
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Medical education and health needs of a community

All countries spend a lot of money on technical education. Training medical personnel is more expensive than training other technical personnel. Undeniably, India needs more doctors who can deliver quality care to patients. Therefore, training of doctors is a hot and cold topic of discussion among medical personnel, hot because urgent reforms are needed and cold because of the frustration experienced by medical professionals over the listlessness that prevails.

The medical examination system

The medical examination system

The medical examination system
good MCQs is important and cannot be ignored for ever. The Americans have perfected the art of formulating MCQs by constantly evaluating and upgrading them and guarding against technical and legal criticisms. Our medical teachers are closed to the demands of objectivizing our examinations and one wonders if they are serious about teaching itself. As of now, teaching and examining are inseparable and both skills demand an identical professional competence.

It is conceivable that we can rise to the call for making theory examinations objective. Practical examinations are extremely difficult to improve. Subjectivity looms large over this aspect of examination. The usual components that are examined include the clinical and practical skills and practical knowledge that is assessed through *viva voce* examinations. Based on the structured pattern of examining candidates’ clinical skills introduced by the Royal College of Physicians, London, an effort was made in the late 1970s to innovate final MD (Internal Medicine) examinations at the Postgraduate Institute of Medical Education and Research, Chandigarh. The success of pilot runs embodied the Institute authorities to extend the system to all other subjects. Although there is a need to improve the methods further, these efforts brought into focus how we could be fairer to the examinees and the examination system if we concede that the examination system is flawed and requires improvement.

Recently, vice-chancellors of some universities in Uttar Pradesh opined that universities must be relieved of the job of examining. They felt that the primary role of teachers was to teach and update their knowledge. If they spent their energies in conducting examinations, they may not find sufficient time for their primary job—teaching. However, if teaching and examinations are delinked, how do others judge the candidates’ competence and suitability for jobs? One vice-chancellor thought that prospective employers must hold their own evaluation systems depending on what they are looking for. If one accepts this contention, the inescapable conclusion is that university education evokes no confidence in the students, employers or organizers of higher courses. Another conclusion is that there is a tremendous variation in standards of education and training between the universities.

About 25 years ago, a number of prominent medical educationists founded the National Board of Examinations (NBE) under the auspices of the National Academy of Medical Sciences with the idea of evolving a central and hence impartial system of evaluating postgraduate medical trainees. They meant to sever the link between trainers and examiners, because of the realization that the existing system permitted examiners to indulge in bountiful favoritism. They were aware that they would be up against several odds, the most important being the reluctance of the examinees to give up their power over the student community. When the cow was nearly milked the Government of India took over the NBE from the Academy, a few years after its inception, because its examinations had become popular with the students. The medical profession did not protest against the government’s high-handedness. A debate on the issue of the government taking over similar organizations is unlikely to yield a consensus even today, as we are divided in our views.

However, it is necessary to debate the delinking of teaching and examining medical students. I would plead strongly in its favour. The first argument for it is that given the tough competition in all these courses, teachers should morally and ethically consider themselves incapable of assessing their own students. If they do not abandon their current rights to examine, they will continue to be accused of influencing external examiners to obtain a favourable result (or an even more abhorred aspect of deliberately failing certain candidates). The second point relates to the similar predicament the external examiners find themselves in when they are hosted by the internal examiners. The third aspect is the examinees’ views which are of importance. Many of them have been brought up through school to believe that the entire system is unfair and rigged against them. Though some of them realize that it often helps them to pass, even if they do not perform well, they want far-reaching reforms in the examination system, which will provide them a level playing field. If the concept of a central examination is accepted and extended to entrance examinations, students will be saved from travelling to different centres to take examinations held in different parts of the country.

If the two aspects of teaching and examining are separated, it becomes imperative to think of a sound infrastructure and system. A uniform syllabus and teaching methods and the various components of examinations will have to be evolved. We may then dream to have independent examining organizations some day. There is need for further debate before we come to that stage. A possible benefit to teachers could be that they might have a shorter waiting period to become examiners, since presently heads of departments get a greater opportunity to examine.

Examinations have so many facets that it is not possible for anyone to come up with all the right answers. Having raised a number of issues, and provided no clear answers, I hope this letter will trigger a debate to help improve the prevailing medical examination system in India.

12 December 1998

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We report a case of recurrent mania with a seasonal pattern in a patient with head injury. To the best of our knowledge, seasonality in organic mania has not been reported.

**The case**

A 26-year-old businessman sustained a right parietal injury following an incident of mugging in 1974. On regaining consciousness after 3 days, he was noticed to be overtly cheerful and talkative, and had hallucinatory behaviour and decreased sleep, though he was fully conscious. He recovered spontaneously within 2 weeks.

Between 1978 and 1987 he had brief episodes (maximum duration 3 weeks) characterized by cheerfulness, oversocialization, overactivity, excessive spending and decreased sleep, annually in October–November. In 1989, he had one episode in February. He was treated with antipsychotics.

The patient developed right hemiparesis in 1991. A CT scan done at this time showed a leftthalamic infarct. No abnormality relating to the old injury could be detected. Since this facility was not available in 1974 when the patient had been injured, comparison with a previous scan could not be made. He recovered substantially within 3 months. He displayed no psychopathological abnormality for the next four years.

In April 1995, he became hypomanic. Though the severity of illness was less, the recovery period was 3 months. He was then referred to our centre. The haematological and biochemical tests were normal. The electrocardiogram, chest X-ray and electroencephalogram were also normal. Neuropsychological testing revealed poor performance on the visual retention subtest of the PGI memory scale,1 a discrepancy between verbal and performance intelligence quotients2 and marked perceptuo-motor dysfunction on the Bender–Gestalt1 and Nahar–Benson tests.3 His overall performance on the intelligence and memory tests was within normal limits. This suggested the presence of a brain pathology. He was treated with loroxamine and recovered completely.

Since 1985 the patient had developed diabetes and hypertension. These were under control. The past and family history were not contributory.

**Discussion**

Due to the presence of a temporal relationship between the head injury and the onset of manic episodes, and the absence of a past or family history of an affective disorder, a diagnosis of organic manic disorder (F06.30—ICD 10) was made.7 The patient also fulfilled the criteria for the same disorder according to the Diagnostic Criteria for Research of ICD 10.10

Manic episodes in bipolar patients have been reported to have a seasonal pattern, with mania occurring in winter.11 However, the occurrence of seasonality in organic manic disorder is unusual. One possible explanation could be that the head injury precipitated a seasonal affective disorder in a vulnerable person. The patient was in his third decade at the time of receiving the injury, so the absence of a past history of an affective episode does not run counter to this hypothesis. However, a negative family history weakens any argument for a vulnerability hypothesis.

A more likely explanation is that the head injury caused the seasonal organic mood disorder. The alteration in the course of the illness following the
second cerebral insult adds to this hypothesis. Right-sided cerebral pathology has been reported to be associated with mania, while left-sided basal ganglia pathology with depression. Thus, it was interesting that the manic episodes were associated with right parietal trauma, and there was a decrease in the frequency and intensity (though not the duration) following the left-sided thalamic infarct. Reports of cases such as this have the potential to generate hypotheses regarding the aetiologic relationships and the possible pathophysiological mechanisms underlying affective disorders.

4 December 1998
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Development of knowledge-based therapy for cancer: Identification of unique targets

Chemotherapy plays a key role in the treatment of cancer, but it suffers from lack of selectivity. This stems from the fact that the concepts of cancer chemotherapy evolved in an era when knowledge of cancer was rudimentary. Now with advances based on the cellular and molecular biology of several cancers, our knowledge base has grown enormously. Therefore, novel therapeutic agents directed against selective targets, specific to different cancers are being developed. These agents, when developed, are expected to target cancers effectively with minimum toxicity to normal cells. These novel agents will not merely be cytotoxic but may also be differentiation inducers, or induce selective apoptosis—programmed cell death. Among all cancers, chronic myelogenous leukaemia (CML) is unique, in that molecular defects of this disease are now well understood. With the discovery of the unique PHi translocation, our knowledge has extended to the molecular lesion resulting from this translocation and the consequences of the expression of this chimaeric gene.

It is now clear that the bcr-abl translocation confers auto-phosphorylation function to the tyrosine kinase which is encoded by this gene. The bcr-abl encoded tyrosine kinase is a 210 kD protein, which while preserving the kinase activity of its normal precursor p145 coded by c-abl, also acquires a constitutive expression as opposed to p145, a growth factor-regulated gene, induced by GM-CSF binding to its receptor on the committed myeloid progenitor (CFU-GM). It has been shown to be essential for myeloid differentiation. In its absence myeloid progenitors do not undergo clonal proliferation; thus affecting myelopoiesis.

Evidence that p210 is a transforming tyrosine kinase which plays a key role in the pathogenesis of CML, is now beyond doubt.

Transfection of cloned bcr-abl into normal stem cells has demonstrated its potential for transformation. An antisense oligonucleotide construct against a unique junctional sequence in the bcr-abl gene demonstrated that inhibiting the expression of bcr-abl leads to cell death (apoptosis). Therefore, two unique targets can be identified in the haemopoietic progenitors of CML patients—the nucleotide sequence forming the junction between the bcr and abl (the region has about 18 nucleotides) and the protein coded by this chimaeric gene, bcr-abl. This protein has a molecular weight of 210 kD and preserves the tyrosine kinase activity of the normal counterpart p145. However, with the bcr-abl translocation, the localization signal seen in p145 and, therefore, remains in the cytoplasm, where it may associate with the signal transduction elements located at the cell membrane. It is possible that some of these proteins may be aberrantly phosphorylated by this kinase. p210 also shows changes in the SHI, SH2 and SH3 domains which confer an increased half-life to this tyrosine kinase due to its inability to activate specific phosphatases. Of the two unique targets, the first can be exploited by an antisense oligonucleotide approach and the other by developing inhibitors specific to the target kinase. Both these approaches have recently shown promise as viable therapeutic approaches to treat CML.

The antisense nucleotide construct approach is remarkable for its simplicity and specificity. It consists of synthesizing an oligonucleotide which is antisense to a nucleotide sequence in the junctional region of the bcr-abl gene. This sequence has to be at least 18 nucleotides long to form a stable complex with the DNA transcript and inhibit translation into a protein product. Though antisense oligonucleotides can be against the target DNA sequence, as it ensures a higher efficiency in inhibiting the expression of the gene. This approach has shown excellent results in the in vitro system. However, there are some drawbacks. The major drawback is in delivering the antisense nucleotides in the patients. Even in the in vivo system, an extremely high extracellular concentration of the antisense oligonucleotide was needed before effective intracellular and intranuclear concentration of the antisense oligonucleotides could be achieved. This can be overcome by an appropriate delivery system such as the unilamellar liposome. The liposomes are capable of enclosing sufficient antisense oligonucleotides without much difficulty and delivering them into the cell. However, this method does not ensure delivery into the nucleus. In vivo, the liposomes are known to be sequestered by the reticulo-endothelial system, which may prove beneficial in case of leukemias. Conjuncting the liposomes with polyethylene glycol would allow for a longer circulation time.

Tyrosine kinase inhibitors, on the other hand, represent a novel approach which targets the p210 bcr-abl tyrosine kinase. Several phytochemicals, such as flavonoids, genistein and quercetin have been shown to have tyrosine kinase inhibitory activity. These compounds induce apoptosis and differentiation. Genistein inhibits proliferation of K562, a CML derived p210 bcr-abl expressing cell line. Both quercetin and genistein inhibit p210 bcr-abl expression.

Genistein inhibits clonal proliferation of myeloid progenitors (CFU-GM) from CML patients, while the progenitors from the normal human umbilical cord are minimally affected (unpublished observation). Druker et al. have shown that the kinase TKI which are more specific to the transforming kinase p210 bcr-abl can be synthesized by computer-aided molecular modelling.

Tyrophostins are another class of organic molecules that act as inhibitors of tyrosine phosphorylation involving a tyrosine kinase. Tyrophostins can be tailor-made for any of the substrates, are directed against the ATP-binding site of the substrate and do not bind ATP as kinase inhibitors do. Thus, the tyrophostins can be made for a specific substrate such as p210 bcr-abl leukemic cells, which are very unstable in circulation and may have to be modified for therapeutic use, though they have shown promise in the laboratory.

Unique targets have been identified in a few other cancers. Of these, acute promyelocytic leukemia is the most important, in which translocation occurs between chromosomes 15–17, involving the PML gene and the RAR-α gene. The PML gene controls myeloid differentiation and RAR-α codes for a nuclear receptor for retinoic acid. The PML-RAR-α fusion protein interferes with the nuclear receptor function by forming heterodimers with PML which accounts for the differentiation block. Retinoic acid-α can disrupt this complex and trigger restoration of nuclear body localization resulting in terminal differentiation, making this a unique treatment directly targeted at the causative genetic lesion. A recent interesting observation is that arsenic can bring about the same changes and by a similar mechanism as retinoic acid in acute promyelocytic leukemia.

Juvenile myelocytic leukemia, also known as juvenile CML, is a rare and lethal childhood
malignancy probably of clonal origin. It occurs as a result of endogenous secretion of GM-CSF by monocytes coupled with hypersensitivity of the progenitors to this cytokine. An antagonist to GM-CSF receptor E21R, has been constructed which binds to the α-chain of the GM-CSF receptor and inhibits clonal proliferation. Given the hypersensitivity of these progenitors to GM-CSF, E21R brings about their apoptosis.17

Another instance of a unique target which can be manipulated is the truncated EGF receptor in cancers of epidermal origin. Truncation of the EGF receptor makes it capable of autophosphorylation in the absence of EGF binding to its receptor.16 Mutant p53 is another specific target which has been shown to be a ubiquitous defect in many cancers.

Advances in our knowledge of the cellular and molecular biology of cancer will permit us to identify many more unique targets, which can be manipulated by drugs selective to these and thus eradicate these malignant cells without causing serious damage to normal counterparts. Such an advance will make cancer chemotherapy truly rational.

3 December 1998
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Competence in English and academic performance

It is conceivable that knowledge of English is one of the determinants of academic performance, as the medical literature is published and examinations conducted in the English language. This is particularly likely to be true in a multilingual country like ours where English is not the first language of most students. We are unaware of any studies in India which have addressed this issue in relation to medical education. Students at our medical college come from various parts of India and have gone through different examinations, making a comparison of marks obtained at the examinations prior to the medical course difficult.

Since objective assessment of competence in the English language by medical teachers is difficult and time-consuming, we asked students to rate their own competence in reading, writing and speaking English on a five-point Likert type scale. We are otherwise capable, may not perform as well at examinations because of a language problem, given the fact that they are already vulnerable to stress during the medical course.

There are several implications of this data:

1. Students’ evaluation of their own competence in English (as we did) may be a simple and useful surrogate for actual testing of competence, and will allow for identification of the bulk of students with difficulties in English.
2. Teachers need to be aware of this problem and examiners must frame questions without ambiguities in language, during both theory and viva voce examinations. Our findings suggest that problems with language affect performance in tests involving both written and verbal skills; the latter apparently persisting for a longer duration.
3. Students with a language problem will need interventions. In an earlier study, we found that students did not improve communication skills during normal learning experiences such as small group tutorials.6 This suggests that a specific programme to enhance competence in English is required. The challenge will be to devise an appropriate method to achieve this within a short time, particularly in view of the newly introduced shorter first MB,BS course.

While the present data are limited to our own

### Table I. Perception of competence in English and academic performance in Physiology at 6 months and 1 year

<table>
<thead>
<tr>
<th>Part of examination</th>
<th>Group 1 (n=30)</th>
<th>Group 2 (n=60)</th>
<th>Group 3 (n=27)</th>
<th>Overall value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Theory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average/Poor</td>
<td>49.6 (11.5)</td>
<td>50.3 (12.3)</td>
<td>57.4 (9.3)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Practical</td>
<td>29.2 (5.5)</td>
<td>31.0 (5.8)</td>
<td>32.5 (5.1)</td>
<td>p&lt;0.09</td>
</tr>
<tr>
<td><strong>Viva voce</strong></td>
<td>26.4 (4.8)*</td>
<td>28.4 (5.4)</td>
<td>29.9 (5.2)</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>At 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theory</td>
<td>56.9 (14.9)†</td>
<td>58.1 (10.8)†</td>
<td>59.9 (8.4)</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>Practical</td>
<td>29.7 (4.6)</td>
<td>31.6 (5.0)</td>
<td>32.5 (4.5)</td>
<td>p&lt;0.07</td>
</tr>
<tr>
<td><strong>Viva voce</strong></td>
<td>28.4 (6.1)‡</td>
<td>30.3 (5.2)‡</td>
<td>32.1 (3.5)‡</td>
<td>p&lt;0.03</td>
</tr>
</tbody>
</table>

The maximum marks were 100 in theory and 50 in both the practical and viva voce. All data are mean (SD). Comparison across groups using a one-way ANOVA with Scheffe, *p<0.05 Group 3 v. Groups 1 and 2 p<0.01, †p<0.05, paired ‘t’ test of 1 year v. 6 months within each group.
I have read with interest the correspondence, 'Indian medicine and the Nobel Prizes', which states that Professor S. N. De 'discovered the endotoxin of Vibrio cholerae which proved to be responsible for the symptoms of cholera'. However, a perusal of the correspondent's source of information, and a reproduction of De's classical paper, shows that in this work De and Chatterjee observed accumulation of fluid similar to cholera stool 24 hours after introduction of living Vibrio cholerae into loops of small intestine isolated by ligatures. While this work is notable for inventing an experimental model for testing the pathogene-
city of intestinal bacteria, it does not prove that Vibrio cholerae produces an exotoxin or endotoxin. A good account of the life and work of De by his colleagues, Sen and Sarkar, shows that De began working under the age-old belief that Vibrio cholerae produces an endotoxin but disproved it and showed that it was an exotoxin (which he called cholera enterotoxin) which was responsible for the outpouring of fluid in the intestine—
the fundamental pathology of cholera.

I felt deeply moved by a letter from Bagchi who tried to diagnose the ills of Indian medical research. Our medical research has certainly failed to rise to the expectation of the committee awarding the Nobel Prize in Physiology or Medicine. He puts the blame partly on our temperament and inadequate facilities. He also wonders whether the Nobel Prize Committee has a bias against us. Among various reasons that can be postulated, one is partly visible in this letter itself. Bagchi says that doctors doing research are almost non-existent in our country in comparison to the crowd of practising physicians. In making such a statement, he has probably forgotten that most Nobel Prizes in Medicine are won by scientists with non-medical qualifications and not medical doctors. Not that Indian doctors are not capable of winning a Nobel Prize. They certainly are. But the appreciation that medical research transcends barriers of academic degrees seems to be lacking in India. That good medical research can be done only by medically qualified doctors is a deep-rooted myth. This goes down to such an extent that it has generated bias in some cases against those medical scientists in India who do not have an MBBS tag. This bias is being perpetuated by some vested interests. I can list a large number of scientists in the USA who are not MD but have impeccable medical research to their credit. Many of our medical doctor colleagues still consider medical education and research their exclusive domain. The fact, however, is that modern medicine is multidisciplinary. Inputs from disciplines such as biotechnology and psychology are as important as from clinical and para-clinical disciplines. It would perhaps not be wrong to say that the frontiers of modern medical research are more 'non-medical' than 'medical' in the conventional sense. Medical research in India can reach its pinnacle when this fact is realized by our medical colleagues, and by administrators of medical institutions and organizations.


Erratum

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