Introduction

Data accumulated in past years suggest that host factors may operate to confer greater or lesser susceptibility to carcinogenic action. Such variable susceptibility factors might explain why only 10–15% of cigarette smokers develop lung cancer. Several biochemists have alluded to the possibility that in humans sensitivity to environmental carcinogens and cancer susceptibility may be a reflection of individual variation in DNA repair capability (1, 2). A working hypothesis proposed by Hsu (3) expanded this concept more explicitly and considered the use of mutagen sensitivity as a biological marker for carcinogen susceptibility. This review presents a summary of results obtained over the past eight years.

Although the molecular mechanisms of mutagens vary, the end result is the same, i.e., gene mutation and/or chromosome breakage. Estimating mutations in mammalian and human cells requires a rather elaborate setup and time-consuming procedures, but enumerating chromosome aberrations, especially chromosome breaks, is relatively simple. One should keep in mind, however, that chromosome breaks represent only a fraction of the total mutation output, because most gene mutations are not microscopically detectable. But a spot of a leopard skin at least gives us an opportunity of imagining the entire animal. Thus assays of mutagen effects on human or mammalian cells, using chromosome breakage frequency as a criterion, serve a useful purpose.

It should also be borne in mind that, unlike many toxic substances (such as cyanides and carbon monoxide), the toxicity of mutagens or clastogens (agents that can cause chromosome breakage) is seldom immediately fatal. The principal targets of mutagens and clastogens are cellular DNA and chromosomes, and their toxicity is insidious. Most mutations and chromosome aberrations, once established, persist, unless the cell dies or a reverse mutation occurs. A cell with induced mutations can accumulate additional mutations, thus increasing the danger of acquiring, in a specific tissue cell, appropriate genetic alterations that can initiate neoplastic conversion.

Mutagen Sensitivity in Chromosome Instability Syndromes

If permanent genetic alteration is to be avoided, genetic damage induced by carcinogens must be repaired. It has been hypothesized that there may be a spectrum of DNA repair capabilities within the general population (3). At the extreme end of the spectrum are patients with chromosome breakage syndromes. These diseases are characterized by high rates of spontaneous chromosome breaks, unusual susceptibility to induction of breaks by clastogens, and increased cancer risk. Although such syndromes occur infrequently, their unique cytogenetic and biochemical characteristics have thrown much light on the problem of genetic predisposition to cancer. In fact, our own work stemmed from the progress in studies on the chromosome instability syndromes.

In chromosome preparations of patients with Bloom’s syndrome, German (4) found a unique phenomenon, i.e., many cells exhibited a high frequency of chromosome breakage and rearrangements. This particular phenotype was found to be characteristic of Bloom’s syndrome, suggesting that the Bloom’s genotype has a defect that causes DNA (hence chromosomes) to fracture. Of more significance was the correlation between chromosome instability and cancer proneness, because most Bloom’s patients eventually succumb to cancer.

In the following years cytogenetists found several more syndromes that also exhibited chromosome instability. These well-documented syndromes are Fanconi’s anemia, ataxia telangiectasia, Werner’s syndrome, and XP. Except for XP, all the other syndromes share two properties: high rates of spontaneous chromosome breakage and a propensity for cancer development (5).

XP is included in the instability syndromes, even though XP patients do not exhibit a spontaneous chromosome breakage rate higher than that of normal individuals, because they are particularly sensitive to UV light. When XP cells are UV irradiated, they exhibit a higher rate of chromosome breakage than cells of normal persons and of other instability syndromes (6, 7). It is well known from biochemical investigations that UV light induces pyrimidine dimers in DNA if two pyrimidines are situated adjacent to each other on the same DNA strand. There also has been good evidence to show that in living cells a repair mechanism, employing excision repair enzyme, operates by cleaving off the damaged DNA segment, thus allowing DNA polymerase to synthesize a new segment by using the undamaged, complementary strand as its template.

Received 6/17/91.

1 To whom requests for reprints should be addressed, at Box 181, Department of Cell Biology, M. D. Anderson Cancer Center, Houston, TX 77030.

2 Present address: Department of Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10021.

The abbreviations used are: XP, xeroderma pigmentosum; b/c, chromatid breaks per cell; OR, odds ratio.
In microorganisms, investigations on mutants sensitive to UV light have revealed that these mutants are deficient in the excision repair mechanism. Therefore, the DNA lesions are not repaired following UV irradiation, and mutations or cellular death will result. The genetic defect of XP patients is apparently the same, i.e., deficiency in excision repair (8, 9). XP individuals, therefore, develop multiple skin malignancies in sun-exposed body areas, because mutations and chromosomal aberrations are not corrected.

Although much work remains to be done on the chromosome instability syndromes, available information suggests several important conclusions:

(a) Patients with chromosome instability syndromes also have defective DNA repair systems, but not the excision repair (10, 11). There is reasonably good evidence to show that patients with the N syndrome (12) have a defective DNA polymerase α (13). It is quite possible that ataxia telangiectasia cells, being hypersensitive to ionizing radiation and the radiomimetic drug bleomycin, may also have defective polymerases. (For a detailed account of sensitivity to various mutagens and possible repair defect, see Ref. 14.)

(b) In the human population, mutant individuals with defective DNA repair genes exist. In all cases, the mutation load in somatic cells of such individuals is significantly higher than that of normal individuals.

(c) The relationship between chromosome instability and cancer proneness is well established.

(d) The challenge of cells of one syndrome with mutagens, whose mechanism of action is known, can provide indirect evidence for the syndrome's genetic defect.

(e) Since the phenotype within each syndrome is not exactly the same, i.e., some individuals show a higher rate of instability than others, the genetic background with respect to repair defect may be quantitative, i.e., it is not an all-or-nothing phenomenon.

**Mutagen Sensitivity and Cancer Susceptibility in Humans**

To demonstrate the existence of minor differences in mutagen sensitivity among normal individuals requires not only a workable experimental procedure but also a large number of human volunteers. Hsu and coworkers decided to test this hypothesis by using primary cultures of lymphocytes of peripheral blood as the principal test cells. Since a large number of human subjects must be assayed, blood samples would be most convenient. In standard blood cultures, the lymphocytes actively proliferate in 3 to 4 days, yielding a good supply of mitotic cells for observation of chromosomes. The radiomimetic antibiotic, bleomycin, was chosen as the test mutagen. Bleomycin induces DNA breaks (15), which may express, within a short time span, as chromatid breaks.

After a number of preliminary trials, a set protocol was established by treating the cells of blood cultures with bleomycin (0.03 units/ml) for 5 h and then harvesting the cells with conventional cytogenetic methods. A minimum of 50 well-spread metaphases were examined, and the number of chromatid breaks (Fig. 1) was recorded. The average b/c value was then used to estimate an individual's sensitivity to this drug. Results from two preliminary papers (16, 17) and later a more comprehensive report (18) can be summarized as follows.

(a) Spontaneous chromosome breakage rates. The spontaneous chromosome breakage rates of 182 randomly selected normal individuals and 232 cancer patients ranged from 0.00 to 0.12 b/c (one subject), with a mean value of 0.02 b/c. These data indicated that none of the subjects belonged to any of the chromosome instability syndromes. Since the spontaneous b/c values

*Fig. 1. Chromatid breaks (arrows) induced in cultured lymphocytes by bleomycin. A. one break; B, multiple breaks.*
were so low, it was considered unnecessary to deduct the control b/c value of each individual from the bleomycin-induced b/c rate.

(b) Bleomycin sensitivity profile of normal individuals. In practically all cases, the breakage values of bleomycin-challenged cells exhibited much higher rates than the spontaneous rates. From a total of 335 normal volunteers assayed (18), the b/c values varied from 0.12 to more than 2.00, but a large proportion (77%) showed b/c values below 0.80, and nearly 88% showed values below 1.00. The distribution profiles (as a percentage) of the populations analyzed are graphically illustrated in Fig. 2, using increments of 0.40 b/c. The mean b/c value of the control population was 0.60, and 1 SD was 0.35. Using the mean \( \pm 1 \) SD (0.96 b/c, rounded out as 1.00 b/c) as a cutoff to arbitrarily separate bleomycin-sensitive from less sensitive populations, sensitive individuals comprised 11.6% of the control population.

(c) From several pedigree analyses and other indirect evidence (16–20), bleomycin sensitivity appears to have a hereditary basis. However, concrete data remain to be obtained.

If the bleomycin sensitivity profile of normal individuals described above is representative of the human population in general, and if sensitive individuals are more likely to be susceptible to environmental carcinogens than less sensitive individuals, then sensitive individuals may have a higher incidence of environmentally induced cancers. To test this hypothesis, however, would necessitate a prospective analysis. An alternative, although somewhat less direct, approach is to retrospectively analyze the bleomycin sensitivity profiles of patients who have already developed cancer. Fig. 2 includes, in addition to the profile for normal persons, the bleomycin sensitivity profiles of head and neck cancer patients \( (n = 77) \) and lung cancer patients \( (n = 71) \). The profile of colon cancer patients \( (n = 83) \) is essentially the same as that of lung cancer patients (data not shown). It can be seen that a much higher proportion of the cancer patient populations (approximately 50%) belonged to the sensitive fraction \( (b/c > 1.00) \) compared with only 12% of the control population. Of interest is the finding that the bleomycin sensitivity profiles of breast cancer \( (n = 82) \) and central nervous system cancer \( (n = 13) \) patients were indistinguishable from those of the control population (data not shown).

In view of the relationship between cigarette smoking and aerodigestive tract cancers, an attempt was made to measure the bleomycin sensitivity of asymptomatic individuals with long smoking histories. If the hypothesis were valid, we would predict a higher proportion of less sensitive individuals among “old smokers” (individuals above 50 years of age with a minimum 20 pack-year smoking history and no symptoms of cancer). The bleomycin sensitivity profile of old smokers showed only 1.78% of subjects to be in the hypersensitive class \( (>1.0 \) b/c). These data suggest that this group of individuals represents the bleomycin-resistant subpopulation of the control population, perhaps because the sensitive subpopulation had already developed smoking-related malignancies. This finding contrasts sharply with the observation that there was no significant difference between the sensitivity profiles of young smokers and normal controls \( (\pm 25\% \text{ mutagen sensitive}) \), indicating that there...
are no immediate shifts in bleomycin sensitivity due merely to smoking itself.

Several working hypotheses can be drawn from these results:

(a) As far as cellular responses to the genotoxicity of bleomycin are concerned, human individuals do not respond uniformly. A gradation from relatively resistant to highly sensitive reactions has been recorded. Moderately sensitive to hypersensitive individuals comprise approximately 23% of the population.

(b) Sensitivity to the genotoxicity of mutagens may be closely related to susceptibility to environmental carcinogens, i.e., persons more sensitive to mutagens may acquire malignancy more easily than those who are more resistant.

(c) Tissues and organs directly in contact with the environment, i.e., the digestive system, the respiratory system, and the integument, are more vulnerable to environmental mutagens than organs not directly exposed to the environment.

(d) Since the genotoxic mechanisms of bleomycin and ionizing radiations are similar, it is inferred that individuals sensitive to bleomycin may be also sensitive to ionizing radiations.

Head and Neck Cancer as a Model System for Testing Mutagen Sensitivity and Cancer Susceptibility

Head and neck cancer is the common term for squamous cell cancers that develop within the upper aerodigestive tract mucosa. Sites of disease commonly included within this region are the oral cavity, pharynx, and larynx. In the United States, head and neck cancer is a relatively infrequent disease, with 42,000 cases estimated to occur each year (21). Because of their anatomical contiguity and histological homogeneity (over 90% are squamous cell cancers), they are an ideal group of cancers for etiological research. Furthermore, the etiological importance of tobacco exposure in risk assessment of these cancers is well documented and quantitated, and dose-response effects have consistently been demonstrated.

In our own experience at M. D. Anderson Cancer Center, risk estimates for cigarette smoking among male head and neck cancer patients increased linearly with each successive pack-year stratum from 1.8 to 4.0 to 7.5 in the heaviest smokers (22). For women, the corresponding risks were 1.5, 9.0, and 12.0. In both instances, linear trend analysis was statistically significant (22). We also noted subsite-specific differences in cigarette smoking risk estimates. The highest odds ratio estimates (OR = 15.1) were documented for laryngeal cancers, and the lowest risks were noted for oral cancers (OR = 2.1).

An interaction between alcohol and tobacco in elevating the risk of oral, pharyngeal, and laryngeal cancers has also been well demonstrated (23, 24). Recently, a large population-based case-control investigation of oropharyngeal cancers resolved many of the questions about the relative impact of alcohol and smoking (25). This study showed a separate effect for alcohol, a dose-response relationship, and demonstrated that tobacco was not a requisite cofactor for these cancers (25). Increased risks were associated with each type of alcohol (hard liquor, beer, and wine), suggesting a role for ethanol, the common ingredient in these beverages, as a causative agent.

These factors make head and neck cancers an ideal model for the study of environmentally induced malignancies. This is reinforced by their characteristic propensity for multiple malignancies. Individuals cured of the index cancer are at risk of developing a second malignancy at a constant rate of 3 to 6%/year (26, 27). This rate is constant over time. Most reports suggest that more than 20% of the head and neck cancer patient population will develop a second primary malignancy (26–29). The majority of these malignancies occur in tobacco-exposed aerodigestive mucosa, principally in the lung and the upper digestive tract.

The risk of malignant transformation is not confined, however, to tobacco-exposed tissues. Winn and Blot (29) showed a modest but significantly increased risk of colon cancer in patients with an index pharyngeal cancer. Newell et al. (30) reported an increased association of cervical cancer with head and neck cancer in women beyond that expected.

The fact that the majority of second primary malignancies in head and neck patients occur in tissues that are exposed to tobacco carcinogens has led to the term "field cancerization" (31). All tissues exposed to a specific cancer-causing agent will express varying degrees of genetic damage. Accumulated damage over time will lead to a propensity for malignant transformation at multiple sites. Head and neck cancer patients can thus be considered a target population of individuals who are at risk of developing the most common environmentally induced cancers identified in this country, i.e., lung and digestive tract cancers. To understand and prevent malignancies in these individuals through the use of mutagen susceptibility markers would have broad implications. The natural history of these individuals who develop multiple cancers within a relatively short interval after identification of their index cancer would facilitate testing the validity of using biological markers to assess cancer risk.

Case-Control Analysis of Mutagen Sensitivity. We have compared sensitivity to bleomycin-induced chromosome damage in 75 patients (53 men and 22 women) with previously untreated upper aerodigestive tract malignancies with that in 62 healthy control subjects selected from among hospital employees (32). Data on tobacco and alcohol use were derived from detailed, self-administered cancer risk factor questionnaires that are distributed to all newly registered adult patients at the M. D. Anderson Cancer Center (33).

Baseline mutagen sensitivity values were established for the patients and the controls. Forty-five patients and 13 controls were sensitive to bleomycin-induced mutagenesis (average breaks/cell > 0.8). Differential susceptibility was detected in patients who were categorized by primary tumor location. ORs for chromosome sensitivity were significantly elevated for all sites (OR = 10.3 for pharyngeal cancers, 8.0 for laryngeal cancers, and 3.8 for oral cavity cancers). On logistic regression analysis, mutagen sensitivity remained a strong and independent risk factor after adjustment for potential confounding from age, sex, and tobacco and alcohol use (OR = 4.3; 95% confidence limits = 2.0, 10.2) (33).

To evaluate the independent effect of chromosome sensitivity and the interaction of chromosome sensitivity with cigarette smoking and alcohol consumption, risk estimates for various combinations of sensitivity and smoking or alcohol use were computed in stratified anal-
yses. These analyses were restricted to study participants for whom all relevant information was available. Referent categories were study participants who were not mutagen sensitive and who were nonusers of either cigarettes or alcohol. The data were sparse in some categories, and the resultant measures of effect were therefore somewhat unstable. Mutagen sensitivity was a risk factor in the absence of both smoking (OR = 5.8) and alcohol use (OR = 3.6), and there were significantly elevated risks associated with smoking and tobacco use (OR = 5.4 in each instance). The combined effects of chromosome sensitivity and smoking (OR = 19.8) or alcohol use (OR = 17.1) were consistent with a multiplicative effect.

Prospective Study of Mutagen Sensitivity. Our next focus was to evaluate the usefulness of mutagen sensitivity as a predictor of cancer risk. As just mentioned, patients with upper aerodigestive tract cancers incur high risks for the development of second malignant tumors, especially in tobacco-exposed tissues. They are thus ideally suited to prospective analysis.

Eighty-four patients with previously untreated aerodigestive tract cancers were assessed at baseline for mutagen sensitivity and self-reported life style exposures (34). Sixty-two of these patients were included in the previous case-control study (32). After definitive therapy, they were followed longitudinally (median time, 20 months; range, 4–31 months) for the development of second malignancies. Histologically confirmed multiple primary malignancies were defined by criteria established by Warren and Gates (35).

Of the 33 hypersensitive individuals, 9 (27.3%) developed subsequent primaries, compared with 4 (7.6%) of the 51 less mutagen-sensitive patients. The risk ratio for second primaries in mutagen-sensitive individuals was 4.4 (95% confidence limits = 1.2, 15.8). There were no substantive differences between mutagen-sensitive and less sensitive patients with regard to age, sex, treatment modality, or tobacco and alcohol use.

Predictably, patients who developed second malignant tumors had a more extensive smoking history than those not developing subsequent malignancies, although these differences were not statistically significant. Logistic regression analysis of multiple primary cancer risk, independent of any categorical grouping, showed a significant relationship between an increasing risk of multiple primaries and an incrementally increasing mutagen sensitivity value (P < 0.02). Despite the small study size and the short period of follow-up evaluation, the data support the hypothesis that mutagen-sensitive patients constitute a target subpopulation for careful scrutiny. The identification of high-risk subpopulations thus has both clinical and prognostic relevance.

The Enigma of Alcohol as an Etiological Factor of Head and Neck Cancer

In a variety of test systems, from microorganisms to higher animals, ethyl alcohol has not been shown to have mutagenic or clastogenic properties prior to its metabolic conversion by alcohol dehydrogenase into acetaldehyde, which is a mutagen (36). Yet alcohol has been implicated in the etiology of several human cancers, especially in the upper aerodigestive tract (37). This is particularly evident when the bleomycin sensitivity factor is taken into consideration (38).

Unless the epithelial cells of the oral cavity, larynx, pharynx, and esophagus possess a high activity of alcohol dehydrogenase, it is difficult to explain alcohol as a carcinogen. The suggestion that alcohol is a cocarcinogen (38) also lacks support from credible experimental data to explain its mechanism of action.

Nevertheless, an interaction between alcohol and tobacco in upper aerodigestive tract carcinogenesis is well documented in the epidemiological literature. We have noted a dose-response relationship between alcohol use and the risk of these cancers, with an over 40-fold elevated risk for those in the highest category of alcohol consumption. Site-specific differences in risk were also noted. Highest risk (OR = 6.7) was noted for pharyngeal malignancies compared with 4.3 for cancers of the larynx and 3.3 for oral cavity cancers (32). But these data do not support the hypothesis that the effect of alcohol is local and is a result of its solvent properties, in which case highest risks would be predicted for oral cavity lesions.

The conclusion from the epidemiological analyses of Spitz et al. (32) stimulated us to test several possibilities: (a) ethanol might increase the permeability of the cellular membrane; (b) ethanol might alter the kinetics of the cell cycle by hastening the G2 phase movement in a way similar to that of caffeine; and (c) ethanol might potentiate the genotoxicity of mutagens. Using the trypan blue dye exclusion test, we found no evidence for an increase of cellular permeability; using [3H]thymidine autoradiography, we observed the opposite effect for ethanol, i.e., alcohol retarded or even inhibited DNA synthesis. To test the last-mentioned possibility, we treated cultured human cells with bleomycin at a fixed concentration, together with ethanol at concentrations varying from 0.1% to 4%. The frequency of chromosome breaks, compared with that of the bleomycin control, was unchanged at 0.1% and 0.5% ethanol, but beginning at 1% ethanol the frequency was dramatically elevated (39). This series of experiments indicated that alcohol, although itself not a clastogen, could potentiate the genotoxic property of bleomycin with a dose-dependent effect.

Since bleomycin causes DNA damage, we decided to test the potentiation property of ethanol on mutagens with different molecular mechanisms. Four additional mutagens were chosen: the base analogue cytosine arabinoside; the UV-mimetic carcinogen 4-nitroquinoline-1-oxide; the alkylating agent triethylene melamine; and a sample of cigarette smoke condensate. In all cases, ethanol enhanced their genotoxicity. Thus, it appears that the potentiation effect of alcohol is a general phenomenon, not the formation of a particular molecular complex that increases the potency of a mutagen. Our results agree with those of Lin et al. (40), who used Chinese hamster cells as the principal test material and a protocol only slightly different from ours.

Nevertheless, finding an increase of mutagen genotoxicity by ethanol still does not explain the mechanism of potentiation. In our experiments to determine the alcohol effect on cell cycle kinetics, we noted that 2% ethanol slightly retarded the cell cycle movement and that 4% ethanol practically shut off DNA synthesis. One possibility is that at high concentrations of alcohol, the activity of enzymes required for DNA synthesis becomes impaired or even inhibited. The question, therefore,
arose as to whether DNA repair activities might also be inhibited by ethanol. We designed a test protocol by pulse treating cell populations with bleomycin for 10 min and then thoroughly washing off the excess bleomycin by two changes of growth medium without the drug. The cells were then reincubated in the growth medium or medium containing 0.5% or 2% ethanol. In four different cell lines, we noted that chromatid break frequency quickly declined in cells reincubated in growth medium only and in medium containing 0.5% ethanol, indicating the occurrence of repair. In medium containing 2% ethanol, not only did the break frequency fail to drop, but it showed a slight rise (41). These data strongly suggest that ethanol at concentrations of 2% or higher interferes with DNA synthesis as well as DNA repair.

In another series of experiments, we found that the inhibition effect was reversible, i.e., after removal of alcohol from the medium, repair activity resumed. We think these experiments answer the questions of why alcohol is a cocarcinogen, and why its effect is most pronounced in individuals who consume alcoholic beverages, the epithelial cells inhibit effect was reversible, i.e., after removal of alcohol from the medium, repair activity resumed. We think these experiments answer the questions of why alcohol is a cocarcinogen, and why its effect is most pronounced in individuals who consume alcoholic beverages, the epithelial cells repair activity resumed. We suggest that ethanol at concentrations of 2% or higher inhibited by ethanol. We designed a test protocol by pulse treating cell populations with bleomycin for 10 min and then thoroughly washing off the excess bleomycin by two changes of growth medium without the drug. The cells were then reincubated in the growth medium or medium containing 0.5% or 2% ethanol. In four different cell lines, we noted that chromatid break frequency quickly declined in cells reincubated in growth medium only and in medium containing 0.5% ethanol, indicating the occurrence of repair. In medium containing 2% ethanol, not only did the break frequency fail to drop, but it showed a slight rise (41). These data strongly suggest that ethanol at concentrations of 2% or higher interferes with DNA synthesis as well as DNA repair.

In another series of experiments, we found that the inhibition effect was reversible, i.e., after removal of alcohol from the medium, repair activity resumed. We think these experiments answer the questions of why alcohol is a cocarcinogen, and why its effect is most noticeable in the upper aerodigestive tract. When individuals consume alcoholic beverages, the epithelial cells are in direct contact with very high concentrations of ethanol, far higher than the 2% concentration used in our experiments. Even without tobacco use, the upper aerodigestive tract already has chemical carcinogens as contaminants from air, drinks, and food. Once DNA repair is prevented by the action of alcohol, the genetic damage is irreversible and will accumulate, thus increasing the risk of developing malignancies. However, the basic biochemical mechanisms of alcohol inhibition of DNA repair remain to be elucidated.

Summary
We intend to continue our exploration of the bleomycin assay as a biological marker for the development of environmentally induced cancers. The impetus for such efforts would be enhanced through effective integration of cancer screening and intervention to achieve diminished cancer mortality. Currently, we are integrating combining bleomycin sensitivity screening to chemopreventive therapy against second primary malignancies in head and neck cancer patients. Previous studies have demonstrated that cis-retinoic acid, the agent used in our chemopreventive trial, is effective in such circumstances (35). Our purpose is to identify a high-risk subpopulation through application of the bleomycin sensitivity assay and then demonstrate that we can modulate the carcinogenic process with cis-retinoic acid.

The use of genetic markers clearly enhances the power and precision of epidemiological research. The preventive implications of precise and valid markers for carcinogen sensitivity are obvious. We are aware of the need for extensive validation of the assay and for rigorously designed and conducted epidemiological studies. The strength of the association between cancer risk and mutagen sensitivity, despite the inherent problems in the size and design of the studies, is noteworthy. The thesis that chromosome instability and defective DNA repair may underlie susceptibility to environmental carcinogenesis is plausible and presents a promising avenue for further multidisciplinary research.

References


T C Hsu, M R Spitz and S P Schantz


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