by double-blind studies to compare the preventive effects of the retinoid with those of a placebo.

Prevention of new primary cancers. Nearly 400,000 new cases of basal cell carcinoma, one type of skin cancer, are diagnosed each year. Although surgery yields a cure rate of at least 95 percent, the development of new tumors in these patients ranges from 20 percent in patients with one or more previous basal cell carcinomas to nearly 100 percent in patients with eight or more.

The subject of four chemoprevention trials is the prevention of new primary skin cancers in patients previously treated for basal cell carcinoma. Two studies use beta-carotene and two use the synthetic retinoid 13-cis retinoic acid (isotretinoin). For example, Drs. Joseph Tangrea and Earl Gross of the National Cancer Institute are conducting a 5-year study of 1,800 white men and women, ages 45–70 years, who have had two or more basal cell carcinomas. This study will evaluate the effectiveness of low-dosage levels of 13-cis retinoic acid in reducing new incidence of basal cell carcinomas and will examine possible side effects associated with long-term administration of this agent. The knowledge from these trials will also provide insights useful in the design of studies aimed at preventing more aggressive types of cancer.

The relationship between diet and cancer has not yet been precisely defined. Published estimates of the percentage of cancer deaths attributable to diet range as high as 60–70 percent (*10,11*), but 30 percent seems a reasonable, conservative estimate. Although we hope chemoprevention initiatives will be useful against many types of cancer, including lung cancer, the best thing we can all do about lung cancer is to encourage people not to smoke. Chemoprevention and diet-and-cancer research are promising areas that will receive increasing emphasis.

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The Task of Epidemiology in Designing Strategies for the Use of Hepatitis B Virus Vaccine

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THE RECENT DEVELOPMENT OF SAFE, immunogenic, and effective vaccines to prevent hepatitis B virus (HBV) infection has been rightly hailed as a major advance in medical science. It has been estimated that more than 200 million persons worldwide are chronically infected with this virus, which takes an unmeasured toll of lives from cirrhosis and primary hepatocellular carcinoma (PHC) (*1*). This is one of the most common causes of deaths from cancer in the world, and it may now be considered a vaccine-preventable disease. The development of strategies to utilize these vaccines effectively poses an exciting challenge to epidemiologists, since patterns of HBV transmission and the risk of acquiring infection vary from continent to continent, from the

neonatal period to adulthood, and as a function of both lifestyle and occupation.

Epidemiologic Background

Conceptually, the world may be divided into three zones of HBV endemicity (*2*). The zone of high endemicity, represented by Southeast Asia, the Pacific Islands, and Sub-Saharan Africa, is characterized by a lifetime risk of HBV infection of more than 50 percent. In this zone, most infections occur perinatally or during childhood, acute hepatitis B with jaundice is not common, 5 to 20 percent of the population become chronic HBV carriers, and cirrhosis and PHC are major causes of death. Strategy for using the vaccine in these areas should be aimed at preventing acquisition of the carrier state perinatally or in childhood.

At the other extreme is the zone of low endemicity represented by Western Europe and North America. It is characterized by a lifetime risk of HBV infection that is less than 10 percent and a prevalence of HBV carriage of less than 1 percent. HBV infection is common only in some high-risk groups defined by certain lifestyles, occupations, medical conditions, or ethnic backgrounds (*3*). In this zone, infection occurs mostly in young adults, and both acute and chronic hepatitis B contribute significantly to morbidity and mortality. In the remainder of the world, both the lifetime risk of infection (20 to 40 percent) and the prevalence of carriers (2 to 5 percent) are intermediate. In Israel, one would expect low prevalence in European immigrant families and intermediate rates in Middle Eastern Jewish and Arab populations.

In North America and Western Europe, epidemiologic studies that defined the high-risk groups for HBV infection were necessary to lay the groundwork for current HBV vaccine strategy. First, the high-risk groups needed to be identified. Second, the prevalence of serologic markers and, where possible, the incidence rates of HBV infection needed to be measured. Third, the amount of hepatitis B attributable to each high-risk group needed to be estimated. Fourth, specific epidemiologic studies of each high-risk group needed to be undertaken to understand the modes of transmission within the group and the special problems that might arise with respect to vaccine delivery, acceptance, immunogenicity, and costs (*4*).

At the Centers for Disease Control (CDC), three surveillance systems help to define the epidemiology of hepatitis B in the United States. The first is the system in which the cases are reported weekly to the Morbidity and Mortality Weekly Report (MMWR) by local and State health departments. This system is the most extensive, but it collects little demographic and no risk factor data. The second system is the Viral Hepatitis Surveillance Program (VHSP), which collects case reports passively on a form that includes demographic, serologic, and risk factor data. Using VHSP data, we were able to identify a probable source of infection in more than 50 percent of reported cases of hepatitis B. The third is the sentinel county system. In an attempt to improve our understanding of transmission, an active surveillance system was instituted in certain counties with excellent reporting systems. This system, which employs public health nurses to investigate cases and collect blood samples for confirmatory testing, has allowed us to find a probable source of infection in 70 percent of hepatitis B cases. In addition to these large systems, we conduct more specific epidemiologic studies, including outbreak investigations, serologic prevalence surveys in high risk groups, refugee screening programs, and surveys in dialysis units.

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Evaluating the Vaccine

With the development of a hepatitis B virus vaccine, the epidemiologist faced additional tasks. These included design and implementation of methods to evaluate the vaccine's immunogenicity, efficacy, and safety. Initially, two large vaccine trials were conducted in homosexually active males (*5,6*), and smaller trials were conducted among patients in hemodialysis units, health care personnel, and children in endemic areas (*7*). These vaccine trials showed that the HBV vaccine induced protective antibody in 85 to 95 percent of susceptible recipients with normal immune systems, was almost completely effective in preventing infection in those who developed protective antibody, and had remarkably few short-term side effects. Vaccine demonstration projects are now underway among several high-risk groups such as medical personnel, clients and staff of institutions for the retarded, Alaska Eskimos, and infants of HBV carrier mothers.

Programs to monitor vaccine safety are also in progress to assess vaccine safety continuously as the vaccine is administered to larger populations. A passive system for reporting side effects, which is a cooperative effort of the Centers for Disease Control, the Food and Drug Administration, and the vaccine's manufacturer in the

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United States, is now maintained by CDC. Other systems in operation include collection and analysis of forms documenting side effects on all Veterans Administration employees who receive vaccine and continued followup of recipients in certain earlier vaccine trials.

Specific strategies for use of HBV vaccine have also been designed by epidemiologists. Decision analysis and cost-effectiveness analysis were done to determine the most cost-effective strategies for prevaccination screening (*8*). Direct and indirect costs of acute and chronic hepatitis B were calculated. Analysis of the cost effectiveness of vaccine programs as a function of incidence rates in high-risk groups and evaluation of vaccination versus other strategies for hepatitis B control in hospitals and dialysis units were also done. In addition, we attempted to project the impact of vaccine under various assumptions (*4*).

In terms of public policy, perhaps the most useful document is the "Guidelines for Use of the Hepatitis B Vaccine" prepared by the Immunization Practices Advisory Committee (*8*). This document, prepared after consideration of the data generated by hundreds of clinical, laboratory, and epidemiologic studies, represents the official policy on vaccine use of the Public Health Service. Although these are guidelines, not laws or administrative rules, they are usually carefully considered by Federal, State, local, and private providers of health care when decisions about the use of hepatitis B vaccine need to be reached.

Notable achievements in the control of HBV infection have been made, but the gap between knowledge and delivery of vaccine to those who need it is vast. The current cost of vaccine, $100 U.S. for an adult 3-dose series, precludes its use in most of the developing world, where per capita health expenditures are often less than $1 per year. Only when vaccine can be obtained for a few cents a dose and effectively combined with other childhood immunization programs will it be widely used in much of the world (*9*). Even in the United States, costs are perceived as a major impediment to vaccine use by administrators of many large programs responsible for high-risk groups. It is sometimes necessary for administrators to apply for special legislative grants to fund vaccine programs.

In the future, the development of new vaccines will require epidemiologic input to plan and monitor safety, immunogenicity, efficacy, and strategies for use of the vaccine. Since yeast-derived, synthetic, and multiple antigen vaccines are being developed, this field of disease prevention promises to be an active one for the epidemiologists for a long time to come.

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