

## SMOKING AND CHEWING OF TOBACCO IN RELATION TO CANCER OF THE UPPER ALIMENTARY TRACT

BY

L. D. SANGHVI, Ph.D.

K. C. M. RAO, M.Sc.

AND

V. R. KHANOLKAR, M.D.

*Indian Cancer Research Centre, Parel, Bombay, 12*

There is accumulating reliable and well-sifted evidence to suggest that the tendency for cancer generally to grow in man is about the same in most parts of the world. On the other hand, the "organ distribution" of cancer is often strikingly dissimilar in different groups of population, varies greatly from one country to another, and differs in different communities in the same geographical region. Thus, for instance, an earlier study (Khanolkar, 1950) showed that intraoral cancer was relatively more prevalent in Bombay than in New York or London. It accounted for 35.9% of all cancer cases at the Tata Memorial Hospital, Bombay, as against 16% of cancer cases in the New York and 6.7% in London hospitals. Further, even as regards the commonest site for the occurrence of oral cancer there is a noticeable difference in various localities in India. Cancer of the lip is the commonest type of oral cancer in Bihar, of the buccal mucosa and alveolar margin in Travancore and some parts of Madras, of the base of the tongue in

During recent years a large number of studies have demonstrated that there is an association between lung cancer and the amount of tobacco smoked (Doll and Hill, 1950, 1952, 1954; Levin *et al.*, 1950; Mills and Porter, 1950; Schrek *et al.*, 1950; Wynder and Graham, 1950; McConnell *et al.*, 1952; Koulumies, 1953; Sadowsky *et al.*, 1953; Wynder and Cornfield, 1953; Breslow *et al.*, 1954; Watson and Conte, 1954). So far as mouth cancer was concerned, it became evident that the habit of smoking and chewing tobacco, with or without other ingredients, called for a special investigation.

### The Investigation

In Western India the chewing of betel nut, betel leaf, and tobacco, and the smoking of locally prepared cigarettes ("bidis") are common habits.\* It was therefore decided to collect and analyse the information available in this respect in the records of the Tata Memorial Hospital. The routine form to be filled up for every patient who is registered in the hospital contains under the head "Personal History" an item "Habits (alcohol, tobacco, etc.)." In 1952 an analysis was carried out of the information collected in this column of the cases registered during the period 1941-9. The information was scanty in the case sheets of patients with cancer other than intraoral, and those suffering from non-neoplastic conditions. This circumstance did not permit a comparison of oral cancer cases with a control group. Even in intraoral cancer, information concerning these habits was not available in as many as 19.1% of cases. Nevertheless, an analysis of the available information on the habits of patients with

TABLE I.—Data on the Habits of Smoking and Chewing of Tobacco in Relation to Cancer of the Upper Alimentary Tract

	Men					Women				
	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total
Control: Non-cancer	69 (24.0%)	144 (50.0%)	25 (8.7%)	50 (17.3%)	288	—	7 (6.3%)	26 (23.2%)	79 (70.5%)	112
I: Buccal mucosa	42 (44.2%)	18 (18.9%)	28 (29.5%)	7 (7.4%)	95	—	—	19	5	24
II: Oral cavity (excl. group I)	58 (40.9%)	57 (40.1%)	23 (16.2%)	4 (2.8%)	142	1	2	19	6	28
III: Oesophagus	29 (39.7%)	33 (45.2%)	7 (9.6%)	4 (5.5%)	73	2	4	9	14	29
IV: Hypopharynx	56 (38.9%)	73 (50.7%)	11 (7.6%)	4 (2.8%)	144	1	1	4	2	8
V: Base of tongue	73 (38.2%)	105 (55.0%)	11 (5.8%)	2 (1.0%)	191	1	1	6	4	12
VI: Oropharynx	26 (30.6%)	54 (63.5%)	4 (4.7%)	1 (1.2%)	85	—	1	4	4	9
I-VI: Total	284 (38.9%)	340 (46.6%)	84 (11.5%)	22 (3.0%)	730	5 (4.5%)	9 (8.2%)	61 (55.5%)	35 (31.8%)	110
Misc.: Other cancer	28 (26.2%)	49 (45.8%)	14 (13.1%)	16 (14.9%)	107	3 (2.7%)	4 (3.5%)	24 (21.2%)	82 (72.6%)	113

Bombay, of the oral surface of the palate in Andhra, and of the hypopharynx in Assam. In Bombay, cancer of the inner lining of the cheek was four times more common among Deccani (Marathi-speaking) Hindus than among Gujarati Hindus, though their total attendance at the hospital was in the ratio of 3:2. Cancer of the base of the tongue and tonsils was more than twice as common among Gujaratis than among Decanis, and more than 9 out of 10 cases occurred in men, although the male to female ratio of attendance of Gujaratis was roughly 3:1.

A study of these relative differences revealed several facts of considerable interest, particularly as the communities under investigation showed notable differences in habits, customs, occupations, and nutritional status. It was therefore felt that a detailed analysis of such data may yield valuable information. It may also help in assessing the contributory role of hereditary and environmental factors in the production of cancer in man.

intraoral cancer at three different sites—namely, (1) buccal mucosa, (2) anterior third of the tongue, and (3) base of the tongue—seemed to indicate that the habit of chewing tobacco was more common in persons with cancer of the buccal mucosa and that the habit of smoking was more common among cases of cancer of the base of the tongue.

These tentative inferences obviously suggested that a systematic investigation of the chewing and smoking habits of patients with cancer of the upper alimentary tract, if it was carried out along with a corresponding control series of "no cancer" and "other cancer," was worth while. A detailed questionnaire was therefore drawn up and filled in for 1,460 new patients who attended the clinic during the years 1952-4. The present paper deals with an analysis of the data collected for the purpose of this investigation.

\*A short note on the substances used for chewing and smoking in Western India is given in the Appendix.

**Data**

Table I contains the data on smoking and chewing of tobacco. Patients who were referred to the cancer clinic for a "check-up" and who showed no evidence of neoplastic disease were taken as the "control group." Cases of cancer of the upper alimentary canal in men were numerous enough for further analysis. There was a sufficient number of cases of cancer of the buccal mucosa to treat these as a single group (Group I). The rest of the cases of oral cancer (Group II) included: cancer of anterior tongue, 56; cancer of alveolus, 39; cancer of palate, 37; cancer of lip, 6; and cancer of floor of mouth, 4. Group VI (cancer of oropharynx) included 54 cases of cancer of the tonsil. Further analysis was not possible for women, owing to the small number of cases. The "other cancer" group consisted of cancer at sites other than the upper alimentary canal, and cancer of the breast and cervix uteri predominated in women.

The data in Table I are graphically presented in Fig. 1, which shows the percentages of smoking and chewing of tobacco in cancer cases. In Fig. 2 the percentages of men

addicted to smoking and chewing are added to those accustomed to smoking only, so as to obtain the total percentages of "all smokers." Similarly, those smoking and chewing are added to persons accustomed to chewing tobacco to give the percentage of "all chewers."

The figures show that for both men and women the "non-cancer" group is similar to the "other cancer" group in smoking and chewing habits. Women with cancer of the upper alimentary tract show a higher incidence of smoking and about two and a half times the incidence of chewing compared with the control group. In men the results are more striking. It is possible to see several gradients in the incidence of habits among the different types of cancer. The proportion of men with "smoking and chewing" habits is higher in all the six groups compared with the control group, showing a diminishing proportion from group I to group VI. Similar gradients are also seen with "no habit" and the habit of "chewing only"; whereas a reverse gradient is seen with the habit of "smoking only." Fig. 2 shows the gradients of smoking and chewing separately for groups I to VI and for the control group.

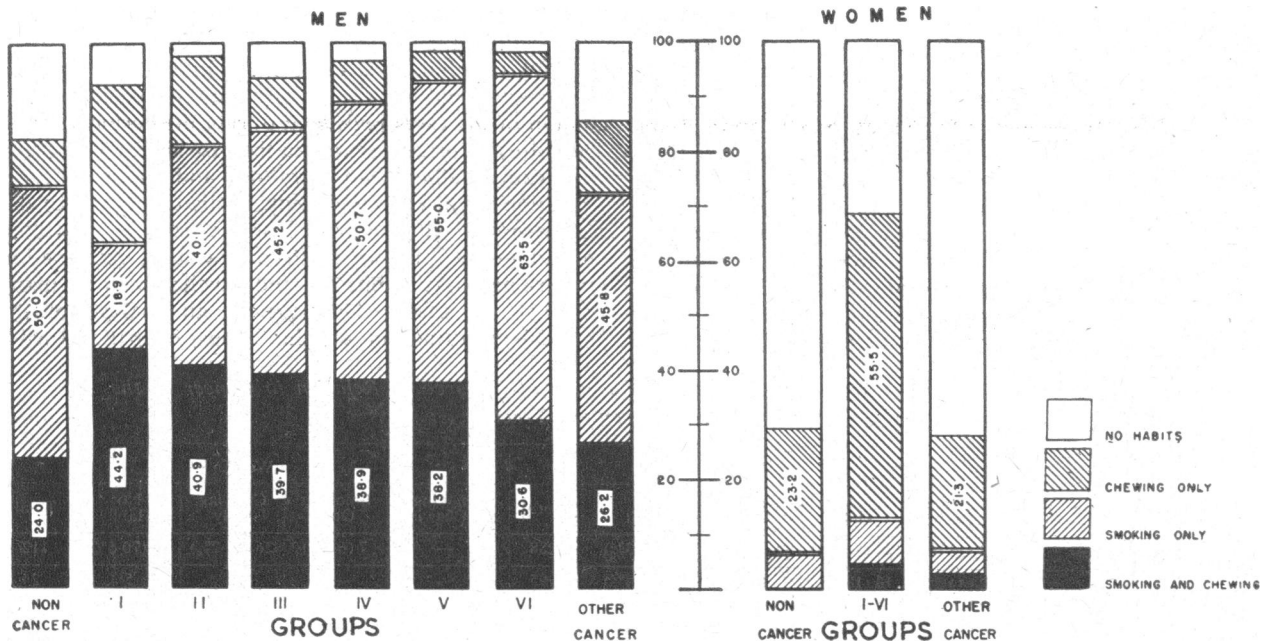


FIG. 1.—Analysis of cases of cancer of upper alimentary tract in relation to tobacco habit.

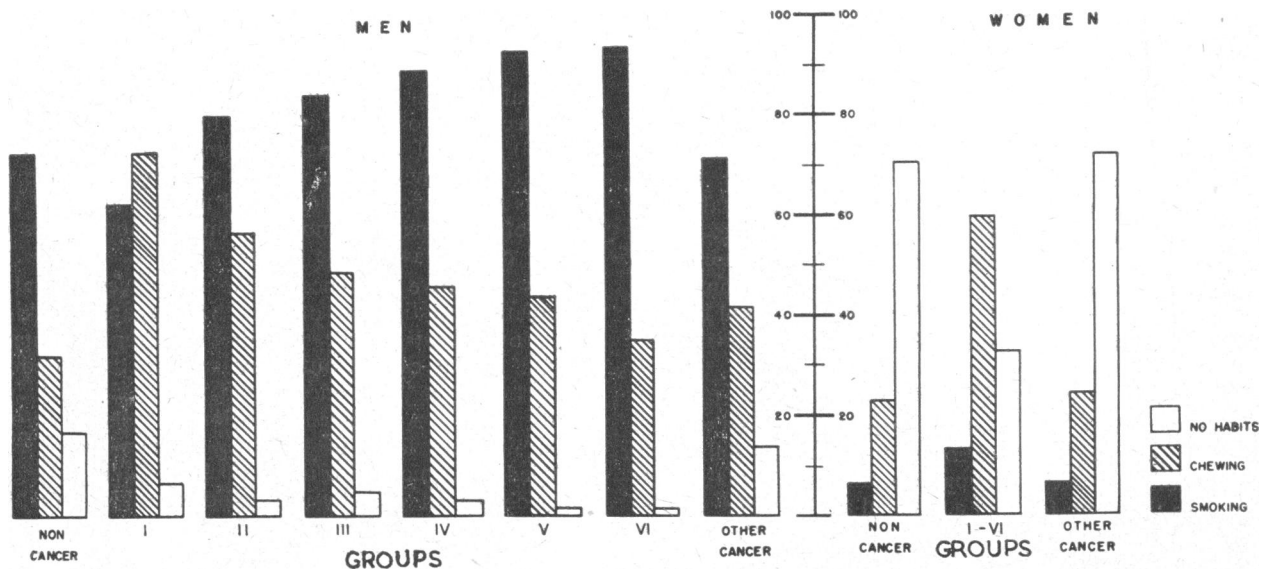


FIG. 2.—Percentage of "all smokers" ("smoking and chewing" plus "smoking only"), "all chewers" ("smoking and chewing" plus "smoking only"), and of those with no habits.

**Statistical Analysis**

It was necessary to take into account four variables—community, age, occupation, and sex—for purposes of evaluating the statistical significance of the smoking and chewing of tobacco in relation to cancer of the upper alimentary tract. As the two sexes presented very different patterns in habits, they were treated separately. No further analysis was carried out on the data on women owing to the small number of cases. For men, the data concerning community and age could be broken down into well-defined classes. Table II shows the differences in the smoking and chewing habits in the “non-cancer” group with respect to these two variables.

TABLE II.—Percentage of Smokers and Chewers Among Non-cancer Men Classified According to Community and Age

	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	No. of Persons
<b>Community:</b>					
Hindu Deccani	31.9	39.8	12.4	15.9	113
“ Gujarati	9.2	70.4	—	20.4	54
Muslim	27.3	43.6	10.9	18.2	55
Other	19.7	56.0	7.6	16.7	66
<b>Age:</b>					
Less than 50	21.7	50.2	10.2	17.9	207
50 to 60	30.9	45.5	5.4	18.2	55
More than 60	26.9	57.7	3.9	11.5	26

An attempt to subdivide data dealing with occupation in different classes turned out to be unprofitable. It was necessary to introduce so many groupings that finally it was difficult to justify them. Moreover, an analysis carried out on such groupings did not change the significance pattern of the types under consideration.

Dr. C. A. B. Smith, of the Galton Laboratory, London, suggested a method of analysis suitable for the present purpose. The method in essence consisted in breaking down the cancer and control cases into a number of cells for which it could reasonably be assumed that the internal variability had been substantially reduced and studying the difference and its variance for each cell. Such differences and variances could then be weighted and added to give the significance for the whole group.

Consider the following cell:

	With Habit	Without Habit	Total
Cancer cases	$a_r$	$b_r$	$a_r + b_r$
Control	$c_r$	$d_r$	$c_r + d_r$
Total	$a_r + c_r$	$b_r + d_r$	$a_r + b_r + c_r + d_r = n_r$

$$\text{Difference } D_r = \frac{a_r}{a_r + b_r} - \frac{c_r}{c_r + d_r}$$

$$\text{Variance of difference } D_r = \frac{(a_r + c_r)(b_r + d_r)}{(a_r + b_r)(c_r + d_r)(n_r - 1)}$$

This variance is calculated on the basis of the exact distribution, keeping the marginal totals fixed.

The weighted combination of differences  $D = \sum W_r D_r$ , summed over all the cells, accordingly has the variance  $V = \sum W_r^2 \text{ var } D_r$ .

The weights  $W_r$  can be chosen arbitrarily, provided that, of course, they are decided upon previously and not in-

fluenced by the observed experimental results. Since the larger cells will give more reliable information than the smaller ones, it seems reasonable to take the weight  $W_r$  to be proportional to the total number  $n_r$  of observations in the cell. That is, we can take  $W_r = \frac{n_r}{N}$ , where  $N = \sum n_r$ .

It is obvious that the method will fail if there are no cases, either cancer or control, in any particular cell. This limitation made it necessary to restrict the analysis to three age groups—namely, under 50, 50 to 60, and over 60. Table III gives the weighted differences, and their standard errors.

This analysis shows that the habit of chewing is associated with cancer of the oral cavity (groups I and II). It shows that the combined habit of smoking and chewing is associated with cancer of the hypopharynx (group IV) and of the base of the tongue (group V). Finally, only smoking is associated with cancer of the oropharynx (group VI) and of the oesophagus (group III). There is no significant difference in smoking and chewing habits in patients with other cancers compared with the “non-cancer” group.

It was possible to make a further analysis of the smoking habit. Of the persons who smoked, 88.7% smoked bidis. During the course of the investigation, information was collected about the number of cigarettes (bidis) smoked by the patients. This information must admittedly be approximate because, even if the exact number smoked could be ascertained, there is bound to be a variability in the length of the bidis smoked by different persons. Table IV gives the average number of bidis smoked by the men in the various groups.

TABLE IV.—Number of Bidis Smoked Daily by Patients (Men) With Different Types of Cancer of the Upper Alimentary Tract

Control group.	Non-cancer	14.1 ± 0.6
Group I.	Buccal mucosa	12.5 ± 1.1
“ II.	Oral cavity (excluding group I)	14.6 ± 0.8
“ III.	Oesophagus	15.3 ± 1.2
“ IV.	Hypopharynx	16.9 ± 0.8
“ V.	Base of tongue	17.4 ± 0.7
“ VI.	Oropharynx	18.5 ± 1.0

It is interesting to note that the percentage of smokers and the average number of bidis smoked show a similar trend in groups I to VI. It was not possible to carry out a further analysis of the chewing habit, as the quantities reported were often unreliable. Information regarding the duration of smoking and chewing was also unreliable.

**Discussion**

Experimental work on cancer has made it clear that to resort to a single or a simple explanation for the aetiology of cancer, however tempting it may be, is likely to result in failure. The contributory factors may be broadly grouped as hereditary and environmental. Such a classification is probably arbitrary, but it satisfies the needs of the present discussion.

The present study indicates that tobacco may be one of the environmental factors responsible for a large number of cases of cancer of the upper alimentary tract seen at the Tata Memorial Hospital. These populations differ sharply from other populations in their habits of tobacco chewing. The habit of chewing tobacco and the associated types of cancer lead to an assumption of the existence of a sub-

TABLE III.—Statistical Significance of the Differences in Smoking and Chewing Habits in Patients (Men) with Different Types of Cancer Compared with the “Non-cancer” Group

Group	Smoking and Chewing	Smoking Only	Chewing Only	No Habit	Total Smokers	Total Chewers
I: Buccal mucosa	0.133 ± 0.057*	-0.233 ± 0.071†	0.175 ± 0.040†	-0.075 ± 0.058	-0.100 ± 0.066	0.308 ± 0.061†
II: Oral cavity (excl. group I)	0.200 ± 0.048†	-0.157 ± 0.051†	0.100 ± 0.034†	-0.143 ± 0.036†	0.043 ± 0.046	0.300 ± 0.050†
III: Oesophagus	0.137 ± 0.066*	0.017 ± 0.076	-0.014 ± 0.041	-0.140 ± 0.053*	0.134 ± 0.065*	0.123 ± 0.070
IV: Hypopharynx	0.160 ± 0.046†	-0.021 ± 0.052	0.000 ± 0.030	-0.139 ± 0.036†	0.139 ± 0.044†	0.160 ± 0.049†
V: Base of tongue	0.200 ± 0.046†	-0.040 ± 0.049	-0.005 ± 0.027	-0.155 ± 0.032†	0.160 ± 0.040†	0.195 ± 0.048†
VI: Oropharynx	0.109 ± 0.062	0.083 ± 0.070	-0.030 ± 0.041	-0.162 ± 0.050†	0.192 ± 0.061†	0.079 ± 0.067
Misc.: Other cancer	-0.023 ± 0.051	-0.006 ± 0.059	0.051 ± 0.036	-0.022 ± 0.046	-0.029 ± 0.054	0.028 ± 0.055

\* Shows significance at 5% level. † Shows significance at 1% level.

stance or substances in tobacco which may initiate or promote the production of cancer at the sites of prolonged contact.

The marked differences in the chewing and smoking habits among the Deccanis and the Gujaratis partly explain the differences in the incidence of cancer of the buccal mucosa and of the base of the tongue in these two communities. They also presumably explain the striking difference in the incidence of base of tongue cancer in the two sexes.

It is, however, not possible to explain all the differences on the basis of the habit of smoking and chewing of tobacco, as in all the types of cancer of the upper alimentary tract there were some persons who did not smoke or chew tobacco at all. Therefore it is necessary to explore other environmental and hereditary factors.

Sanghvi and Khanolkar (1949) encountered striking differences in the distribution of seven genetical characters among the six endogamous groups in Bombay. Data were obtained on the ABO, A<sub>1</sub>A<sub>2</sub>, MN, P, and Rh blood groups, taste reactions to phenylthiocarbamide, and colour vision. One endogamous group belonged to the Gujarati Hindu community, and the rest to the Deccani Hindu community. No information is available about the association of susceptibility to cancer of the upper alimentary tract with genes responsible for the above characters. It may, however, be suggested that similar differences exist for many of those genes responsible for susceptibility to cancer among different communities in India as well as in the rest of the world.

Strong and Sanghvi (1951), as a result of their study on the effects of selection on chemically induced tumours in mice, suggested tentatively that the control of tissue susceptibility to cancer might be at a different level in the mechanism of heredity than total susceptibility to cancer. They found that in mice, by selecting breeders with a longer and longer latent period (time between the injection of carcinogen and development of tumour), large variations could be brought about in the sites at which the two sexes of mice developed tumours during the course of 16 generations, without affecting to any appreciable extent the total incidence of cancer. The net result of the experiment was to increase considerably the latent period and hence the life-span of the mice which developed tumours. The mice therefore developed tumours at the sites which took an increasingly longer time interval to develop them. Such differences in the tissue susceptibility may offer one of the reasons for the habit of smoking affecting the mucosa of the upper alimentary tract in one population and the lung in another. There exists a possibility that the physical state and internal dispersal of smoke particles from bidis might differ from those of ordinary cigarettes.

### Summary

The 1,460 patients who attended the cancer clinic during 1952-4 were questioned regarding the habit of smoking and chewing of tobacco in relation to cancers of the upper alimentary tract. Results of the statistical analysis showed that the habit of chewing was associated with cancer of the oral cavity; that the combined habit of smoking and chewing was associated with cancer of the hypopharynx and base of the tongue; and that only smoking was associated with cancer of the oropharynx and oesophagus. These findings are discussed.

### APPENDIX

The Indian form of cigarette is known as bidi, a smoke for the common man in the country. It is made by rolling with the fingers 0.25 to 0.5 g. of tobacco flakes in a rectangular piece of dried leaf of temburni (*Diospyros melanoxylon*). Leaves of other genera and species such as *Bauhinia racemosa*, *Bauhinia vahlii*, *Butea frondosa*, and *Castanopsis indica* are also used for wrapping the tobacco. Out of about 50 known species of tobacco, only two are

grown in India—namely, *Nicotiana tabacum* and *Nicotiana rustica*. Both types are used for making bidi, as well as for chewing. The tobacco is usually sun dried and cured. Bidis vary in length from 5 to 8 cm. (Fig. 3). They are conical in shape, with the tucked end (the end which is lighted) broader than the end which is held between the incisor teeth. This end is tied with a thread and flattened by pressing.

In Western India the common ingredients used for chewing are betel nut, betel leaf, and tobacco. The betel nut is the fruit of the areca or betel palm (*Areca catechu*). The betel leaf is the leaf of the betel vine (*Piper betle*). Cracked or powdered dried betel nut, or slices, may be chewed alone along with a preparation of betel leaf, known as

pān. Pān is prepared by applying slaked stone or shell lime and catechu to a betel leaf, and wrapping it around pieces of betel nut, with spices like the cardamom, cloves, aniseed, and several others. Catechu is an extract obtained from the wood of two species of acacia (*Acacia catechu* and *A. suma*). In Gujarat, plain tobacco is sometimes added in the preparation of a pān, whereas in the Deccan the dried and cured tobacco is commonly chewed along with betel nut and lime.

The active co-operation of our clinical colleagues at the Tata Memorial Hospital, particularly Drs. J. C. Paymaster and P. D. Schroff, made it possible for us to collect the data which have been analysed above. We should like to record our gratitude to our colleagues and to Dr. C. A. B. Smith, of the Galton Laboratory, London, for his suggestion of an appropriate statistical method.

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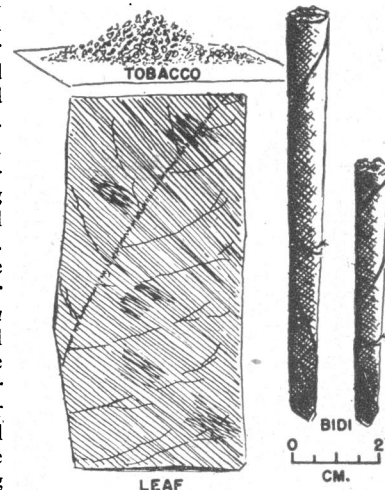


FIG. 3.—Indian cigarette (bidi).

Mr. KENNETH PICKTHORN speaking on April 26 in a Parliamentary debate on education: "Everyone goes on repeating the stuff about science getting more and more specialized, technicalized, departmentalized, compartmentalized, and my impression, not as a scientist but as a man who has spent his life partly in intimate conversations with many of the greatest and best-informed scientists, is that the opposite has been the fact for some considerable time: the sciences have all tended more and more, during the last 20 years especially, to approximate to mathematics, and to need mathematics for any understanding of them. In that sense they have come together again."