A review of the first year's efforts of the National Cancer Institute's Colon Cancer Segment in establishing a sponsored research program to explore the role of dietary factors as the most likely environmental hazards in the etiology of carcinoma of the large bowel

Dietary Hypotheses and Diet-Related Research in the Etiology of Colon Cancer

JOHN W. BERG, MD, MARGARET A. HOWELL, PhD, and SIDNEY J. SILVERMAN, PhD

DIET as a possible etiological factor in the development of carcinoma of the large bowel (colon plus rectum) is receiving high priority in epidemiologic studies of the Colon Cancer Segment of the National Cancer Institute (NCI). The Segment is a problem-oriented work group within the Carcinogenesis Program of the Division of Cancer Cause and Prevention (DCCP). This Segment and eight other Segments, organized around major areas of cancer research, constitute the major program management vehicle within the Carcinogenesis Program for the conduct of collaborative research between NCI staff and contractors. In effect, the Segments form a task-group organizational structure superimposed upon the more traditional, formal organization.

The authors are members of the Epidemiologic Pathology Unit, Carcinogenesis, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health. Dr. Berg is head of the Unit, Dr. Howell is a research epidemiologist, and Dr. Silverman is a microbiologist. Tearsheet requests to Dr. Sidney J. Silverman, Division of Cancer Cause and Prevention, National Cancer Institute, Room C 329, Landow Bldg., 7910 Woodmont Ave., Bethesda, Md. 20014.

The Colon Cancer Segment was not formed to serve as the general focal point for NCI-sponsored research on large bowel cancer since that is the function of the grant-awarding National Large Bowel Cancer Project, headquartered at the M.D. Anderson Hospital and Tumor Institute in Houston, Tex. Rather, the Segment is charged with evolving the multidisciplinary program necessary to develop and test specific hypotheses about diet and bowel cancer. Through both laboratory research and special epidemiologic studies, the Segment's work supplements and elaborates on findings relating to bowel cancer as they arise from general epidemiologic studies, which are an ongoing part of NCI in-house research. Segment activities are supported by direct funding and through use of substantial resources of other work areas in both the Carcinogenesis and the Field Studies and Statistics Programs.

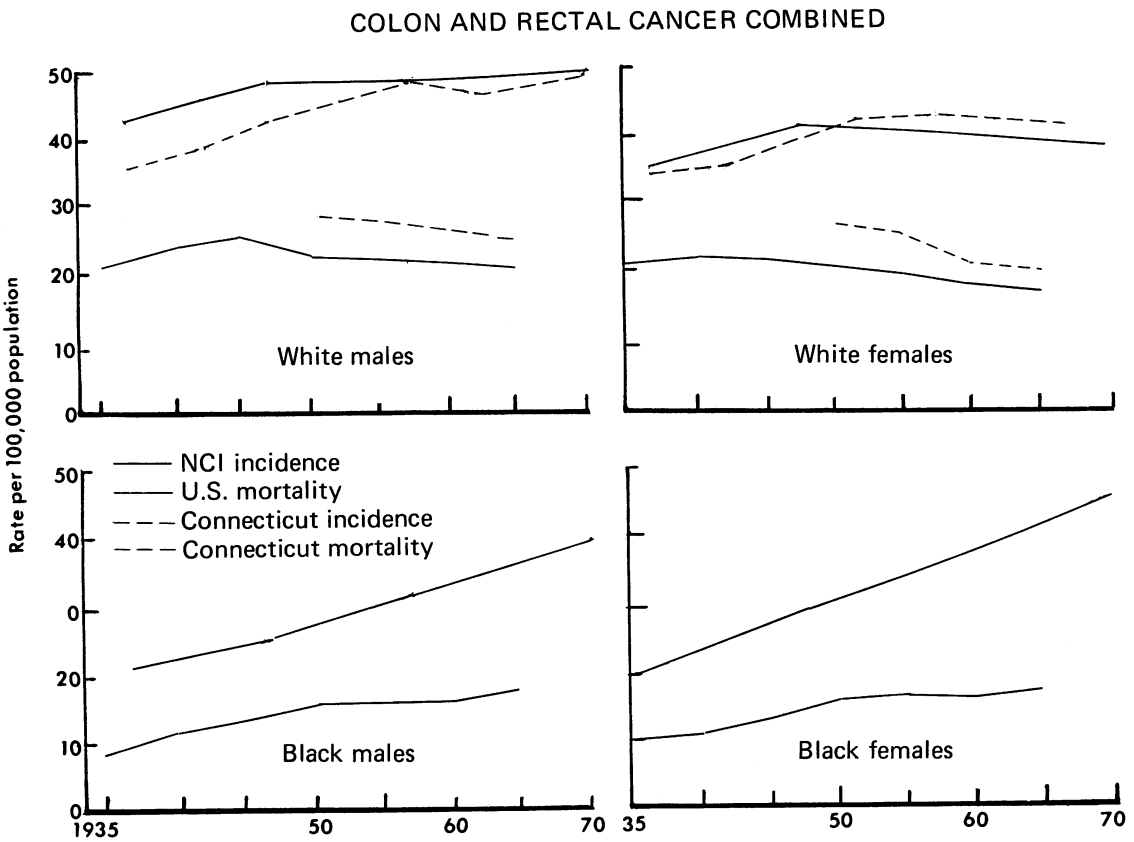
The rationale of the studies on diet being sponsored by the Colon Cancer Segment is based on a review of epidemiologic and other considerations that highlight the possible significance of diet in the cause and perhaps prevention of the disease.

Incidence and Mortality

Cancer of the large bowel is a major cancer problem in this country. Colon and rectal cancers together account for more new cancer cases, an estimated 92,500 per year, than any other organ site (*1*). Resulting in an estimated 47,400 deaths per year, colon-rectal cancer as a killer is second only to lung cancer (*2*).

From the time of diagnosis, prospects for sur-

Figure 1. Trends in colon and rectal cancer rates [1]



[1] Age adjusted to a standard population, 1950. National Cancer Institute incidence based on periodic surveys by the Institute. U.S. mortality from the National Center for Health Statistics. Connecticut incidence and mortality from the Connecticut Tumor Registry.

SOURCE: reference 4.

Age-adjusted incidence rates per 100,000 population for colon and rectal cancer, 1969[1]

U.S. area	Total			White			Black [2]		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
North	47.4	53.7	42.7	46.8	52.7	42.4	48.0	53.3	43.2
South	36.7	40.4	34.3	37.2	41.3	34.7	30.4	30.8	30.3
West	47.0	54.6	41.9	47.7	55.4	42.3	30.8	34.7	27.8
Total	45.3	51.5	40.9	45.3	51.4	41.1	38.4	42.1	35.5

[1] Age-adjusted to the 1970 U.S. population.
[2] In 1970 blacks accounted for 88.7 percent of the nonwhite U.S. population.
SOURCE: reference 1.

vival are better for patients with colon-rectal cancer than for lung cancer patients. For patients who had surgery for colon-rectal cancer and whose lesions were localized—limited to the organ of origin—the 5-year relative survival rate in 1955–64 was 75 percent while the 10-year rate was 67 percent (*3*). Considering all cases, however, the median survival time for colon cancer patients is only 2.2 years (*3*). Survival prospects are better at younger ages, but the disease occurs primarily in later life, with an estimated 85 percent of current new cases occurring in patients age 55 and older (*1*).

Surveys conducted by NCI in selected large U.S. communities in 1937–39, 1947–48, and 1969 provide a basis for considering trends over time in cancer incidence. From 1937 to 1947, both colon and rectal cancer showed an increase in incidence. From 1947 to 1969, the incidence of rectal cancer decreased and colon cancer generally showed an increase, but this may partially reflect changes in assignment of lesions to the two sites (*4*). If the two sites are considered together, the results are as presented in figure 1. The figure shows a decrease in incidence in recent years among white females and a leveling off of rates for white males, with a decrease in mortality for these groups which is consistent with improvement in patient survival. In the black population, both incidence and mortality are increasing.

That the disease does not strike the population uniformly is reinforced by the data in the table, which gives incidence rates age-adjusted to the 1970 population (*1*). The table shows that for all groups, rates for males are higher than for females. For the white population and for the total population, which largely reflects the white figures, rates are higher in the North and in the West than in the South. For the black population, rates are relatively low in the West as well as in the South, while in the North the rates for blacks have somewhat exceeded those for whites.

Not only are there variations in incidence within the United States, but the geographic distribution of the disease shows wide variations from country to country. Figures 2 and 3 for males and females, respectively, show age-adjusted mortality rates from combined colon and rectal cancer in 24 countries, with separate rates for U.S. whites and nonwhites.

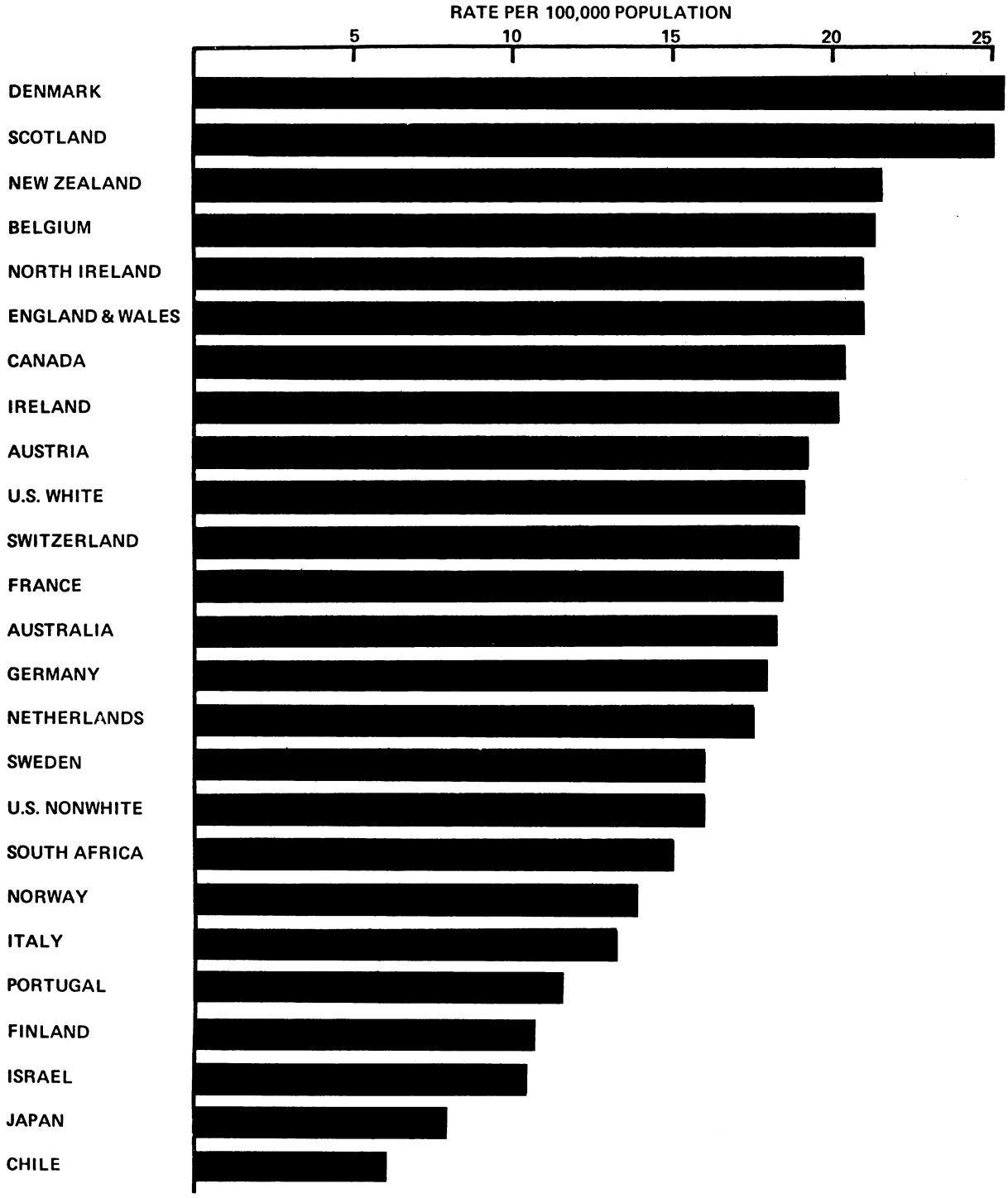
Changing rates within a population as well as wide variations in occurrence of a disease within and between populations suggest causative environmental factors. However, only through the study of migrant groups have genetic and environmental factors been sufficiently separated to warrant a conclusion that environmental factors play a role—perhaps a major one—in the etiology of cancer of the large bowel.

Changed Risk With Migration

For the epidemiologist interested in the respective roles of the environment and of host characteristics in the development of disease, migrating populations constitute an "experiment of nature." Comparisons of mortality rates among the native born, the foreign born, and the population in the country of origin of the foreign born have enabled determination of the change in cancer risk that is associated with a change in environment. Changes in risk associated with migration differ for the different organ sites (*6*). For cancer of the colon, migrant studies have generally shown that a group moving to an area of different risk for colon cancer fairly quickly assumes the risk of the new place of residence.

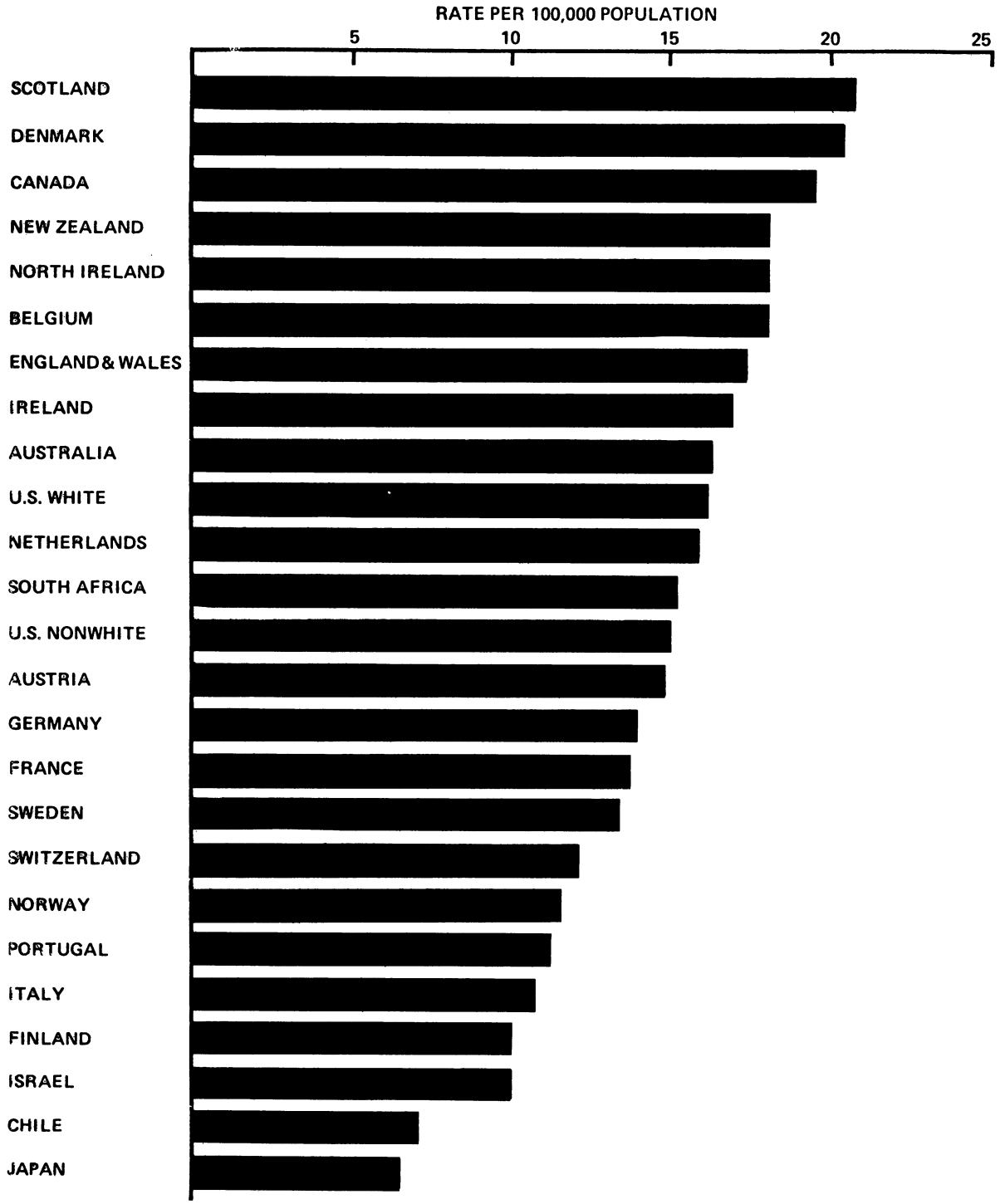
We mention only a few of the migrant studies because they have been reviewed by Kmet (*7*). In 1961, Haenszel reported an analysis by country of birth of decedent of more than 34,000

Figure 2. Age-adjusted [1] death rates for malignant neoplasm of all large bowel, males, 1964–65



[1] Age adjusted to a standard population, 1950.
SOURCE: recalculated from reference 5.

Figure 3. Age-adjusted [1] death rates for malignant neoplasm of all large bowel, females, 1964–65



[1] Age adjusted to a standard population, 1950.
SOURCE: recalculated from reference 5.

cancer deaths among foreign-born whites in 35 States in 1950 (*8*). Generally, mortality from cancer of the large bowel for the various ethnic groups approached that of U.S. native whites.

Among Polish migrants to the United States, mortality rates for colon cancer follow the country of adoption, being displaced upwards (*9*). Similarly, among Polish migrants to Australia, Staszewski, McCall, and Stenhouse (*10*) found cancer mortality for the intestinal tract to be displaced upwards, from the low Polish level to the much higher Australian one.

In Japan, the death rates for cancer of the large bowel have been low (figs. 2 and 3). In 1968, however, Haenszel and Kurihara (*11*) reported a study of mortality among U.S. Japanese in which migrants showed a displaced risk for colon cancer toward that of the host population. For the Japanese-born Issei, particularly males, the rates had risen close to those of white males; for the second-generation U.S.-born Nisei, the data suggested that the shift to higher U.S. risks was continuing. The results for colon cancer were in striking contrast to data for cancer of the stomach, which showed that the migrants typically retained risks close to those of the country of origin. For U.S.-born Japanese living in California, Buell and Dunn (*12*) earlier had reported a decline in stomach cancer and an increase in colon cancer.

The risk for bowel cancer changes with migration within the United States in a manner similar to that for foreign migrants. Haenszel and Dawson, in a study of a sample of U.S. deaths from cancer of the colon and rectum, found that for migrants between urban and rural areas, mortality approximated that of the place of residence rather than the place of birth (*13*). Rates are generally higher in urban than rural areas; a rural population moving to an urban area shows an upward displacement toward urban rates.

The epidemiology of cancer of the large bowel thus suggests that environmental factors are important in etiology. This does not preclude the operation of genetic factors, which are most evident in a disease such as familial polyposis (*14*). Nonetheless, the fact that risk changes with migration indicates that immediate attention should be directed toward environmental hazards that may be eradicable. Among environmental factors possibly affecting the rates of intestinal carcinomas, diet is considered a likely candidate (*15*).

Dietary Hypothesis

At present, there are relatively little empirical data to implicate diet as a source of colonic carcinogens. Food additives have been considered as a possible source of carcinogens, but as has been noted, Denmark has stringent regulations on food additives yet has one of the highest mortality rates, and in India there are widely contrasting regional differences in incidence in a population with relatively little exposure to food additives (*16*). A number of hypotheses have been advanced to link food components per se, not additives, and carcinogenic activity in the intestinal tract, primarily through the effect of diet on bacterial flora and intestinal motility. The three major dietary hypotheses follow.

Fats. Wynder and Shigematsu suggested that the dietary pattern that may fit the distribution of cancer of the large bowel includes a high intake of fat (*17*). They pointed out that colon cancer is uncommon in Japan; an analysis of the intake of nutrients in the United States and Japan in 1962 showed that saturated fats were lower in the Japanese than in the American diet. Second-generation Japanese in Hawaii are at an increased risk for colon cancer; for this group, both the percentage of calories derived from fat and serum cholesterol levels were similar to those for the continental United States. A relatively high risk among the Jewish population in New York, the authors suggested, may be related to high content of animal fat in the diet. They also indicated that among Seventh Day Adventists in California, known to eat little meat, colon cancer rates are relatively low, as are serum cholesterol levels and the intake of saturated fats.

Animal protein. This hypothesis assumes that higher intake of animal protein is associated with the frequency of large bowel cancer. Based on data for 28 countries and two periods, 1947–48 and 1962–63, Gregor and associates found significant positive correlations between standardized mortality rates for intestinal cancer and national levels of the intake of animal protein (*18*). In a later study of changes over a period of 8–12 years in 23 countries, these investigators found a faster rise in mortality from intestinal cancer in countries having the more rapid increases in intake of animal protein (*19*). From a diet history point of view, this hypothesis is, of course, difficult to separate from the preceding one since

many food items are sources of both animal protein and fats.

Refined carbohydrates. Based on studies by Cleave and others linking diseases characteristic of economic development to the refining of carbohydrate foods, Burkitt suggested that a low residue diet is a major factor in the etiology of colon and rectal cancer (*20*). He pointed to the overrefining of carbohydrate foods, particularly white flour and sugar, with reduction of unabsorbable cellulose content in the diet.

In fuller development of his ideas, Burkitt discussed studies indicating that changes in dietary fiber alter intestinal transit time, stool bulk, and consistency, and he noted a report by Hoffman that a high carbohydrate diet alters bacterial content of the feces (*21*). Burkitt suggested ". . . that carcinogens produced by action of an abnormal bacterial flora when held for a prolonged period in a concentrated form in contact with the bowel mucosa may account for the high incidence of these diseases in economically developed countries" (*21a*).

Since studies of bacterial flora are related to dietary hypotheses, in the following section we review one study in which the dietary aspects of the results are emphasized.

Studies of Bacterial Flora

The general working hypothesis to account for a possible relationship between the incidence of colon cancer and diet is: "(*a*) the composition of intestinal bacterial flora is dependent on the nature of the diet; (*b*) diet also determines the types and amounts of compounds that come into contact with the bacterial flora; (*c*) intestinal bacteria are able to form carcinogens from dietary compounds or from digestic secretions. . . ." (*22a*).

In 1969, Aries and associates compared the bacterial flora of the feces from people in England and in Uganda (*23*). Incidence of cancer of the large bowel is high in England and low in Uganda. Fecal specimens from the English were found to contain significantly more Bacteroides and Bifidobacteria than specimens from Ugandans. Results, described as preliminary, indicated that bile salts in feces of the English persons were more degraded. The investigators stated that presumably the more degraded the bile salts the more likely they are to be converted to carcinogens. The differences in bacterial flora were viewed as probably attributable to dietary differences. The English lived on mixed animal and vegetable foods and the Ugandans on a high carbohydrate vegetarian diet which contained little fat and animal protein.

Case-Control Studies

Any conclusion that diet is related to cancer of the large bowel and any specific tests of dietary hypotheses, regardless of the bacterial or other mechanisms postulated, must await demonstration of dietary differences between bowel cancer patients and persons free of the disease.

A number of case-control studies have compared dietary histories of patients with cancer of the large bowel and matched hospital controls (17, 24–26). In general, these studies did not yield consistent dietary differences between patients and controls, although Pernu (*25*) did find that male, but not female, patients had a higher intake of animal meat and fat than did controls.

Wynder and associates (*27*), in a study of 157 patients and 307 controls in Japan, noted that the diet of colon cancer patients tended to be lower in rice and higher in fruit and milk than that of the controls. They interpreted the findings as a reflection of higher socioeconomic status and a more westernized type of diet for the patients as compared with the controls.

An ongoing study by Haenszel and co-workers (*28*) of Japanese migrants to Hawaii is the one study which found statistically significant differences in food intake between patients and controls. As might be expected, the bowel cancer patients ate more "Western-style" meals. In particular, the patients' diets had been characterized by more frequent use of meat, especially beef. A preliminary report of the findings is available (*29*).

Results from the Haenszel study contrast sharply with the generally negative results from other case-control studies. Positive findings are attributed to the fact that the study was conducted on a population undergoing displacement from low to high risk for colon cancer and in varying stages of transition from one type of diet to another.

Current Research

As mentioned earlier, findings from the general epidemiologic studies in NCI—particularly those of the Japanese migrants—were the basis for the initiation of the program of the Colon Cancer Segment. A multidisciplinary approach was essential to seek epidemiologic confirmation of dietary

differences such as those found in Hawaii and concurrently to perform bacteriological, chemical, and other laboratory testing related to diet as a possible source of carcinogens.

Epidemiologic diet studies. Since the only demonstration of diet history differences in patients with bowel cancer and matched controls was based on a group in transition in terms of bowel cancer rates and dietary habits, the logical extension of the Japanese migrant studies was a search for other populations in transition. Blacks, who are currently undergoing displacement toward higher risk of bowel cancer but whose incidence rates in the South and in the West are still lower than those for whites, appeared to be a suitable transitional group for a study of dietary differences.

The Medical College of Georgia in Augusta and the Kaiser Foundation Research Institute in Oakland, Calif., are conducting case-control studies in which diet history before the onset of symptoms in black patients having cancer of the large bowel is compared with the diet history of matched controls. In both studies, patients and controls will be compared statistically on items in a diet history questionnaire which focuses on dietary sources of fats, animal proteins, and cellulose. Comparisons will also be made on pertinent demographic information such as residence histories and socioeconomic status.

The initial effort of the Colon Cancer Segment was to sponsor a few research studies while assembling data from disparate sources to assess the significance of dietary factors in carcinogenesis of the large bowel. Information is being sought about people whose diets and bowel cancer rates contrast with those of groups already studied. For instance, the Argentineans (*30*) and the Eskimos, although not on a diet associated with the affluence of highly developed countries, are at high risk for bowel cancer. For both these groups, meat consumption is high, but there is little use of refined carbohydrates. Other groups of interest are the largely vegetarian Seventh Day Adventists and the residents of nonurbanized parts of Scotland. Scotland ranked high in mortality rates from bowel cancer during 1964–65 (figs. 2 and 3), and it is the one high-risk country known to have rural rates that are at least as high as those in conurbations (*31, 32*). These natural experiments may be more revealing of dietary effects than questionnaire studies, even those conducted on heterogeneous populations.

Determination of disease linkages. If diet is a factor in large bowel carcinogenesis, it may, as an environmental hazard, have effects other than cancer. Even with cancer, the correlation across populations between colon cancer mortality and mortality from coronary heart disease (*33*) has led to speculation concerning a common cause of the diseases. The Oxford (England) Record Linkage System is a source of patient data which will permit study of diseases associated with cancer of the large bowel in individuals. Similar searches from existing data banks are being made through a collaborative effort with the National Heart and Lung Institute in Framingham, Mass., and in Honolulu.

Fecal flora studies. Concurrently with the epidemiologic studies, a number of studies of fecal flora have been undertaken.

The Anaerobe Laboratory, Virginia Polytechnic Institute and the State University at Blacksburg, Va., is determining which bacterial species constitute the predominant fecal flora of individuals, particularly Japanese from Hawaii with intestinal polyps and with early known carcinoma of the bowel. As in the London studies of Aries and colleagues (*23*), the concentration of bacterial degradation products of cholesterol and bile acids will also be determined.

The Wadsworth Hospital Center of the Veterans Administration and the University of California Medical Center at Los Angeles have undertaken a comparison of the fecal flora of Japanese in California, who are on typical American diets, with the flora of those on a more traditional Japanese diet.

A program of bacterial research is being developed at NCI's Frederick (Md.) Cancer Research Center to follow up the results of the bacterial "surveys." Various bacterial species isolated from the intestinal tract will be studied, especially in mixed culture, for metabolic activities that could lead to the production of carcinogens from such substrates as steroids and amino acids. The activity of cell-free enzyme systems on specific substrates will also be studied to ascertain the conditions required for carcinogen production.

Experimental chemical carcinogenesis. For many, probably most, of the metabolic products harvested from bacterial and enzyme systems, it will not be known whether or not they are actually carcinogenic. Since no direct testing on hu-

man bowel epithelium is yet possible, resources for more traditional carcinogenic testing are being established. In particular, the American Health Foundation is undertaking subcutaneous injection, skin painting, and intrarectal application in normal and germ-free rodents.

Among highly suspect potential carcinogens are nitrosamines. Nitrates, common to many food sources, can be converted to nitrites by bacterial reduction; further, nitrites in varying amounts are present in foods. Secondary and tertiary amines have been shown to react with nitrites to form carcinogenic nitrosamines. While nitrosamines have not yet been found in the human intestine, the potential danger of these compounds is so great that study of their chemistry, biology, and role in gastrointestinal cancer is being supported at the Biology Division of the Atomic Energy Commission's Oak Ridge National Laboratory.

Regulatory control of cell proliferation. Whatever the etiological factors in bowel cancer, the result is abnormal differentiation of colonic epithelial cells. Familial polyposis is an inherited disease in which a gene mutation produces colonic adenomas. Cancer is almost inevitable if these patients remain untreated. There is every reason to believe that the transition to cancer in polyposis is the same as in bowel cancer generally. The metabolic regulatory error that leads to the abnormal differentiation is being sought at Memorial Hospital for Cancer and Allied Diseases in New York City. Attempts are being made to detect differences in the synthesis of nucleotide precursors and DNA in polyposis cells or to detect defects of DNA repair.

Studies of bowel pathology. Premalignant lesions of the large intestine that are epidemiologically related to bowel cancer can serve to identify persons at high risk and perhaps provide early warning of recent exposure to an environmental hazard. Groups contrasting epidemiologically by being at different levels of risk should show different frequencies of precursor lesions. Data on the prevalence and type of benign tumors are being or have been collected by Louisiana State University Medical Center, Kuakini Hospital in Hawaii, Universidad de Valle in Cali, Colombia, and several hospitals in Japan. In addition, pathology data on bowel cancer are being collected from tumor registries and being analyzed with regard to exact locations of lesions and the significance of specific histological patterns.

Discussion

The growing complexity of the Colon Cancer Segment program reflects the complex nature of present ideas about the etiology of human cancer. Even if only one etiological hypothesis were tenable, the cancer research task would not be greatly simplified as long as prevention is accepted as the goal. It is likely that a major cause of bowel cancer is an environmental hazard that is ubiquitous in the society and cannot be easily removed. Prevention may well begin with alteration of cofactors that promote carcinogenesis or increase host vulnerability. Adequate preventive measures depend on knowledge of human fecal flora, of the carcinogenic potential of metabolites of suspect foods, and of the reactivity of bowel epithelium. Such knowledge is particularly crucial if causal agents cannot be identified through questionnaire analysis. Then, it will be necessary to rely completely on laboratory studies to mark exposures and to test the reality of hypothetical causal chains by tracing the steps in victims and potential victims of bowel cancer.

The basic problem is no different from that which brought about the field-laboratory partnerships in studying the epidemiology of infectious disease and environmental toxicology. The difference lies in the multitude of laboratory disciplines that are relevant to cancer problems and even, as indicated here, to a single cancer problem. An interdisciplinary approach is not likely to be fully mobilized spontaneously. Rather, we believe there first must be in-depth analysis of the problem to identify the types of laboratory involvement needed. Then a structure must be created so that the problems and results can be phrased in ways that make sense to all disciplines. For example, the bacteriological questions must make scientific sense to bacteriologists and at the same time reflect the best current knowledge of epidemiology. Results obtained from bacteriology must be stated so that they are meaningful to epidemiology and other specialties. Finally, the overall program structure must be goal oriented so that it will be responsive to new knowledge.

Coordinated multidisciplinary programs like the one described here are likely to become the rule rather than the exception in cancer epidemiology. The problems demand it. For the Public Health Service, this will mean no more than applying old policies in a new way.

REFERENCES

(1) U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health: Preliminary report, Third National Cancer Survey, 1969 incidence. DHEW Publication No. (NIH) 72–128. U.S. Government Printing Office, Washington, D.C., 1971.

(2) National Cancer Institute: Fact book, 1973. DHEW Publication No. (NIH) 73–512. National Cancer Institute, Bethesda, Md., 1973.

(3) Axtell, L. M., Cutler, S. J., and Myers, M. H., editors: End results in cancer, Report No. 4. DHEW Publication No. (NIH) 73–272. National Cancer Institute, Bethesda, Md., 1972.

(4) Cutler, S. J.: Report on the Third National Cancer Survey. *In* Seventh National Cancer Conference Proceedings. J. B. Lippincott Co., Philadelphia. In press.

(5) Segi, M., Kurihara, M., and Matsuyama, T.: Cancer mortality for selected sites in 24 countries, No. 5 (1964–1965). Department of Public Health, Tohoku University School of Medicine, Sendai, Japan, 1969.

(6) Haenszel, W.: Studies of migrant populations. J Chronic Dis 23: 289–291, November 1970.

(7) Kmet, J.: The role of migrant population in studies of selected cancer sites: A review. J Chronic Dis 23: 305–324, November 1970.

(8) Haenszel, W.: Cancer mortality among the foreign-born in the United States. J Natl Cancer Inst 26: 37–132, January 1961.

(9) Staszewski, J., and Haenszel, W.: Cancer mortality among the Polish-born in the United States. J Natl Cancer Inst 35: 291–297, August 1965.

(10) Staszewski, J., McCall, M. G., and Stenhouse, N. S.: Cancer mortality in 1962–66 among Polish migrants to Australia. Br J Cancer 25: 599–610, December 1971.

(11) Haenszel, W., and Kurihara, M.: Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 40: 43–68, January 1968.

(12) Buell, P., and Dunn, J.: Cancer mortality among Japanese Issei and Nisei of California. Cancer 18: 656–664, May 1965.

(13) Haenszel, W., and Dawson, E. A.: A note on mortality from cancer of the colon and rectum in the United States. Cancer 18: 265–272, March 1965.

(14) Fraumeni, J. F., and Mulvihill, J. J.: Persons at high risk of colorectal cancer. *In* Cancer epidemiology and prevention: current concepts, edited by D. Schottenfeld. Charles C Thomas, Springfield, Ill. In press.

(15) Wynder, E., Graham, S., and Eisenberg, H.: Conference on the etiology of cancer of the gastrointestinal tract. Report of Research Committee, World Health Organization on Gastroenterology, New York City, June 10–11, 1965. Cancer 19: 1561–1566, November 1966.

(16) Walker, A. R. P.: Diet, bowel motility, faeces composition and colonic cancer. S Afr Med J 45: 377–379, April 1971.

(17) Wynder, E. L., and Shigematsu, T.: Environmental factors of cancer of the colon and rectum. Cancer 20: 1520–1561, September 1967.

(18) Gregor, O., Toman, R., and Prusova, F.: Gastrointestinal cancer and nutrition. Gut 10: 1031–1034, December 1969.

(19) Gregor, O., Toman, R., and Prusova, F.: Relation of gastrointestinal cancer mortality in general. Scand J Gastroenterol 6: 79–85 (1971).

(20) Burkitt, D. P.: Related disease—related cause? Lancet 2: 1229–1231, Dec. 6, 1969.

(21) Burkitt, D. P.: Epidemiology of cancer of the colon and rectum. Cancer 28: 3–13, July 1971, (*a*) p. 3.

(22) Hill, M. J., and Aries, V. C.: Faecal steroid composition and its relationship to cancer of the large bowel. J Pathol 104: 129–139, June 1971, (*a*) p. 129.

(23) Aries, V., Crowther, J. S., Drasar, B. S., Hill, M. J., and Williams, R. E. O.: Bacteria and the aetiology of cancer of the large bowel. Gut 10: 334–335, May 1969.

(24) Stocks, P.: VIII. Dietary histories. *In* British Empire cancer campaign, Thirty-fifth Annual Report (suppl. II), 1957, pp. 51–113.

(25) Pernu, J.: An epidemiological study on cancer of the digestive organs and respiratory system, a study based on 7,078 cases. Ann Med Interne Fenn (Helsinki) 49, suppl. 33: 1–117 (1960).

(26) Higginson, J.: Etiological factors in gastrointestinal cancer in man. J Natl Cancer Inst 37: 527–545, October 1966.

(27) Wynder, E. L., Kajitani, T., Ishikawa, S., Dodo, H., and Takano, A.: Environmental factors of cancer of the colon and rectum. Cancer 23: 1210–1220, May 1969.

(28) Haenzel, W., Kurihara, M., Segi, M., and Lee, R. K. C.: Stomach cancer among Japanese in Hawaii. J Natl Cancer Inst 49: 969–988, October 1972.

(29) Berg, J. W., Haenszel, W., and Devesa, S.: Epidemiology of gastrointestinal cancer. *In* Seventh National Cancer Conference Proceedings. J. B. Lippincott Co., Philadelphia. In press.

(30) Puffer, R. P., and Griffith, G. W.: Patterns of urban mortality. Pan American Health Organization Serial No. 151. Pan American Health Organization, Washington, D.C., 1967.

(31) Berg, J. W.: Bowel cancer in Scotland. [Letter to the editor.] Lancet 2: 486, Sept. 2, 1972.

(32) Gillis, C. R., MacLean, D. S., Gillies, W. C., and Stewart, G. T.: Bowel cancer in Scotland. [Letter to the editor.] Lancet 2: 593–594, Sept. 16, 1972.

(33) Wynder, E. L., Hyams, L., and Shigematsu, T.: Correlations of international cancer death rates, an epidemiological exercise. Cancer 20: 113–126, January 1967.